Nanomedicine and Nanotoxicology

Uche Chude-Okonkwo
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Advanced Targeted Nanomedicine

A Communication Engineering Solution

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A Communication Engineering Solution

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Preface

Molecular communication is an interdisciplinary subject that has become an interesting topic of discussion among scientists, engineers and lay commentators. This type of communication is defined on the principle of using biochemical signalling to achieve information exchange among naturally and artificially synthesised nanosystems. Among its envisaged application areas is the promising field of nanomedicine. The fundamental idea behind nanomedicine is to improve the efficiency of medical and healthcare systems, using the concepts, devices, tools, technologies and techniques of nanotechnology. Due to its ability to address disease challenges at the fundamental level of the cell, nanomedicine has become a promising tool in the diagnosis, therapy and monitoring of numerous chronic diseases, such as cancer, cardiovascular disease, Alzheimer's disease and diabetes.

Many studies on nanomedicine have been widely discussed and reported in the literature. However, several challenges have prevented the satisfactory translation of expectations and promises to clinical reality. To address these challenges, it is important to note that many chronic diseases are embedded in the fundamentals of biology; hence, uniting experts from a broad cross-section of related and unrelated fields would be of great benefit to solving these medical problems. To this end, the exploration of nanomedical applications and solutions on the platform of the interdisciplinary field of molecular communication engineering has been considered as an interesting option in the recent times. Molecular communication taps into the fundamentals of communication engineering, the gains of nanotechnology, the progress in tissue/molecular engineering and the outstanding results in the overall medical/natural science fields to proffer solutions to medical challenges. An offshoot of the application of molecular communication to nanomedicine is the concept of *advanced targeted nanomedicine*, which is the focus of this book. Advanced targeted nanomedicine is the term coined to define the exploration of medical challenges and their solutions by looking at them from the perspective of a communication engineer cum nanomedical scientist. Specifically, it provides practical knowledge, tools and functionality for designing and configuring nano, micro and macro communication/control devices to enhance their functionalities as nanomedical tools in order to address medical challenges.

The main objective of this book is to provide a motivation for engineers, scientists and lay commentators to explore the concept of molecular communication from the interesting application perspective of advanced targeted nanomedicine. This perspective considers, and rightly so, the occurrence of diseases as communication anomalies among biological entities in the human body. Consequently, communication principles and approaches can be employed to model, analyse and solve disease challenges, especially the chronic and indefatigable ones, such as cancer, Alzheimer's disease, HIV and cardiovascular disease.

This book is structured in a way that provides some understanding for beginners and idealistic insight to experts in molecular communication. In order to do this, we divided this book into seven chapters:

- Chapter 1 presents the role of communication principles, ideas and systems in understanding and treating diseases, and introduces the concept of advanced targeted nanomedicine.
- Chapter 2 presents some interesting discussions on the principles of communications among/between living and non-living systems as the basis for advanced targeted nanomedicine.
- In Chap. 3, the various components of the ATN systems are discussed.
- Chapter 4 explores the different modalities for administering nanosystems into the body, as well as the modelling, analysis and evaluation of nanosystems' delivery routes from the perspective of a communication engineering problem.
- Chapter 5 presents a case-driven classical framework for the design and development of ATN solutions.
- In Chap. 6, the concept of Internet of things as a tool in the delivery of effective ATN solution is discussed. The chapter also discusses some of the most poignant examples of the utility of nanomedicine in the detection and treatment of cardiovascular disease that have recently been reported.
- Chapter 7 presents exemplary suggestions to define possible ATN solutions to medical challenges such as cancer, Alzheimer's disease, HIV and cardiovascular disease.

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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

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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

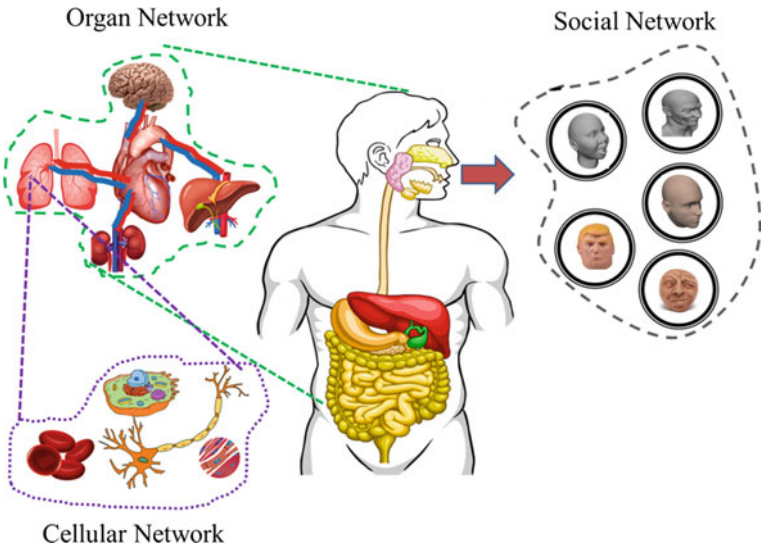

Fig. 1.2 Illustration of the different levels of communication networks associated with humans (and other multicellular animals)

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

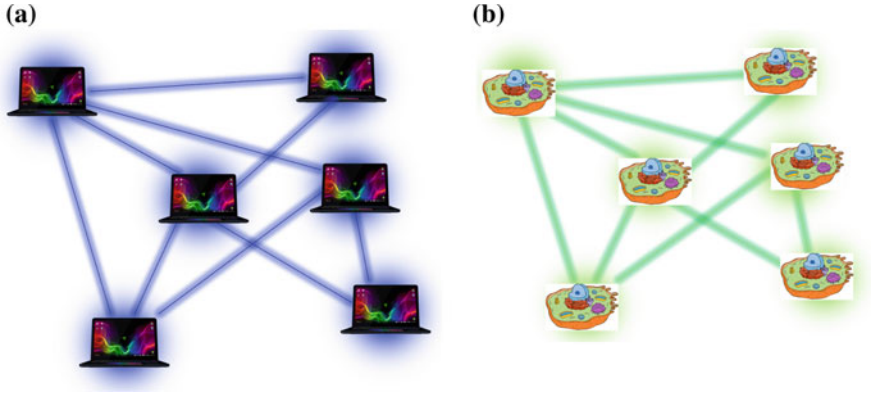

Fig. 1.3 Simplified communication network abstracted to represent, **a** a typical electronic communication network and **b** a communication network of biological nanosystems

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].

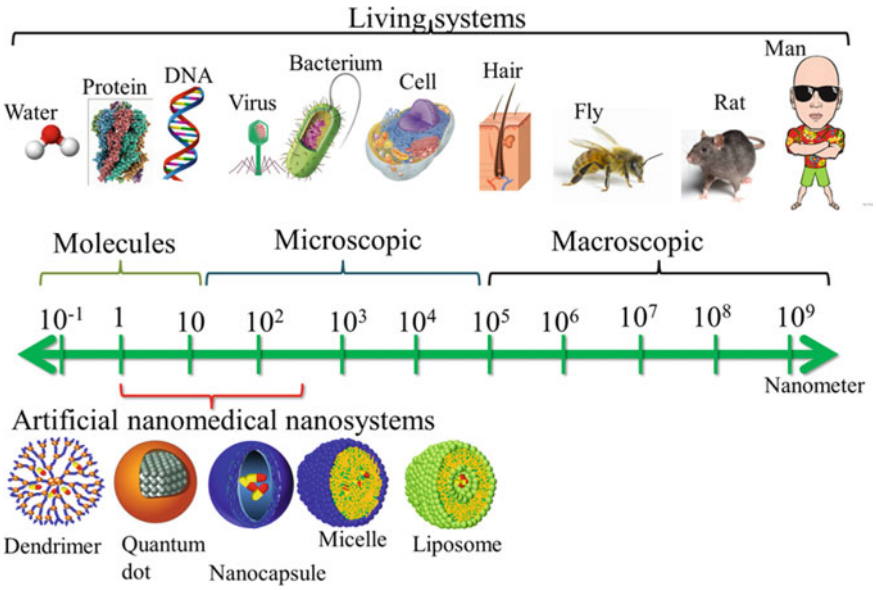

Fig. 1.4 Comparative exposition of some objects from macro- to nanoscales

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.

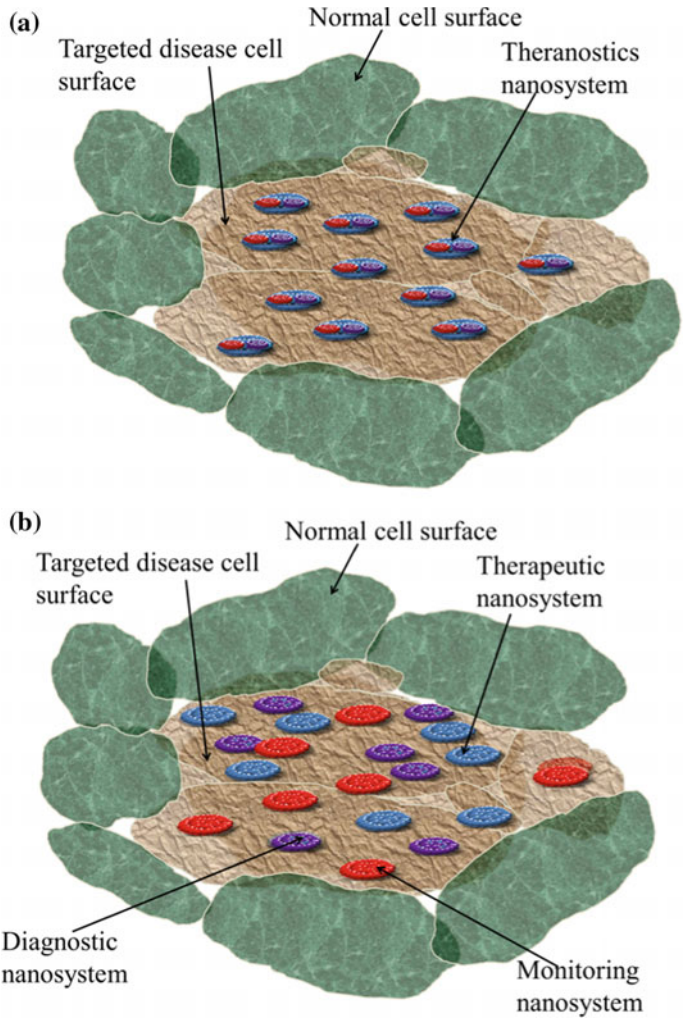

Fig. 1.5 Illustration of the difference between **a** theranostic approach and **b** MC-based nanomedical approach for disease treatments

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

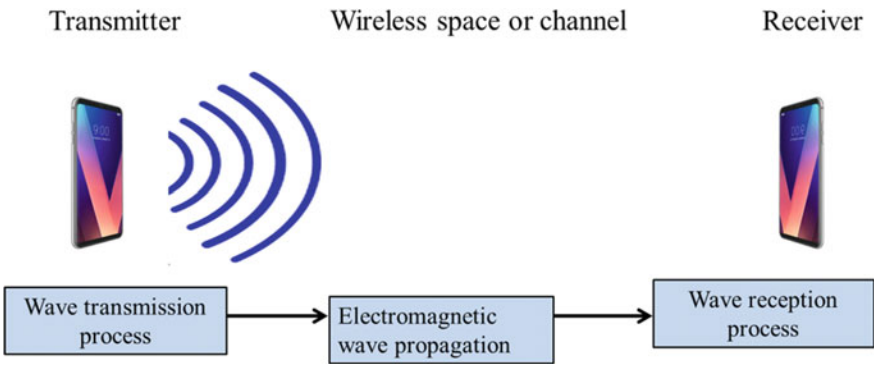

Fig. 1.6 Illustrative block diagram of electronic communication system

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.

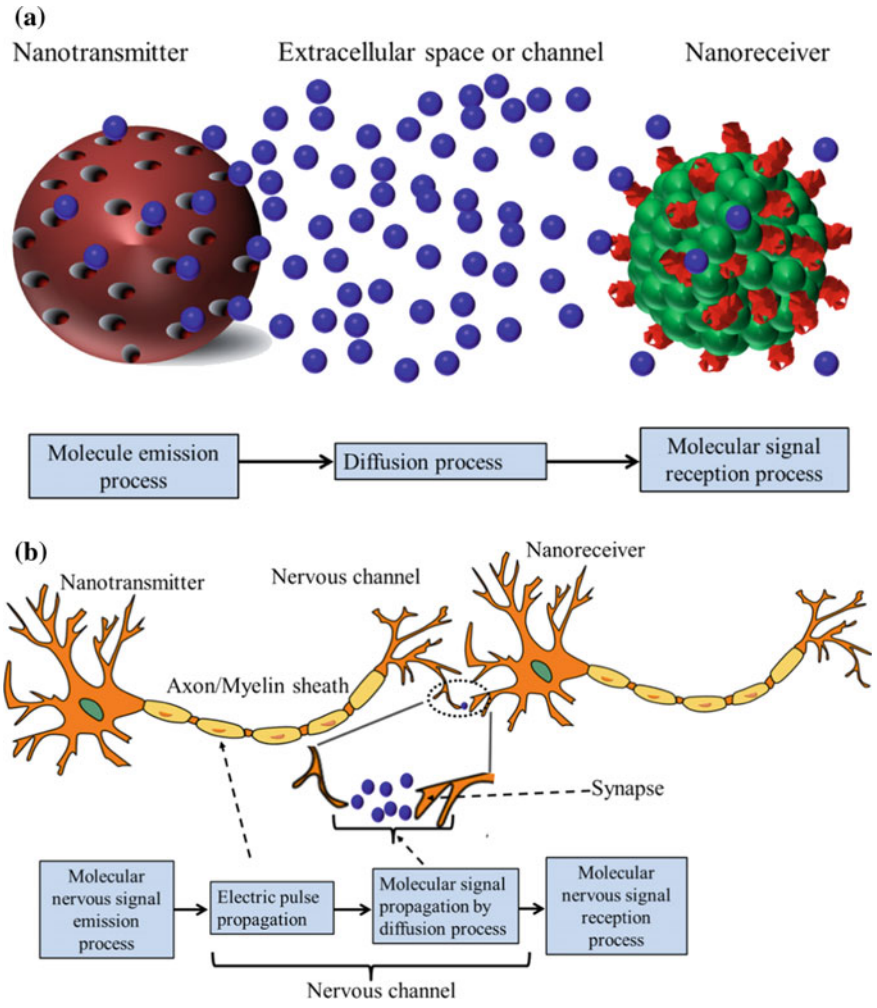

Fig. 1.7 Illustrative block diagram of biological systems communication system representing, **a** cell-to-cell communication and **b** nervous systems communication

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

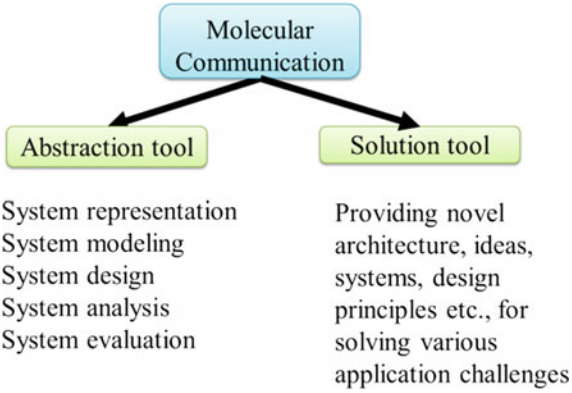

Fig. 1.8 Illustrative categorisation of molecular communication

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.

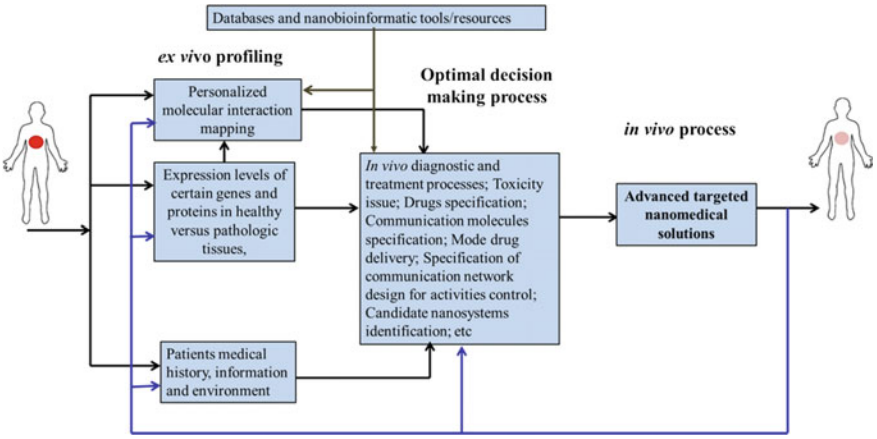

Fig. 1.9 Illustrative framework of advanced targeted nanomedicine solution

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.

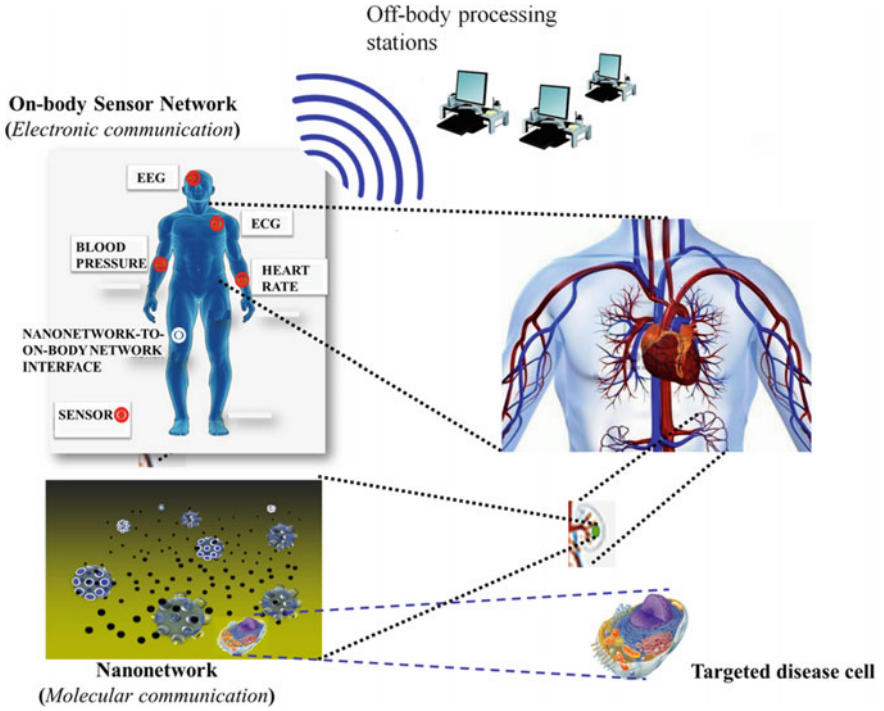

Fig. 1.10 Illustration of typical ATN solution

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Chapter 2
Communication Between Living and Non-living Systems: *The Basis for Advanced Targeted Nanomedicine*

2.1 Introduction

Every system known to man can be categorised as either a living system or a non-living system. There are many features and factors which differentiate the categories. Living systems are distinguishable from non-living systems by their ability to maintain stable, ordered states far from thermodynamic equilibrium [1]. For the living systems to maintain the ordered nonequilibrium states, they continuously exchange information/entropy with their environments, grow and reproduce. Examples of living systems include humans, animals, plants and cells. On the other hand, non-living systems, if isolated or placed in a uniform environment, usually cease all motion very quickly such that no macroscopically observable events occur, thereby maintaining permanent equilibrium. Examples include all inanimate objects.

Typically, the living systems are constantly exposed to various degrading factors such as diseases, injuries, threats to life and extreme environmental conditions. Hence, they must find a way to adjust their physiological conditions in order to overcome the challenges. They often achieve this adjustment by their ability to communicate among themselves and with the environment. Communication among living systems is crucial and happens at every level of the systems, from subcellular proteins, through organelles, to tissues and organs and ultimately up to groups of individuals. For instance, communication in humans is needed to carry out daily tasks and coordinate human activities. At the minuscule level, by exchanging information about the ideal constituents of human body fluids and establishing memory banks, certain human cells are able to identify foreign and harmful agents in the body and eliminate them. It is also known that communication among bacteria is needed to slow down or promote protein synthesis during the phases of nutrient starvation and nutrient plenty [2, 3]. Living systems often encounter injuries, and to heal wounds, their bodies employ cellular signalling pathways that involve complex cell-to-cell communication [4]. For cells to acquire and store up energy, communication is required among the pancreatic cells and between the pancreatic cells and the cells that store up energy. The growth and death of an organism also involve complex

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signalling network among cells [5]. Hence, information exchange among living systems is fundamental to their survival and coexistence in a given environment. A poor communication network implies vulnerability and eventual breakdown of the system, which results in the disruption of the hitherto ordered state of the system. In cellular communication, the breakdown in communication leads to the manifestation of disease symptoms. When effective actions are not taken to normalise the breakdown in communication or where such actions are not known yet, the anomaly in communication may lead to the death of the organism.

In the case of non-living systems, complex multilevel information exchange among the systems does not exist. However, over the years, man has become capable of coupling and re-engineering materials that are hitherto non-living into still non-living systems but with the capability to communicate, giving birth to contemporary communication systems such as electromagnetic wave-based communication systems. Over a century, man has acquired knowledge of the basic principles of communication between non-living systems by means of electromagnetic wave propagation. He has been able to establish impressive communication among artificially engineered systems placed thousands of miles apart. It is envisaged that the extension of the knowledge of communication principles acquired over many years to analyse and/or redesign communication at the cellular level can help address challenges in correcting disorders that lead to ill health in humans.

2.2 Basics of Communication and Information Exchange Between Systems

In general, communication involves the conveyance of information or meaningful messages from one system or group of systems to another using mutually understood functions and rules. Therefore, it may be said that every communication must involve at least two systems or entities, namely, the transmitter and the receiver as shown in Fig. 2.1. The transmitter generates the message in the form of a *function* that contains a certain amount of information intended for transmission. In some cases, the function may undergo some conditioning (encoding) in order to make it more suitable and robust for its journey to the receiver. The transmitter then transmits/releases/emits the function into the surrounding space/medium, called the communication channel. Subsequently, based on certain physical principles associated with that particular function, it propagates through the channel and may be received by the receiver system. The reception mechanism depends on the particular function that is transmitted. The receiver then employs certain processing to extract the information that is embedded in the received function and acts accordingly. The mutual information or the correlation between the transmitted message and the received message determines the faithfulness of the communication process.

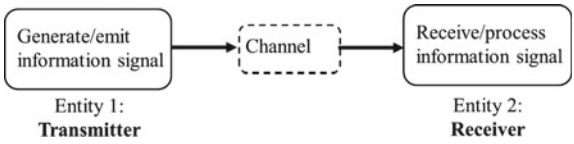

Fig. 2.1 Simple generalised block diagram of communication

2.2.1 Information Conveying Functions

In many forms of communication, the functions that convey information include electromagnetic, magnetic, chemical and mechanical. Under electromagnetic functions, which are synchronised propagating oscillations of electric and magnetic fields, we have sound waves, radio waves and optical waves, each operating at different frequency ranges.

The sound wave is an electromagnetic wave that operates within the lower frequency range of the electromagnetic spectrum and can propagate through air, water and solids. It can be categorised into infrasound waves and ultrasound waves. Infrasound waves are audible to human ears and are between about 20 Hz and 20 kHz [6], while the ultrasound waves are above 20 kHz [7]. Infrasound is the typical information conveying function in human-to-human communication, such as for conversations and speeches, and in animal-to-animal interactions [8]. Ultrasound waves are often used in tissue imaging [9], airborne communication [10] and communication between biosensors [11, 12]. The use of sound waves as a communication function is often constrained by the heterogeneous physical properties of the material medium, the viscosity of the channel, the temperature of the channel (which defines the speed of propagation) and the motion of the channel itself (which induces uneven Doppler shift across the component frequencies of the wave).

Radio waves span the range of frequencies between 3 kHz and 300 GHz. Communications using radio waves as information conveying functions seem to be common to most man-made systems. Hence, it is widely used in communications between systems such as electronic sensors, mobile phones, computers, televisions and satellites. Some animals such as mormyrids and gymnotids communicate (to find food) wholly through complex electromagnetic waves [13]. The use of radio waves as communication functions is often constrained by factors such as attenuation (increases with frequency), delay spread (frequency selectivity), scattering (increases with frequency) and Doppler spread (time selectivity).

Optical waves span the frequency range between 10 THz and 10^6 THz, covering the spectrum from far infrared through all visible light to near ultraviolet. They are employed as an information conveying function in many man-made and animal communication systems. Man-made optical communication technologies such as lasers [14], fibre optics [15] and infrared [16] are available globally. In respect to living organisms, information conveyance using optical waves is found among many animals such fireflies [17], pyrosomes [18], *Noctiluca scintillans* [19], *Quantula striata* [20] and Omphalotus [21]. These organisms use the process of bioluminescence [22] to transmit information intended for organisms of the same species and preda-

tors for the purposes of food search, attraction and defence. Information conveyance using optical waves is naturally suited for communication requiring high data rate. However, it suffers from challenges such as absorption and scattering (except when guided as in the case of fibre optics technology), which attenuate the transmitted optical information and eventually bring about multipath fading, resulting in loss of transmitted information observed at the receiver.

Information can be conveyed using magnetic fields, which operate at low frequency [23]. The magnetic field is generated from a coil and spans very short distances (the near field), which are inversely proportional to the frequency of operation. So, the system uses a low-frequency carrier signal to increase communication coverage up to several metres. This limits the data rate capability of the communication. In the medical field, magnetic fields have been employed to interact with tissues, toxins and nanoparticles so as to achieve remote imaging of tissues [24], detoxification [25], and to guide nanoparticles for targeted drug delivery [26].

Information can also be conveyed to a system by means of chemical (or biochemical) signalling, which may be based on the process of classical diffusion. The chemical function is fundamentally defined by the concentration of molecules whose type and/or pattern desirably influence the activities of the receiving system [27]. This is the type of function involved in many communications among natural cells to coordinate their activities [28]. It is also the communication function between some organelles inside the cells.

The use of mechanical energy as an information conveying function entails the physical conveyance of information from the point of generation to that of reception. This mode of communication is akin to how humans deliver messages to a destination by walking or driving the distance. Such function is also used by cells to convey information from one organelle to another by employing molecular motors such as dynein and protein kinesin [29].

The type of function employed for communication depends on the architecture of the communicating systems and the channel through which the communication is intended to take place. The channel is literarily the space between the transmitter and the receiver defined by its material, temporal and spatial properties. It is the properties of this space that primarily determines the type of function that can propagate through it. For instance, let us assume that the mutually understood function between a transmitter and a receiver is the sound wave. If, for instance, the spatial property of the physical channel indicates a large distance between the communicating terminals, it may imply that a sound wave cannot propagate through such distance, but a radio wave can. Implicitly, effective communication between the two systems can be achieved by conditioning the transmitter sound wave to a radio wave by means of lossless ‘transduction’ before transmission. This process is often termed modulation. At the receiving end, the reverse of the modulation, demodulation takes place to extract the equivalent sound wave. This analogy applies to all forms of functions for conveying information.

2.2.2 Generalised Transmitter/Receiver Model

When a system intends to send information to another system, it acts as the transmitter while the latter is the receiver. The transmitter generates the intended message made up of symbols derived from a set. The information (self-information) in the message is defined by the entropy of the transmitter. The method of generating and transmitting/releasing each of the information conveying functions named above differs from one to another. Hence, different types of functions are generated by different types of transmission mechanisms. Irrespective of the type of transmitter and the transmitted function, a good model of a transmitting system is important in its characterisation and use in a communication scenario. We can generally represent the model of a nanotransmitter by the expression

$$\text{Trigger} \xrightarrow{T\_\text{Model}} \text{Information signal} \tag{2.1}$$

Here, the trigger signal, which may be electromagnetic, electrical, magnetic, optic, chemical or mechanical, initiates the transmission process in the transmitter. This results in the emission of the information signals, which again may be any of the functions named above. The model challenge is that for a given trigger signal and desired information signal, one needs to define the process model *T_Model* that is truly representational of the nanotransmitter information generation, function encoding and signal release/emit mechanisms.

Characteristically, in information theoretic parlance, the transmitted information is termed self-information and by itself does not usually convey any meaning. Rather, it conveys meaning only when there is a receiver that interprets the specific features of the transmitted function to obtain the sent information, which will usually result in state change at the receiver. Implicitly, what is information to one receiving system may not be information to another. Hence, every transmitting system should have a complementary receiving system. A good model for a receiver in general can be expressed as

$$\text{Received signal} \xrightarrow{R\_\text{Model}} \text{Response} \tag{2.2}$$

The model challenge is as follows. Given a received signal, it is required that the receiver model process *R_Model* be defined in a manner that is truly representational of the reception and signal processing mechanism of the receiving system under consideration.

2.2.3 Communication Performance Measures

There are some performance metrics which have to be taken into consideration while designing or analysing a communication system, whether it is between living

systems or non-living systems. Some of these metrics are described below. The metrics discussed here are transmission rate, end-to-end delay, probability of error, throughput, energy efficiency and consumption and environmental compatibility.

2.2.3.1 Transmission Rate

The transmission rate of a system reflects how quickly transmitted information is processed by a communication system. This depends on the rate at which information is released into the channel, the channel bandwidth, the propagation time and the time is taken to sample the information at the receiver.

2.2.3.2 End-to-End Delay

The end-to-end delay metric defines the unit time it takes to transmit a message, and for the transmitted message to propagate through the channel and be processed by the receiver. It is dependent on the time the transmitter released the message after the release trigger, the type of communication function in use, the propagation characteristics (channel properties as well as those of the intermediate nodes) and the receiver processing time.

2.2.3.3 Probability of Error

To explain the concept of probability of error as a communication metric, let X be the transmitted information, and Y the expected output. We want to quantify the likelihood that the discrepancy between Y and any other observed output is within a certain range. We do this by defining the error probability metric. In essence, error probability is the probability of a given receiving system making a wrong decision, in which case an output other than Y is produced. The discrepancy in output results from the uncertainty in transmitting X through the communication channel that is prone to noise and other perturbations.

2.2.3.4 Throughput

The throughput metric quantifies the amount of information processed by the receiving system in a given amount of time. Just like the end-to-end delay metric, this metric is dependent on the type of communication function in use; the propagation characteristics (channel properties as well as those of the intermediate nodes); and the receiver processing capability.

2.2.3.5 Energy Efficiency and Consumption

This metric quantifies the efficiency in energy usage for information exchange between two systems. Typically, energy is required for the generation and trans-

mission of information, the conveyance of the information through the channel to the receiver and the processing of the information at the receiver. The energy required for these operations will most often come from an external power source or be latent in the system. Therefore, the lesser the energy expended for molecule synthesis, emission, propagation, reception and processing, the more efficient the system is.

2.2.3.6 Environmental Compatibility

The environmental compatibility metric reflects the impact of the communication between systems on the environment, which is inclusive of the effective working of other systems in the environment. The effects that are often considered include the impact on the climatic conditions, the biological/chemical/mechanical conditions and noise emission. For instance, in using an electromagnetic function for communication, the interaction/interference of communication electronic and electrical equipment with its electromagnetic environment is always considered. Hence, electromagnetic communication devices are required to emit electromagnetic energy that is lower than a certain value to ensure that interference with other communication systems is reduced. Issues related to the unhealthy absorption of propagating electromagnetic waves by the human body, which may influence biological activities in living organisms, are defined by the quantity and specific absorption rate [30]. In the case of communication using chemical functions, the quantity, termed *supersystem degradation* [31], defined as the impact of the biochemical/chemical communication network upon the host organism with regard to its normal operation, should be considered. This can also be related to how energy harvested from the supersystem by the communication systems affects the primary functions of the host organism.

2.3 Communication Between Living Systems

Communication among living systems happens at every level of the system, from subcellular level, through the tissue and organ levels, and up to the level of the organism. Effective communication among living systems at their various levels of existence is fundamental to their harmonious organisation, which ensures that they collaboratively meet the intended goals of the host environment/organism.

2.3.1 Communication at Organism Level

Communication between organisms such as humans, animals and plants takes place by means of one or more of the information conveying functions discussed earlier. The organisms are naturally equipped with transmit/receive facilities such as an auditory system, olfactory system, visual system, chemoreceptor system and mechanoreceptor system. Hence, they can communicate with each other and their environment using

functions such as sound waves, optical waves, chemical signalling and mechanical energy.

2.3.1.1 Communication Between Animals

Animals, including humans, communicate among themselves to spread knowledge and establish/improve relationships. The result is a more cohesive organisation, greater productivity and strong working relationships at all levels of the organism. Unaided communication among humans is often done with a syntactically organised system of signals, such as voice sounds, intonations or pitch, gestures or written symbols that communicate thoughts or feelings. Animals also communicate with one another (especially those of the same species) to search for food, mates and avoid dangers/predators, by making special sounds, sending out optical signals, emitting/receiving chemical signals (pheromone communication) [32, 33] and tactile communication [34]. For examples, monkeys use calls to warn one another of danger [35]. Birds such as the peacocks can make imposing feather displays to communicate a territorial warning to other competing peacocks [36]. Many different types of animals mark their territories with their scent (chemical signalling) as a clear message to others to stay away.

2.3.1.2 Communication Between Plants

Plants also communicate with each other and their environment. These living systems are usually exposed to various stress factors such as disease, injury, herbivory and extreme heat/cold [37]; hence, they must find a way to adjust their physiological state either in response to or in preparation for such threats to ensure their well-being and survival [38]. To make this adjustment, plants have developed a communication system to transmit information based on volatile organic compounds [37]. As in all organisms, the evolution, development and growth of plants depend on the success of these communication processes [39]. And just like in the case of animals, communication between plants is multilevel: among the cells of a plant; between plants and microorganisms, fungi and insects; between different plant species; and between members of the same plant species. For more in-depth information on plant communication, the reader is referred to [37, 39, 40–41].

2.3.2 Communication at Cell Level

Aside from communication between organisms, communication also takes place inside the organisms at the basic level of cells. All living organisms are composed of cells, which are the basic building blocks of all living systems. The cells in an organism do not live in isolation but interact among themselves. Their survival depends

on receiving and processing information from each other and the extracellular environment. The information may reflect the availability of nutrients in the microenvironment, changes in environmental conditions, the need to reproduce/grow or the need to undergo apoptosis. On the basic cellular level, the information exchange is essentially by means of chemical signalling and electric impulses.

2.3.2.1 Communication at Cell Level in Multicellular Organisms

In multicellular organisms such as animals and plants, there are various kinds of chemical signalling methods with which cells communicate with one another, which is dependent on their proximity to each other. This signalling is grouped into four types, namely, autocrine, juxtracrine, paracrine and endocrine signalling. *Autocrine signalling* occurs when a cell responds to its own biochemical signalling molecules that it produced. Some examples of this type of signalling include lipophilic and prostaglandins binding to membrane receptors. *Juxtracrine signalling* occurs between adjacent cells that are in contact; hence, this type of signalling is often referred to as a contact-dependent signalling. It plays a very significant role in controlling cell fate and embryonic development [42]. *Paracrine signalling* involves signalling between cells that are within the same vicinity. An example of this is the histamines hormone, which is released as a local response to stress and injury [43]. *Endocrine signalling* is the most common type of cell signalling and involves sending a signal throughout the whole body by secreting hormones into the bloodstream or sap of the organism. Examples include adrenal signalling, thyroid signalling and pancreatic signalling [44, 45].

On the other hand, nerve cells called neurons communicate by means of a combination of electrical and chemical signals. Within the neuron, electrical signals driven by the movement of charged molecules across the cell membrane allow rapid propagation of electric pulses from one end of the cell to the other. Communication between neurons occurs at tiny gaps called synapses, where specialised parts of the two cells (i.e. the presynaptic and postsynaptic neurons) come within nanometres of one another to allow for chemical transmission [46].

2.3.2.2 Communication at Cell Level in Unicellular Organisms

In single-cell primitive organisms such as bacteria, viruses and fungi, communication between organisms has been known to occur by means of chemical signalling. Bacteria can communicate by quorum signalling/sensing, especially when they are in high density [47]. This form of collaborative communication provides the group of bacteria a way to adapt to the environment. It has also been reported that there exists some form of communication between viruses [48]. Communication between fungi and plant/bacteria has also been reported [49, 50].

2.4 Communication Between Non-living Systems

While non-living systems cannot communicate among themselves when placed in a uniform environment, they can be engineered to do so as is evident from communication between man-made electronic devices and machines. From the invention of the electric battery by Alessandro Volta in 1799 through the development of the electric telegraph, the Marconi experiment on wireless telegraphy, the invention of electric telephone in the nineteenth century, and the subsequent invention of the television and man-made satellites systems, communication between man-made systems has impacted tremendously on the human race. These feats have been taken further to the development of high-end and smart electronic communication devices, the most common being phones, computers, radio, television, sensors and the Internet. With these communication devices, we are able to communicate effectively and nearly instantaneously with people at different locations and receive information about innumerable developments and proceedings of importance across the globe.

2.4.1 Medical Applications of Man-Made Communication Systems

In recent times, advances in the design and development of electronic communication systems and devices have enabled ubiquitous healthcare systems, which promises an increase in efficiency, accuracy, affordability and availability of medical treatment. This is necessitated by the need to address many challenges facing the healthcare industry. Some of these challenges include societal changes such as an increase in the population that desire access to healthcare service, the size of the ageing population, the number of chronic diseases, the number of people suffering from them and the uneven distribution of healthcare personnel. Moreover, with the appearance of new diseases that are characterised by complicated strains, early detection and novel therapeutic methods are always urgently required to avoid endemic situations that may significantly threaten global population.

The contemporary application and deployment of electronic communication systems to the healthcare sector are usually for the measurement of biosignals [51]. These biosignals are usually associated with various pathological conditions such as blood pressure, sugar level, pulse rate, body temperature variation, electrical activity of the brain, electrical activity of the muscles and electrical activity of the heart. The medical personnel then employ the values of these measurements to make better judgment on the patient's condition and administer the best therapeutic actions. The advent of wearable technologies, shown in Fig. 2.2, that can measure these biosignals has revolutionised the healthcare and fitness sector [52]. In wearable technology, sensors are placed at different areas of the body to collect data (in this case, biosignal readings). With the advancement of low-power integrated circuit (IC) and wireless communication technologies, concepts such as the wireless body area network (WBAN) are becoming an emerging research area [53]. The WBAN or body

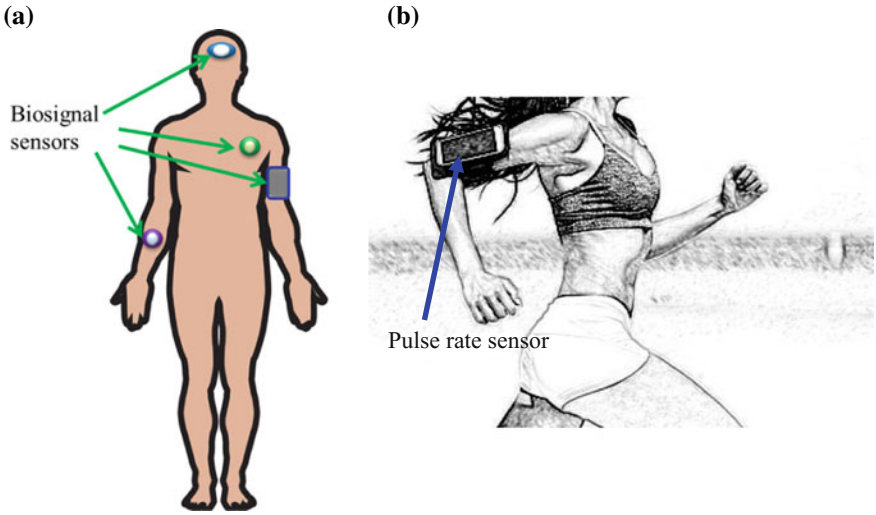

Fig. 2.2 Illustration of wearable technology applied to **a** health care and **b** sports/fitness

sensor network (BSN) is a wireless network that enables health monitoring anywhere and anytime [54]. Also, with the advances in the Internet of things (IoT), concepts like the Internet of humans (IoH) that integrate the BSN to the IoT have emerged, as illustrated in Fig. 2.3. The IoH [55] paradigm is a cutting-edge enabler that can be used for e-health applications, such as computer-assisted rehabilitation for the aged and handicapped and early detection of medical issues.

2.4.1.1 On-Body Sensor Networks

When sensors are places on the human body for the purpose of data acquisition, the BSN is termed an *on-body* sensor network. The data generated by each sensor is conveyed to another sensor or to a nearby central processing system or across to a remote processing system for further processing, as depicted in Fig. 2.3. The information conveying function is usually the electromagnetic wave operating at a defined frequency. Therefore, the knowledge of the effect of the wave propagation channel around the body on communication performance is crucial to the design, placement and operation of the on-body sensor network.

2.4.1.2 Intra-body Sensor Networks

In some scenarios, the positioning of the sensors further into the body provides more accurate reading of some biosignals. The benefits of intra-body sensor technology over on-body sensor technology include lower power demand and less susceptibility

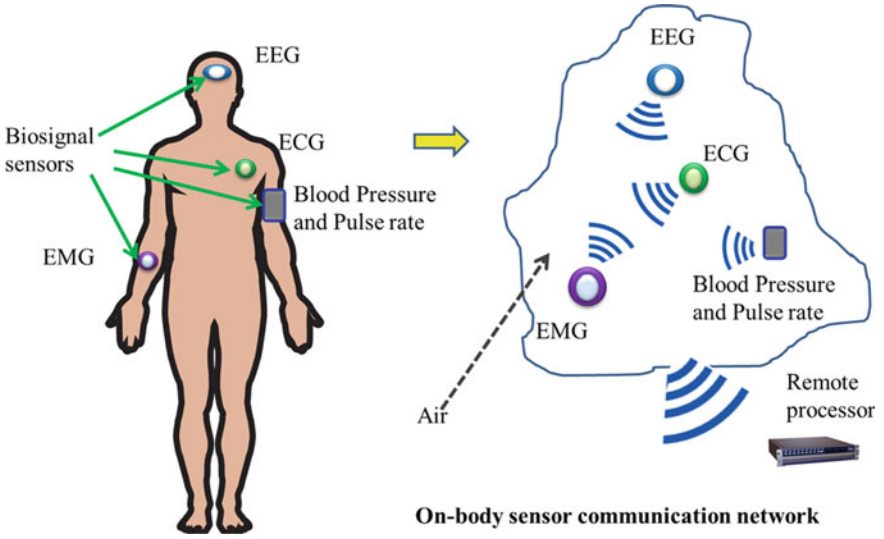

Fig. 2.3 On-body communication network of biosignal sensors

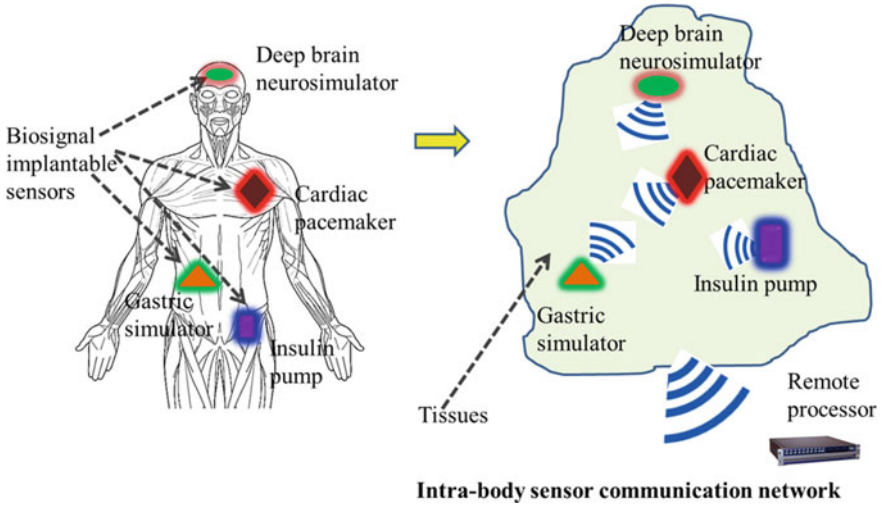

Fig. 2.4 Intra-body communication network of biosignal sensors

Table 2.1 Comparison of on-body and intra-body communication networks

Parameter	On-body network	Intra-body network
Physical channel	Air	Human tissues
Data rate	Less than 13 Mb/s	Less than 2 Mb/s
Range	10 m	Less than 2 m
Attenuation	High	Low
Energy efficiency	Low	High

to electromagnetic interference as well as insecurity issues [56]. Intra-body communications involve the use of non-RF wireless data communication techniques, which employ the human body itself as transmission medium for electric signals. In this case, the sensors are implanted into the body—for instance, under the skin—which implies that they communicate through the body tissues, as shown in Fig. 2. 4. A table showing some comparisons between the on-body and intra-body sensor networks for medical application is given in Table 2.1.

2.5 Communication Between Living and Non-living Systems: *Advanced Targeted Nanomedical Solution Basis*

Communication among humans is integral to their ability to establish relationships and spread knowledge to enhance cohesive organisation, productivity and survival at all levels of human existence. Breakdown in communication brings about ineffective interactions, which results in uncertainty, misunderstanding, confusion, argument/conflict and ultimately poor productivity and sometimes deaths [57]. It is the need to ensure efficient communication among humans at any time, from anywhere or any source, and in any condition that has necessitated the design and development of many man-made communication technologies and devices. Such devices and technologies include phones, computers, telepresence, satellites and the Internet. We have discussed the potentials and benefits of communication between living systems, and between non-living systems. We shall now focus on the possibility of communication between living and non-living systems, which forms the basis of the ATN.

2.5.1 Diseases as Manifestation of Breakdown in Communication Among Cells

Just like a social communication network is crucial to the survival of humans, the same applies to the organs, tissues, cells and molecules inside the human body. Naturally, for the human body to function well and achieve its goal of survival, all

the organs, cells and molecules in the body have to work collaboratively and harmoniously. Such collaboration requires the sending and receiving of information to effect 'social control' [58]. A breakdown in communication at the various points in the cell network shatters this harmony resulting in diseases. In man-made communications, breakdown in communication is caused by faulty devices and connections. The repair or replacement of the faulty devices/links normalises connectivity. The same logic applies to breakdown in communications among cells in human body. Indeed, issues relating to diseases and cell defects can be narrowed down to the breakdown in communication among a group of cells in the body. For instance, breakdown in cell-to-cell communications has been implicated in many diseases such as Alzheimer's [59], diabetes [60], Parkinson's [61], cancer [62], Huntington's [63], etc. The repair or replacement of defective cells and cellular pathways normalises communication, and that is the primary goal of medicine.

In medical science and practice, different modalities are employed to achieve this normalisation. One modality is the introduction of specific drug particles to act as extracellular chemical signals, which inform the defective cells to directly carry out desired chemical, physical and biological modifications to achieve therapeutic results, thereby restoring normal communications. The source that introduces the drug particles represents a transmitter and the targeted defective cells, the receiver. In this case, where the drug-introducing source is a man-made machine-like injection machine, this can be regarded as a communication between living and non-living systems.

In another modality, if isolation of the defective cells is the best option to achieve harmonious communications among all other cells in the body, the cells can physically be removed by means of surgery. But if the isolation of the defective cells will have a significant effect on the harmonious working of all other cells in the body, then the modality will further require that the removed defective cells are replaced with artificially engineered replicas, assuming that the technology for engineering the replica exists. Recent developments in tissues engineering, particularly 3D printing [64], have radically changed our ability to integrate inanimate parts into humans. We are already growing new tissues on artificial scaffolding for transplantation, and prosthetics that can be controlled by the minds of patients with paralysis caused by illness or injury have been demonstrated.

To be able to correct anomalies in cellular communications, one has to first obtain a detailed understanding of the architecture and working of the cells of interest in both healthy and unhealthy conditions. Hence, preceding the design and implementations of any modality for disease treatment, study of the cells and cells signalling is crucial. Such study may also involve communication between certain man-made systems and natural cells and tissues. For instance, the use of sensors to read biosignal information from cells can be regarded as communication between cells and man-made systems.

2.5.2 Nanomedical Solution for Normalising Breakdown in Communication Among Cells

In many cases, the complete knowledge of how to address a given breakdown in communication using the currently existing macro technologies is not available. Examples include the treatment of Alzheimer's, cancer, HIV and many cardiovascular diseases. In some cases, the existing methods of therapy may have side effects that are quite challenging. An example is in the treatment of cancer using chemotherapy, where the issue of toxicity is evident from side effects such as alopecia, compromised immunity, fatigue, haemophilia, loss of appetite, painful urination, nausea and vomiting, nail toxicity and anaemia [65]. Hence, new ideas and concepts are currently being explored to address the challenges posed by various difficult medical conditions.

In the course of normalising breakdown in communication among cells, contemporary medicine often employs non-living, man-made systems to detect anomalies, screen for defects, diagnose disease, treat it and monitor its progress. For instance, man-made systems such as biosignal sensors, magnetic resonance imagers, computed tomography scanners and syringes communicate with living systems such as cells and tissues to detect and treat diseases. These systems use one or more of the information conveying functions discussed earlier to receive information about the cells' condition or convey therapeutic information to the cells.

In line with the above assertion, there has been a recent paradigm shift from the vastly explored contemporary medicine (based on macro-science and engineering) to nanomedicine (based on nano/micro-science and engineering). The idea of nanomedicine stems from the idea that since diseases manifest from miniscule activities in the cells of living organisms, it is insightful and seemingly effective to tackle health challenges at the cell level. Nanomedicine exploits the unique properties of nanomaterials and the tools of nanotechnology to combat health challenges at the cellular level. It has found applications in diverse medical specialties such as oncology, immunology, osteopathy and urology [66]. For instance, in contemporary medicine, drug molecules are injected into the bloodstream with the expectation that a small but significant percentage of the drug gets to the defective cells and initiates the required therapy. In the nanomedical approach, a nanosystem carrying the required amount of drug that is capable of producing the desired therapeutic result is injected into the blood stream, from where it smartly conveys the drug molecules to the defective cells. This nanomedical approach is termed targeted drug delivery technology [67–69]. Aside from delivering drug molecules, genes (for gene therapy) [70] can also be delivered to the targeted tissue or cell using engineered nanomedical nanosystems. Hence, in the context of living-to-non-living systems communication, nanomedicine is concerned with the design of nanoscale systems that can convey or receive information from cells.

In cases where the breakdown in cellular network communication is due to the loss or malfunctioning of tissues, the affected tissue can be replaced by man-made biological substitutes to restore, maintain or improve network performance. The substitute

man-made biological nanosystem can be fabricated by means of nanomedical tissue engineering principles [71], which enables the design and fabrication of biocompatible scaffolds at the nanoscale. Nanomedical tissue engineering can also enable the creation of controllable and predictable implantable tissues [66].

In clear terms, the objectives of nanomedicine are as follows: (i) to explore the communication engineering, biology, chemistry, physics and mathematics of human (animal) systems and diseases at the nanoscale; (ii) to use the knowledge obtained to design nano- to macro-size systems that can communicate directly with each other and with the disease cells to detect, screen, correct and monitor anomalies in the cells; thereby addressing health challenges at the root. Communications among synthesised nanosystems and other man-made devices (such as the on-body sensors, which are non-living systems), and between the non-living nanosystems and natural cells (living systems) define the ATN solution.

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Chapter 3
Nanosystems and Devices for Advanced Targeted Nanomedical Applications

3.1 Introduction

In the previous chapters, we discussed the relationship between communication engineering and medicine/healthcare delivery. We have espoused the view that communication between cells is vital to their health and to the effective working of the human body. Hence, breakdown in communication results in diseases, and to treat the diseases implies normalising the communication breakdown among the implicated cells, tissues and organs. The application of the ATN solutions is proposed to normalise the breakdown in communication within the cellular/organ network, and hence treat diseases. The ATN solution is a very complex one that involves the assembly and operation of materials, techniques, components, devices and networks whose dimensions range from the nanoscale to the macroscale.

A great deal of literature has presented discussions on the various types of nanomedical materials, systems, components and devices. However, for ATN application, there is the added requirement that some or all of the systems, components and devices must have communication functionality. This functionality enables the ATN nanosystems and devices to transmit, receive, process and respond to information signals. Different sets of these systems and components form networks that are interconnected to provide the ATN solutions. The networks that form the ATN solutions are the in-body nanonetwork, the body area network (on-body/intra-body) and the off-body or ex vivo networks (inclusive of LAN, MAN and the Internet). We shall discuss the ATN systems and components under these three networks.

3.2 Nanosystems for ATN In-body Nanonetworks

Figure 3.1 presents a schematic diagram of an ATN nanonetwork zoomed to indicate that the network includes artificially synthesised nanosystems and the natural cells in the body. There are many nanosystem models and fabrication methods that

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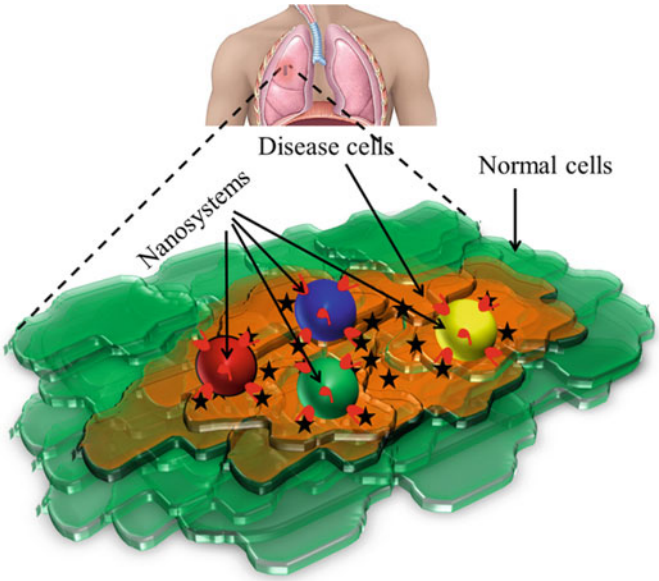

Fig. 3.1 Schematic of ATN in-body nanonetwork of nanosystems

are proposed for use in nanomedicine. Examples of typical nanomedical nanosystems include those artificially synthesised from biomolecules [1] such as liposome, nanosphere, nanocapsule, micelle, dendrimer, fullerene and deoxyribonucleic (DNA) capsule. Another category of nanosystems is those that are genetically engineered by the modification of natural biological systems [2, 3], such as cells [4], viruses [5, 6], bacteria [7], bacteriophage [8], erythrocytes, leukocytes and stem cells [9, 10]. There are possibilities for many more nanomedical nanosystems that can be conceived and designed based on bio-inspiration, or by sparks from the realms of fantasy and science fiction [11].

3.2.1 Fundamental Design Requirements of ATN Nanosystems

Ideally, to reach the targeted nanonetwork sites (cell surfaces) and be positioned on them, the nanosystems have to be introduced into the bloodstream from where they propagate through the blood vessels (interact with the blood and vessel constituents) before getting to the desired nanonetwork location. This journey is a complex one and can be influenced by multiple factors, which include the size, shape, surface chemistry, porosity, stability, sterility and biodegradability of the nanosystem. Therefore, these and other related factors that will be discussed in the next chapter have to be

taken into consideration in the design and development of the nanosystems. These factors are influenced by the characteristic of the nanosystems' route (channel), such as blood vessel geometry, adhesion, reaction, absorption, elimination, extracellular space (ECS) charge and ECS viscosity [12]. For instance, the smallest blood vessel is the capillary, which is about 5–10 μm in diameter [13]. Hence, the capillary size sets the upper size limit for every nanosystem that will traverse the blood vessel to the targeted site. If the nanosystem is to extravasate the blood vessel into the extracellular space where some cells are located, then the diameter of the fenestrae on the endothelial further influences the choice of its size. A fenestration diameter of 60 nm is typical for normal vessels and 240–400 nm for tumour vessels [14, 15].

Moreover, the adhesion, elimination, absorption and reaction of the nanosystems to the blood vessels and other constituents of the media through which they traverse are crucially influenced by the choice of their size, shape and surface chemistry [12]. For instance, large nanosystems with diameters greater than 2 μm readily accumulate within the capillaries of the lungs, liver and spleen. It is known that nanosystems whose diameters are within the range of about 100–200 nm extravasate through vascular fenestrations of tumours and escape filtration by the liver and spleen. As the dimensions of the nanoparticles increase beyond 150 nm, more nanoparticles are entrapped within the liver and spleen [16, 17]. Nanosystems that are smaller than 5 nm are easily filtered out by the kidneys [18]. Additionally, after the extravasation of the nanosystems into the ECS, the ECS properties influence the behaviour and characteristics of the nanosystem. For example, the composition and biophysical properties of the ECS differ between organs and in tissue development pathogenesis, inflammation and remodelling [19]. This implies that a nanoparticle of a specific size and shape will usually experience different ECS viscosities in different organs and tissues with varying physiological conditions. Therefore, as the viscosities of the ECSs vary across the route to the targeted cells, the dependence of ATN on the nanoparticle's diffusion characteristics becomes spread.

Finally, there are the toxicity and biocompatibility requirements [20, 21], which necessitate that the nanosystems be sterile and biodegradable. Properties such as the nanosystem's material, size/shape, surface chemistry and charge, which define the reactivity and eliminability of the nanosystems inside particles, influence its toxicity and biocompatibility.

3.2.2 Transmitting Nanosystems for ATN Nanonetworks

Transmitting nanosystems are those capable of emitting/releasing information molecules or other information conveying functions in the nanonetwork. Existing systems that can function as transmitting nanosystems in ATN nanonetworks include artificially synthesised nanosystems, genetically modified biological systems and artificial cells. We shall place the nanotransmitter architectures into two categories, namely, the generic nanotransmitter and the pre-encoded nanotransmitter architectures. The term *generic* is used here to categorise transmitters that have the capability

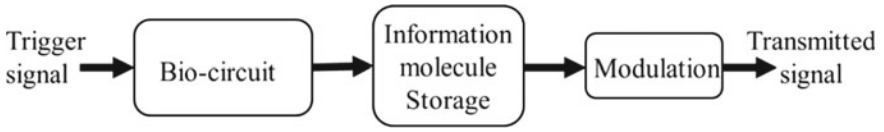

Fig. 3.2 Generalised block diagram of an ATN pre-encoded nanotransmitter

to synthesise one or more types of information molecules in response to trigger signals. On the other hand, the term *pre-encoded* is used here to categorise transmitters that cannot synthesise information molecules but have them stored in an in-built compartment at the time of fabrication.

3.2.2.1 Pre-Encoded Nanotransmitter

The generalised pre-encoded nanotransmitter architecture is depicted in Fig. 3.2. The trigger signal represents the biochemical signal that starts the transmission operation. The trigger could be a change in the concentration of signalling biochemical substances (such as glucose, potassium ion or calcium ion, hormones and pheromones), temperature, lighting, osmotic pressure, pH and magnetic/electric field in the nanonetwork microenvironment. Typically, the trigger signal initiates the execution of a predefined biochemical algorithm in the biocircuit, which triggers the release of the stored information molecules into the environment. Examples of contemporary nanosystems with the capability to function as pre-encoded nanotransmitters include lipid-based vesicles like liposome (and its different versions, namely, niosomes and ethosomes); polymer-based particles such as nanosphere and nanocapsules; and polymer-based self-assembly vesicles such as micelles, DNA-origami capsules and dendrimer. The schematic of some nanocarriers as well as some information on them is shown in Fig. 3.3.

Let us consider the scenario where the liposome or any of the lipid-based and polymer-based information molecule-encapsulating nanosystems shown in Fig. 3.3 is used as a nanotransmitter. We can encapsulate information molecules in the liposome during its preparation. The process of liposome preparation can be found in [22–24]. When the information-carrying liposome is triggered by stimuli such as pH, enzymes and temperature/light variation, a biochemical reaction is activated (execution of predefined biochemical algorithm), which subsequently initiates the degradation of the liposome membrane, thereby releasing the encapsulated information molecules. This mechanism is illustrated in Fig. 3.4.

The information molecules release profiles or patterns, which are also important and depend on the mechanical, chemical and biological structures of the liposome [25]. The release profile is related to the ability of the nanotransmitter to modulate molecular information. Typical examples of the release profiles, depicted as *Profile A*, *B*, *C* and *D*, are shown in Fig. 3.5. *Profile A* depicts instantaneous release of the molecules, and *Profile B* indicates gradual release of molecules. *Profile C* shows a

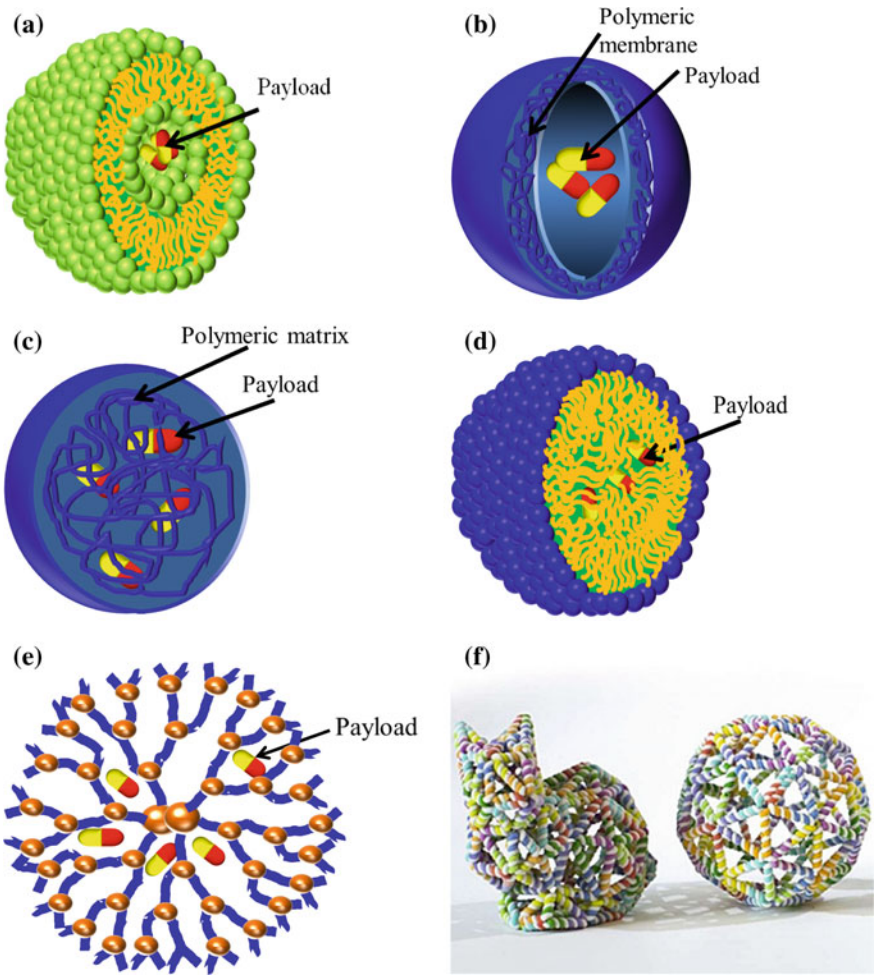

Fig. 3.3 Examples of ATN nanotransmitter structures: **a** liposome, **b** nanocapsule, **c** nanosphere, **d** micelle, **e** dendrimer, **f** DNA capsules Reprint from [12]. Copyright (c) 2017, with permission from IEEE

multiple release profile. *Profile D* also shows a multiple release profile but with a different molecule type. For a given pulse width, some of the profiles in Fig. 3.5, such as *Profile A*, *B* and *C*, can be modelled as an ON/OFF modulation technique. On the other hand, we can regard *Profile D* as the representation of a multilevel modulation scheme [26] with two sources for different molecular types.

One might well want to know how these modulation sequences can practically be produced using a liposome or other pre-encoded nanotransmitter. The release profile, *Profile A*, is achieved by the spontaneous disintegration of the membrane or bond holding the molecules in/on the nanosystem. For *Profile B*, the disintegration

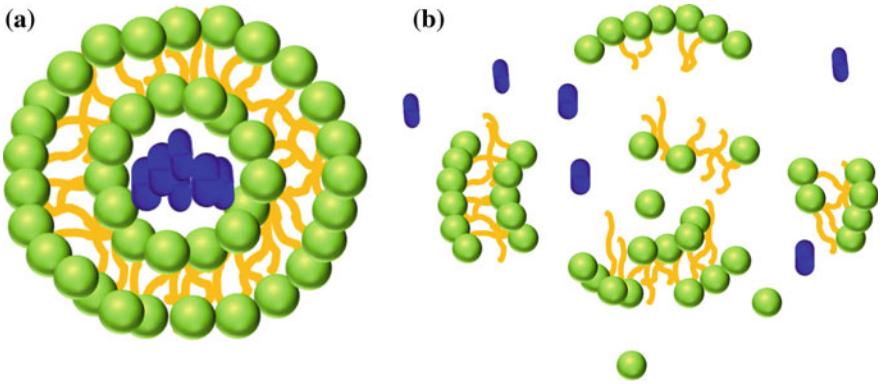

Fig. 3.4 Illustration of liposome information molecule release mechanism indicating, **a** liposome encapsulating information molecules, and **b** liposome rupture and release of information molecules

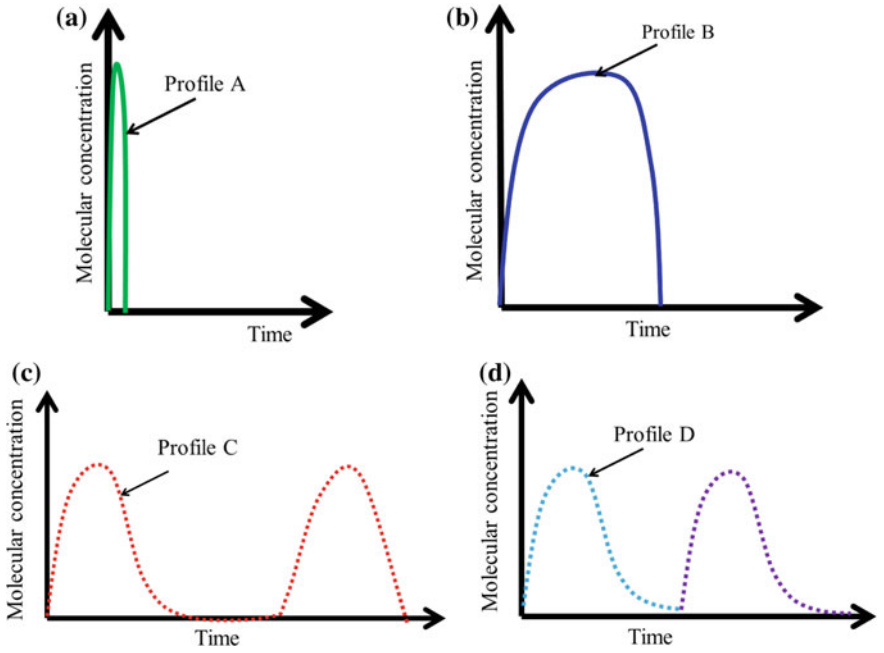

Fig. 3.5 Typical examples of the release profiles depicted as **a** instantaneous release, **b** gradual release, **c** multiple releases of one molecular species, and **d** multiple release of two molecular species

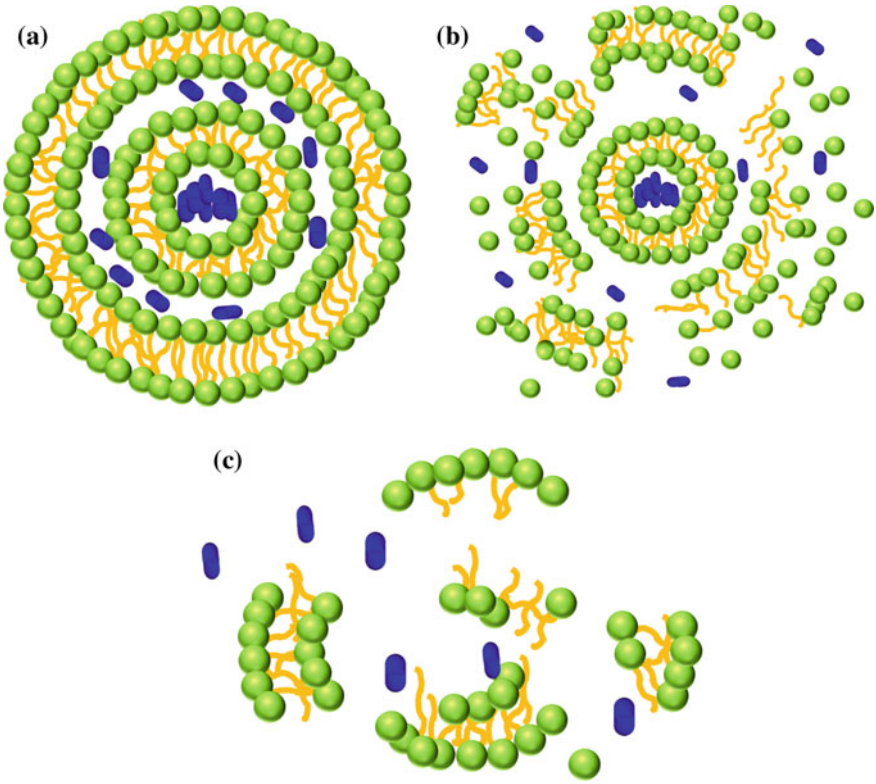

Fig. 3.6 Illustration of multilayer liposome release mechanism indicating, **a** liposome encapsulating information molecules in two layers, **b** rupture and release of information molecules at first layer, and **c** rupture and release of information molecules at the second layer

of membrane or bond, and the eventual release of molecules, is gradual. However, achieving *Profile C* and *D* requires that release can be paused and continued after a given period. This can be practically achieved in multilayer nanosystems such as multilayer liposomes and DNA capsules (as well as in multilayer fullerene). In this case, we may have two or more information molecule storage units, each enclosing a particular type or concentration of message molecules, as depicted in Fig. 3.6. For nanosystems with no capability for multilayer architecture, such as nanosphere, nanocapsule, micelle and dendrimer, *distributed modulation* capability is possible. The term distributed modulation is used here to imply that more than one transmitter works collaboratively to transmit the desired sequence. In this case, a set of unilayer nanosystems release molecules at different specified times to achieve modulation, as shown in Fig. 3.7.

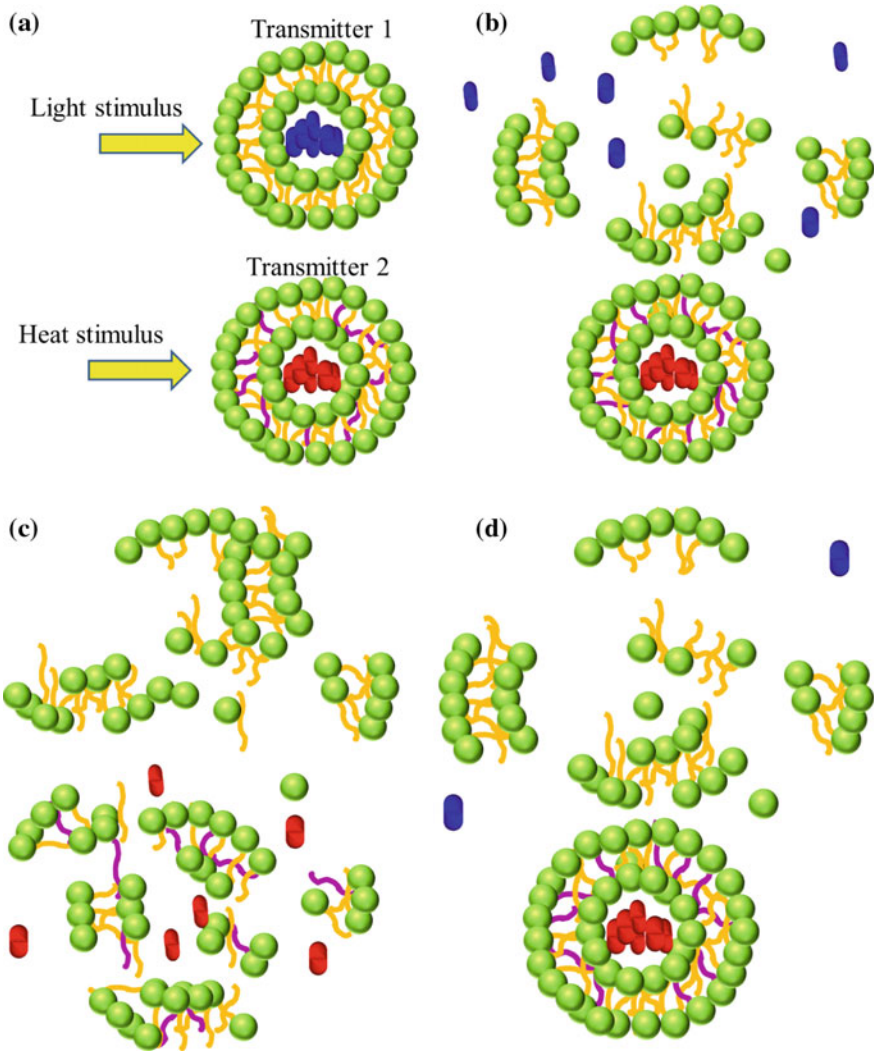

Fig. 3.7 Illustration of two single-layer liposome release mechanisms indicating, **a** the two single-layer liposome encapsulating different information molecules, **b** rupture and release of information molecules by one liposome, **c** release molecules diffuse away over a certain period, and **d** the rupture and release of information molecules by the second single-layer liposome

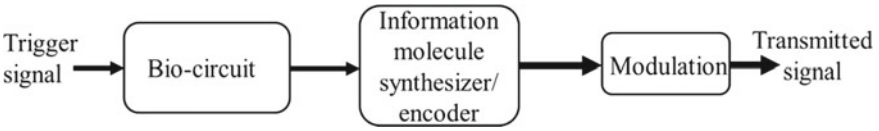

Fig. 3.8 Generalised block diagram of an ATN generic nanotransmitter

3.2.2.2 Generic Nanotransmitter

The generalised generic nanotransmitter architecture is depicted in Fig. 3.8. This architecture generally mimics typical biological systems such as natural cells, viruses, bacteria and bacteriophage. And just like in the pre-encoded nanotransmitter architecture, a trigger signal is required to make the generic transmitting nanosystem synthesise information molecules, encode the message, modulate it and transmit the corresponding set of molecular information. However, unlike pre-encoded nanotransmitters that do not become expendable as a transmitter after transmitting all stored information molecules, the generic nanotransmitter can be reused as a transmitter as often as necessary. If the information to be transmitted is a protein molecule, specialised DNA–ribosome units can be used to encode (transcript and translate) and modulate the information signal before transmission. Hence, the information molecule that is synthesised depends on the trigger signal that drives different algorithms in a given biocircuit. The biocircuit processes the trigger signal and initiates the synthesis of the information molecules. In natural cells, this biochemical algorithm is commonly referred to as *cellular signalling pathways*. Natural cellular signalling pathways can also be re-engineered/modified [27] to respond as desired. This is very crucial to making the transmitter generic, since it defines the number of unique algorithms in the biocircuit for initiating the synthesis of different information molecules. The possibility of developing artificial cells that can synthesise protein has been considered in [28]. In the case of applications like gene therapy, the transmission of DNA is required. Hence, the generic nanotransmitter will have the capability to synthesise DNA molecules by some in vivo oligonucleotide synthesis method. Such nanotransmitters include natural cells that are part of a given nanonetwork (such as cells that excrete hormones/biomolecules); and those that can be realised by artificially modifying the subcellular composition of a natural cell [29], bacteria [30, 31] and other unicellular organisms.

As in the case of the pre-encoded nanotransmitters, one may want to know how generic nanotransmitters can be programmed to modulate molecular signals into the desired information sequence. Typically, the ability of cells to regulate the type and concentration of synthesised molecules can also be employed in designing modulation techniques for the generic architecture. The modulation of the transmitted signal requires the nanosystem to oscillate between an ON state (emit) and an OFF state (do not emit). This oscillatory behaviour can be implemented by making the system automatically respond to variations in the concentration of the trigger signal, or the synthesised information molecules. Periodic or oscillatory phenomena are

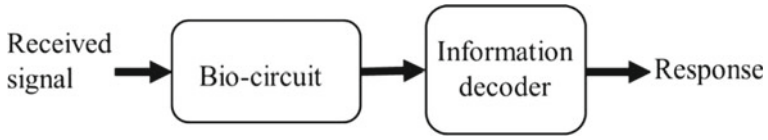

Fig. 3.9 Generalised block diagram of an ATN generic nanoreceiver

widespread in biology and are crucial to the operation of many biological systems [32]. For instance, bacteria use the ON/OFF mechanism to slow down or promote protein synthesis during the phases of nutrient starvation and nutrient plenty [33]. In another example, let us assume that the synthesised molecules are emitted through gated channels on the nanotransmitter membrane; patterned release of the information molecules can be achieved by regulating the presence/absence of specific ions [34] that invariably open or close the gate at given time instants.

3.2.3 Nanoreceiver for ATN Nanonetworks

A nanoreceiver is a nanosystem that can sense the information embedded in the type/concentration of transmitted molecules or electric pulses (in the case of neuronal activities) and further processes the information to initiate a response. The generalised architecture of a nanoreceiver is shown in Fig. 3.9. The biocircuit picks up the transmitted information, processes it using a defined biochemical algorithm and produces an output that is fed to the decoder to initiate an appropriate response. The response can be biochemical/mechanical/control actions such as to stop/initiate a nanosystem's movement, initiate internal reconfiguration, execute a self-annihilation algorithm (apoptosis) or synthesise and release some desired molecules (in this case as a transceiver). It is important to note that most of the nanotransmitters that operate in an ATN nanonetwork function as nanoreceivers in the sense that they pick up an extracellular signal (the trigger signal), process it and respond to it (emit signal).

Typical examples of nanoreceivers in an ATN nanonetwork include natural cells such as the targeted disease cells and other body cells that form part of a given network and synthetic nanosystems. The diseased cells are often the primary therapeutic information destination nanosystems. Nanosystems that can function as synthetic nanoreceivers include artificially synthesised nanosystems, genetically modified biological systems and artificial cells. An example of an artificially synthesised nanosystem is the enzymatic receiver introduced in [35, 36] for the activation of prodrug molecules. The liposome can also function as a nanoreceiver, in which case it can be fabricated to act as a micro-reactor system [37, 38].

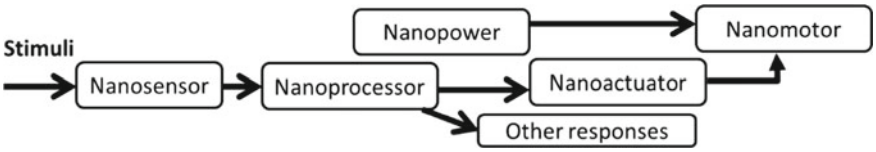

Fig. 3.10 Generalised block diagram of an ATN nanorobot

3.2.4 Nanorobots for ATN Nanonetworks

Nanorobots are nanosize machines designed to perform specific tasks with nanoscale precision. Just like macrorobots are designed to go far into the macroworld where man cannot go, nanorobots are being developed to go far into the nanoworld. Such nanomachines can be used for precise delivery of therapeutic molecules to diseased cells [39, 40], in vivo search of protein overexpression signals in order to recognise initial stages of brain aneurysm [41], in vivo imaging and many other applications. The generalised architecture of a nanorobot is shown in Fig. 3.10.

Components in nanorobot design may include an on-board nanosensor unit, nanomotors (that are powered by a nano power source when actuated) and a nanoprocessing unit. The nanosensor unit has biochemical sensors, which detect specific stimuli. The corresponding molecular signals processed by a programmed nanoprocessor are used to control the response of the nanorobot. The response may be to change direction or velocity of movement, synthesise and transmit information signals, release a pre-loaded payload, grab an identified pathogen molecule, etc.

3.2.5 Nanosensors for ATN Nanonetworks

A nanosensor is an ATN network nanodevice that employs nanomaterials and their characteristic properties to detect the presence of biochemical molecules and other signalling functions such as changes in electric fields, light, heat and pH in a nanonetwork. It is an example of a network nanodevice, which are logical systems that connect one nanonetwork or nanosystem to another to achieve coordinated flow of information. For example, a change in the luminescence of the nanonetwork microenvironment may be set to imply that a certain reaction has taken place, which calls for the execution of a specific task. Nanosensors can be used to coordinate these activities by sensing the change in light condition and subsequently respond by emitting specific signalling molecules to trigger the execution of the desired task.

Such a nanosensor can be designed by using a whole-cell [42–44] and sensor molecules entrapped in a chemically inert matrix [45]. Nanosensors can also be developed using aptamers and enzymes [46], where it has been shown that glucose level can be measured by virtue of the change in colour of some enzymes in the presence

of glucose [47]. In [48], the feasibility of designing nanosensors in a physical domain other than synthetic biology is presented based on electrical biosensor technology.

3.2.6 Nanoswitches for ATN Nanonetworks

A nanoswitch or molecular switch is an ATN network nanodevice that connects two or more nanosystems together within the same nanonetwork [12]. The activities of a nanoswitch basically depend on the change in 'state' of the respective pathways that form its bio-circuitry [49]. The change in state will usually be in response to conditional variation in its microenvironment [50]. The biochemical activities that have been reported as having great potential in achieving molecular switching are enzymatic reactions [51–54] and DNA conformation [55]. Both covalent and noncovalent enzyme-catalysed switching reactions of biomolecules have been considered in the literature and can be significantly employed to achieve desired molecular switching actions. For instance, the model of linear framework for timescale separation is exploited in [56] to characterise covalent enzymatic switching. And an allosteric protein switching action that is a form of noncovalent enzymatic reaction has been considered in [57].

3.3 Devices for ATN Body Area Network

To enhance our understanding of the dynamics of the biological processes underlying both normal biology and disease require robust, sensitive and specific sensors of the molecular events essential to biology and pathology. Over the past few years, various biosensors have been advanced for the understanding of diseases and the associated pathological conditions. These biosensors come in different types [58] depending on the biosignals (measurable body variables) associated to them. In this book, the term biosignal includes molecular signals such as hormonal signals, blood glucose variation, etc.; neuronal signals; electric biosignals such as electroencephalogram (EEG), electrocardiogram (ECG), electromyogram (EMG), etc.; and other closely related signals such as bioluminescence, biofluorescence and pressure variation in blood flow. Recently, design and deployment has been conducted by the networks of some of these biosensors on or around the human body for unobtrusive ambulatory continuous health monitoring. Such networks, often termed body area networks (BANs), offer real-time updates of the patient's status to the physician via standard communication networks over a long period of time [59]. Typically, the primary network of these biosensors can be on the human body (*on-body* network) or as implants in the human body (*intra-body* network), which are connected to sensors and systems that are off the body (*off-body* or ex vivo network).

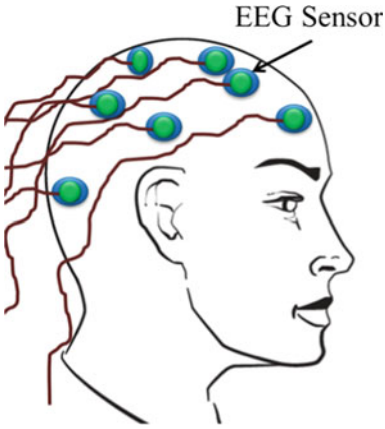

Fig. 3.11 Schematic diagram of EEG sensors on a human body

3.3.1 On-body ATN Nanosensors

As was discussed in Chap. 2, the on-body network defines communication among BAN biosensors through the on-body channel. Various research works on this type of BAN can be found in [60–62]. The communication among sensors in the on-body network is through RF. Hence, channel modelling challenges [63, 64], electromagnetic compatibility issues and power constraints are fundamental challenges that require attention. Examples of on-body biosignal sensors are given below.

3.3.1.1 Electroencephalographic (EEG) Sensor

This is an on-body (non-invasive) sensor that records electrical signals along the scalp to measure brain activity. It can be used to monitor and analyse the patient's overall physiological condition, especially in nanomedical procedures for the treatment of neurodegenerative diseases like Alzheimer's disease [65]. A schematic diagram of EEG sensors on a human body is shown in Fig. 3.11.

3.3.1.2 Electrocardiographic (ECG) Sensor

The ECG sensor is an on-body (non-invasive) sensor placed on the skin as shown in Fig. 3.12 to record electrical activities of the heart over a period of time. It has been reported in [66] that ECG sensors are able to detect the use of some drugs like cocaine; hence, continuous monitoring of the effects of nanoparticle pharmacodynamics is worthwhile in an ATN process. A schematic diagram of ECG sensors on a human body is shown in Fig. 3.12.

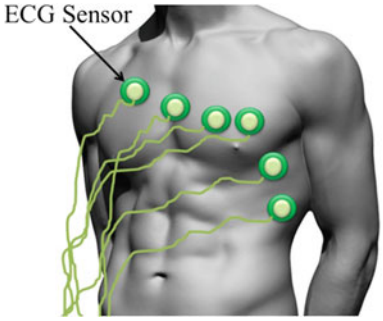

Fig. 3.12 Schematic diagram of ECG sensors on a human body

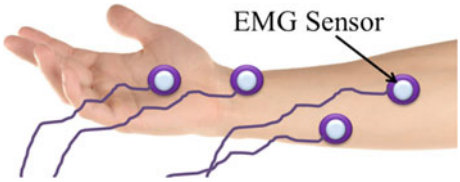

Fig. 3.13 Schematic diagram of EMG sensors on a human body

3.3.1.3 Electromyographic (EMG) Sensor

EMG sensors can be used to detect changes in the skeletal muscle activities of a patient. The sensor readings can be in a biofeedback mode to aid in increasing activities in weak or paretic muscle or facilitate a reduction in tone in a spastic one [67]. The EMG biofeedback can also be used in the treatment of neurogenic orofacial disorders [68]. A schematic diagram of EMG sensors on a human body is shown in Fig. 3.13.

3.3.1.4 Blood Pressure Sensor

The blood pressure sensor is part of a continuous blood pressure monitoring system, often called sphygmomanometer, that measures pressure levels in the blood. The effect the introduction of nanosystems into the blood vessel has on the cardiovascular system [69, 70] can be verified using a blood pressure measurement system in an ATN solution. A schematic diagram of a blood pressure sensor on a human body is shown in Fig. 3.14.

3.3.1.5 Blood Sugar Sensor

The blood sugar sensor is part of a continuous glucose monitoring system that is inserted under the skin and measures glucose level in the blood. Recently, a more advanced, patch-based, wearable/strip-type, disposable system for non-invasive sweat glucose monitoring and a microneedle-based point-of-care therapy have been

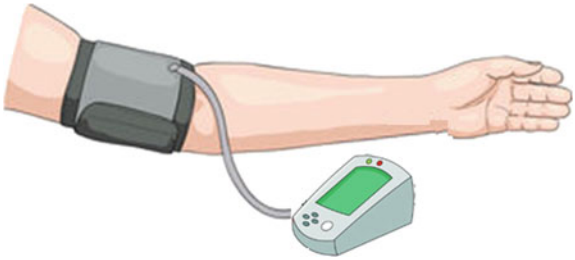

Fig. 3.14 Schematic diagram of blood pressure sensor on a human body

developed [71]. Some nanoparticles may be sensitive to glucose [72], and the introduction of some nanoparticles, just like some drugs [73, 74], may increase blood sugar level. Hence, it is important to monitor the level of glucose in the body in the course of the ATN process.

3.3.2 Intra-body ATN Solution Sensors and Simulators

Over the years, the growth of the ageing population and the associated increase in the number of older people with neurological and cardiovascular conditions has brought about the need to cater to this class of people. This implies the development of a system with remote and continuous monitoring of patient's biosignals, remote diagnosis and therapeutic capabilities. For continuous health monitoring, such a system requires sensors that are accurate in measurement, devices that have low power and communication links that are robust against time variation. Examples of such devices are implantable medical systems for both biosignal monitoring and drug delivery. The possibility of using implantable systems is driven by the tremendous progress in micro/nanotechnologies and wireless technology. The ability of the implants to sense biosignals or simulate tissues from the inside of the body offers the opportunity for early disease diagnosis and therapy. Implantable systems can act as sensors, simulators or interface units.

3.3.2.1 Implantable Biosignal Sensors

Implantable biosignal sensors can be used for in vivo measurement of parameters such as pressure, concentration, force and torque. In the typical ATN setup, the implantable sensors, just like the on-body sensors, acquire physiological data of the patient during the ATN process. Examples of implantable biosignal sensors include temperature, blood sugar, blood pressure, ECG and EEG sensors.

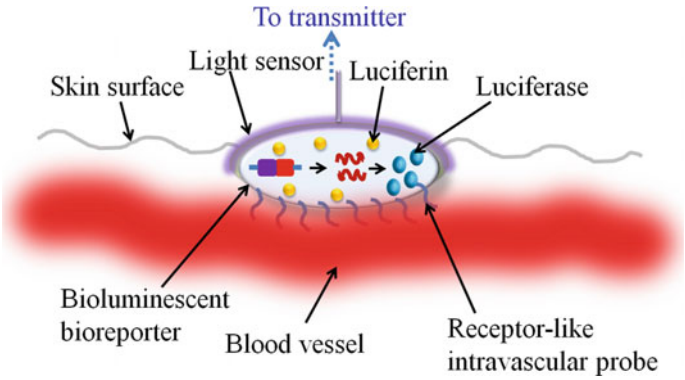

Fig. 3.15 Schematic of a typical bio-cyber interface unit Reprint from [75]. Copyright (c) 2016, with permission from IEEE

3.3.2.2 Implantable Simulators

Examples of implantable simulators include cardiac pacemakers, cardioverter defibrillators, deep brain neurostimulator, gastric simulators, bone simulators, insulin pumps, retina prostheses and cochlear stimulators. In the typical ATN setup, the simulators use information generated by the ATN sensors to stimulate nerves or deliver drug molecules to influence therapy. For instance, the gastric simulator can use information from ingestible sensors on the uptake of gastrointestinally introduced nanoparticles to stimulate gastric nerves in order to increase the uptake of nanosystems through the gastrointestinal system.

3.3.2.3 Bio-Cyber Interface Unit

The bio-cyber interface unit connects the in vivo nanonetwork to the body area network/the Internet. It literally processes and translates information from the in vivo nanonetwork to the electromagnetic-based (or other function) networks and vice versa. The architecture for a bio-cyber interface will depend on the nature of the signal, the channel through which the signal is propagated and the task at hand. While it is possible to have on-body-type bio-cyber interfaces implemented, the recent developments and design seem to favour implantable systems or systems with minimal invasion. The architecture and model of a bio-cyber interface for connecting the conventional electromagnetic-based networks to the biochemical signalling-based in vivo nanonetwork is presented in [75]. The schematic of the bio-cyber interface unit in [75] is shown in Fig. 3.15.

The model in Fig. 3.15 comprises a sensor part and a transduction part. The sensor part consists of a synthesised or genetically modified cellular structure whose membrane receptors or nanopores act as probes into the cardiovascular system. The

membrane receptors (probes) or nanopores detect information molecules circulating in the cardiovascular system and trigger a bioluminescence reaction in the device. The emitted light signal is then detected by a nano-photodetector, which converts the light to electrical pulses needed to start information transmission in a microtransmitter.

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Chapter 4
Understanding Delivery Routes and Operational Environments of Nanosystems

4.1 Introduction

In a typical ATN solution, nanoparticles are delivered to targeted locations in the body where they are meant to operate. Unless the nanoparticles are delivered to the targeted location (nanonetwork site), no effective delivery of the ATN solution can take place. The journey of the ATN nanoparticles from the points of administration into the body system to the targeted location is a complex one and requires accurate understanding. Indeed, the delivery of the ideals and promises of nanomedicine in general, and ATN in particular, crucially depends on the know-how and accuracy of conveying nanoparticles to the desired destinations in the body. Usually, the nanoparticles that are going to embark on this complex journey to the targeted site include drug/signalling molecules, nanotransmitters, nanoreceivers, nanosensors, nanoswitches, etc. These nanoparticles are obviously foreign to the body; therefore, it is expected that the body may react to their introduction. Hence, their structure and composition, the point of introduction, and the route they have to traverse before getting to the desired location define how much their administration affects the body operation. In many scenarios, the nanoparticles may traverse many organs, tissues and cells to get to the targeted site, and in doing so interact with healthy cells, producing adverse side effects, often related to non-specific toxicity. This could result in the manifestation of subjective evidence such as those experienced in cancer treatment using chemotherapy. The non-specific toxicity associated with chemotherapy for cancer treatment brings about side effects such as hair loss (alopecia), compromised immunity, fatigue, poor blood clotting (haemophilia), loss of appetite, painful urination, nausea and vomiting, nail toxicity and anaemia [1]. Implicitly, the fewer normal cells the nanoparticles interact with, the fewer the side effects, and ultimately, the better the ATN solution.

Hence, this chapter provides some understanding of the mode by which nanoparticles, and specifically nanosystems, are conveyed to the targeted sites. The journey of a nanosystem from its introduction into the body system to its final destination can be abstracted as an engineering communication phenomenon. In this sense, the injection systems are the transmitters, the nanoparticles/nanosystems are the infor-

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mation carriers, and the targeted sites or certain predefined locations in the body are the receivers. Just like in every communication system, performance is crucially dependent on the characteristics of the medium through which the information carrying entity/function propagates. The ability to integrate the knowledge of the medium characteristics into the design and analysis of the communication system is dependent on the appropriateness of the model that is used to mimic the propagation behaviour.

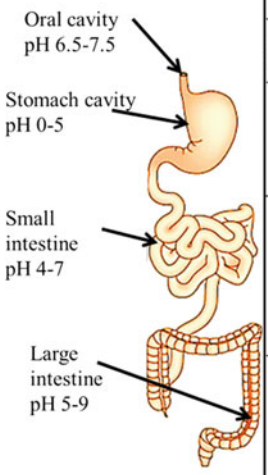
In this chapter, the different modalities for administering nanosystems into the body are explored. And based on these modalities, the different routes the nanosystems take to reach the targeted locations inside the body are discussed. Finally, the possible approaches to the representation, modelling, analysis and evaluation of nanosystems delivery routes and operational environments are presented as communication engineering problems. However, given its interdisciplinary nature, the exposition in this chapter is made as simple as possible for readers from diverse backgrounds.

4.2 Methods of Nanosystems Administration

Just like in conventional drug administration, there are different methods of administering nanosystems/nanoparticles into the body system. The method by which a nanoparticle is delivered can have a significant effect on its efficacy. The choice of nanoparticle administration method is influenced by factors such as the proximity to the targeted site (to ensure minimal inversion), toxicity level (to ensure minimal toxicity), and bioavailability (to ensure delivery of optimum concentration of nanosystems, yet with minimal toxicity). Examples of methods include oral ingestion, pulmonary method, transdermal penetration and intravascular injection [2]. Each of these methods presents different challenges and merits. Let us look at these nanosystem delivery methods and the motivation behind their uses.

4.2.1 Oral Ingestion Method

Oral ingestion is a non-invasive method of drug delivery that is as old as man. Its simplicity, convenience, cost-effectiveness, long-term administration and patient acceptance makes it the most widely used method of drug delivery. In fact, over 60% of marketed drugs in world are administered orally. When a drug is administered through the mouth, it travels the length of the gastrointestinal (GI) tract, where some of its constituent particles get absorbed by the epithelial cells and assimilated into the blood and lymphatic vessels. An illustration of this journey is depicted in Fig. 4.1. The human GI system is divided into the upper (oesophagus, stomach and duodenum) and lower (small intestine and all of the large intestine) gastrointestinal tract. These tracts differ in structure (the presence of villi and enterocytes), constituents (such as enzymes and bacteria) and characteristics (like pH, salinity and temperature values);



Enzymes	*Bacteria*
Oral cavity Salivary amylase	
Stomach cavity Pepsin; Trypsin	**Stomach cavity** Candida; Peptostreptococcus; Lactobacillus; Helicobacter pylori Streptococcus
Small intestine Pancreatic amylase Maltase; Pepsin, Trypsin; Peptidases; Lipase; Nuclease; Nucleosidases	**Small intestine** Coliforms; Streptococcus; Lactobacillus; Clostridium; Bacteroides; Escherichia; Veillonella
	Large intestine Clostridium coccoides; Bacteroides; Clostridium leptum/Fusobacterium; Bifidobacterium; Alistipes; Anaerostipes; Dorea; Eubacterium; Faecalibacterium; Paracteroides; Roseburia; Rumunacoccus

Fig. 4.1 Schematic of gastrointestinal tract

hence, they have varying ability to selectively absorb nutrients and drug molecules. The large surface area of the small intestine makes it the tract where most molecules are absorbed.

However, the oral method of drug delivery has inherent challenges that include non-specific drug distribution, poor stability and low retention in the GI tract, low solubility and/or bioavailability, and the existence of the mucus barrier that can prevent drug penetration/absorption [3, 4]. Therefore, considerable care must be taken during nanoparticle design to take these challenges into consideration. The oral delivery method can target diseases that occur in the GI environment or, as the case may be, diseases that occur elsewhere in the body.

4.2.1.1 Gastrointestinal Environment Target

Diseases that occur in the GI environment are generally referred to as inflammatory bowel diseases (IBD). Examples of IBD are ulcerative colitis and Crohn's disease, which affect millions of patients all over the world. A significant number of people that suffer from IBD eventually develop colon cancer due to the fact that the IBD stimulates carcinogenesis. Oral chemotherapy is preferentially used for the treatment of colon cancer; however, the challenges mentioned above, in addition to low tumour targeting and severe adverse effects, are prevalent [5]. The severe side effects come from the fact that most of the therapeutic molecules get absorbed into the blood from

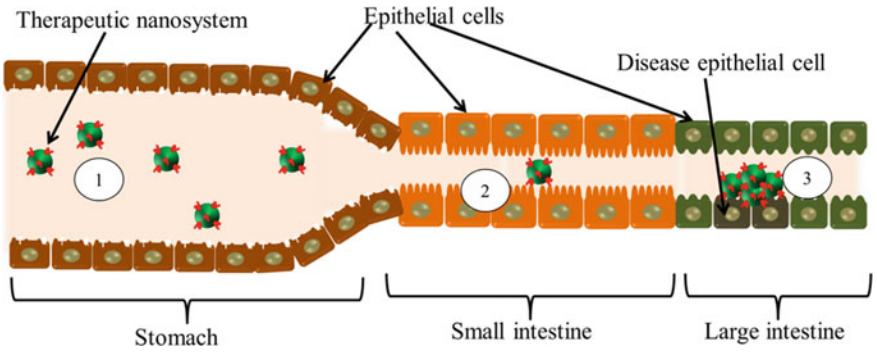


Fig. 4.2 Illustration of nanosystem journey through the GI environment

where they accumulate undesirably in various organs. Consequently, only a small concentration of the therapeutic molecules actually gets to the disease site in the colon.

Advances in targeted drug delivery have encouraged the use of rugged nanosystems that can withstand the harsh GI environment to deliver drugs to colon cancer cells at very low system toxicity. Promising results for orally administered cancer drugs-carrying nanosystems have been presented in [5–8]. An illustration of the journey of a nanosystem to the targeted cells in the GI environment is shown in Fig. 4.2.

There are numerous valid concerns [9] in the development of efficient nanosystems for GI nanonetworks, especially when it is associated with ATN solutions. These concerns arise from the structure and composition/characteristics of the GI environment. The fundamental goal here is to accurately understand the mouth-to-targeted GI site route for a nanosystem and develop ATN nanosystems that can traverse this route without being translocated into the bloodstream to access cells, tissues and organs where they are not required—that is, to achieve targeting and reduced toxicity.

Naturally, the GI system employs its structure, enzymes and bacteria to break down substances into smaller compositions and condition the substances into absorbable nutrients and molecules that can be translocated into the blood vessels and lymphatic networks. Hence, to ensure that nanosystems do not undergo this breakdown process and translocation into the blood, nanosystem design must take into consideration the following: (i) The chemical interaction between the nanomaterials from which the nanosystem is made and the enzymes/bacteria/food components in the GI tract. The different enzymes and bacteria that are often found in the different areas of the tract are shown in Fig. 4.1. (ii) The physical impact of the GI tract on the nanosystem structure. For instance, peristalsis, which is a physical phenomenon, can affect the nanosystems' physicochemical properties, as the pressure can reach 150 mm Hg [10]. In Fig. 4.1, it can be seen that pH varies across the breadth of the GI tract [11]; hence, the effect of the variation in pH for the entire journey of the nanosystems has to be taken into consideration in design. (iv) The design of the nanosystem must also

consider the surface chemistry that will not only withstand the impact of factors in (i)–(iv), but also be able to accumulate at the targeted disease sites.

To ensure that the nanosystems do not translocate into the bloodstream and consequently access cells, tissues and organs, the size exclusion principle has to be observed. For nanoparticles, in general, to enter the blood and lymphatic vessels, they have to diffuse through the mucus lining the GI surface [12] and cross through the epithelial cells. Nanosystems may pass through the epithelial cells primarily by means of paracellular and transcellular transports [13]. In the paracellular transport mechanism, nanosystems pass through intercellular spaces between epithelial cells by diffusion, while in transcellular transport, they pass directly across the epithelial cells by means of endocytosis and transcytosis. The average dimension of the paracellular space is on the order of 1 nm [14], which is very small; hence, many nanoparticles may not pass through it. However, in disease conditions, the intracellular space can undergo alteration, promoting the passage of nanosystems. Normally, many nanosystems will employ the transcellular mechanism to pass the epithelial barrier. It was shown in [15, 16] that small nanoparticles that are less than 50–100 nm in diameter can pass into the blood vessels through the epithelial cells by endocytosis. Larger nanosystems with dimension 200 nm–5 μm may pass the M-cells by transcytosis [17]. Therefore, large nanoparticles with appropriate surface chemistry are ideal for the journey through the GI tract and for orally administered ATN nanosystems.

4.2.1.2 Non-gastrointestinal Environment Target

The oral route can also be used to deliver nanosystems to targeted cells in parts of the body other than the GI environment. To achieve this, the nanosystem has to translocate into the blood vessel network, from where it can extravasate to access the targeted site. The fundamental goal here is to accurately understand the mouth-to-targeted site through the GI/blood vessel route for a nanosystem and develop ATN nanosystems that can traverse this route with minimal toxicity. Hence, aside from the challenges in the GI environment, there are the additional challenges presented by the blood vessel network through which the nanosystem traverses. Like in the scenario where delivery is within the GI environment, targeting a non-GI environment requires that the nanosystem design considers the chemical, physical and biological characteristics of the GI tracts. However, the size exclusion principle is not applicable here; rather, it is required that the sizes and surface chemistry of the nanosystems are such that they can translocate into the blood vessels via paracellular and transcellular methods. The molecular weight, hydrophobicity, ionisation constants, and pH stability of the nanosystem have to be modulated in a way that favours its translocation into the blood vessel [4, 18]. An illustration of the journey of a nanosystem to the targeted cells outside the GI environment is shown in Fig. 4.3.

Once the nanosystems are inside the blood vessel, the concerns are the same as those associated with intravascular nanosystem delivery methods, which will be discussed shortly. Briefly stated, the nanosystems will propagate through the cardiovascular system and extravasate into the extracellular space to reach the targeted

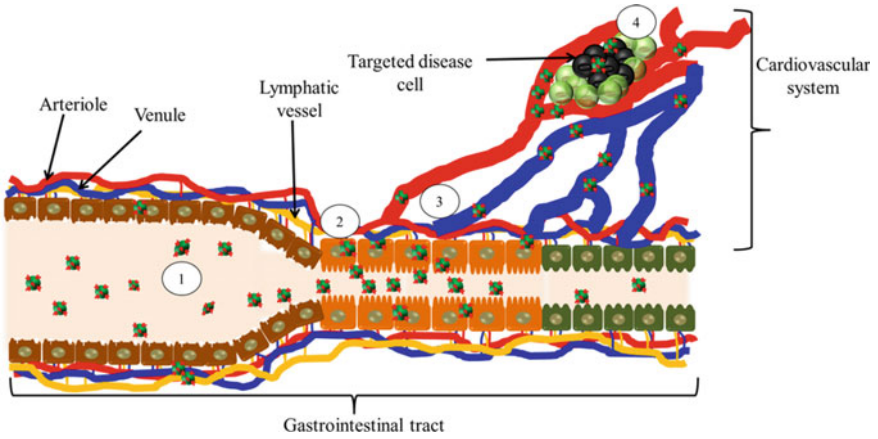


Fig. 4.3 Illustration of nanosystem journey through the non-GI environment

site illustrated in Fig. 4.3. This implies that first-pass metabolism at the liver and the possibilities for systemic toxicity are of concern when considering the oral route for nanoparticle delivery into non-GI environments.

4.2.2 Pulmonary Delivery Method

Pulmonary delivery method describes the process and characteristics of nanosystem delivery to disease sites in the respiratory tract or to other locations in the body using the respiratory system as the route. A schematic diagram of the respiratory tract is shown in Fig. 4.4. The tract starts from the nasal cavity, extends through the trachea, passing the bronchi, which branch up into bronchioles leading into the alveoli. The alveolar sacs have dense capillaries surrounding them as shown in Fig. 4.5; hence, translocation of nanoparticles happens mainly across the alveoli epithelial cells.

The motivations behind the use of the pulmonary system for drug delivery are the ability for local targeting action (which implies small dose), avoidance of first-pass metabolism in the liver (higher bioavailability), as well as being non-invasive. Its local action ability makes it a good candidate for the treatment of diseases such as asthma, cystic fibrosis and lung cancer. In general, the pulmonary delivery route can be used to target the treatment of these diseases within the respiratory area or to access cells and organs way beyond the respiratory tract into the systemic circulatory system [19].

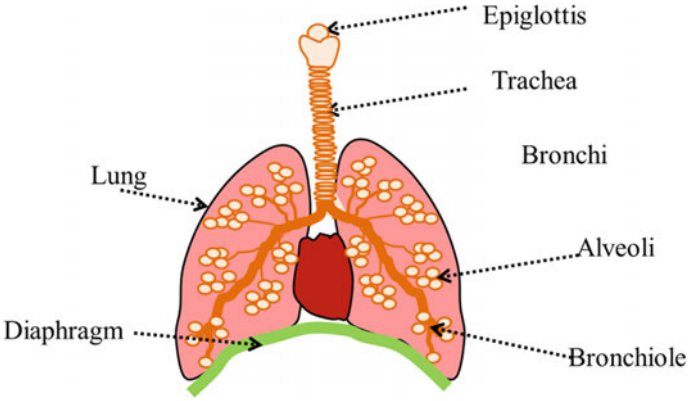


Fig. 4.4 A schematic diagram of the respiratory tract

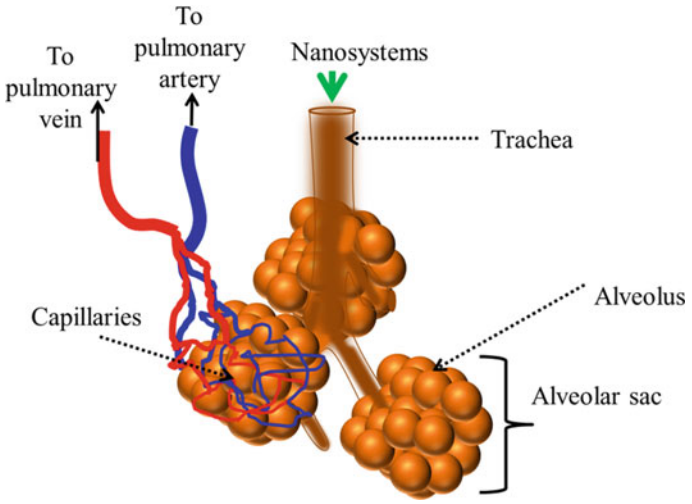


Fig. 4.5 Illustration of alveolar sacs with dense number of capillaries surrounding them

4.2.2.1 Pulmonary Environment Targeting

Diseases that occur in the respiratory tract include lung cancer, chronic bronchitis, asthma, cystic fibrosis, emphysema and pneumonia. These diseases can be treated by delivering nanotherapeutic systems through the pulmonary route [20–22]. For therapeutic applications within the respiratory tract, the fundamental goal is to accurately understand the nasal cavity-to-alveolar route and develop ATN nanosystems that can traverse this route without being translocated into the bloodstream and consequently accessing systemic cells, tissues and organs. The pulmonary route and the primary cells that form the tract are shown in Fig. 4.6.

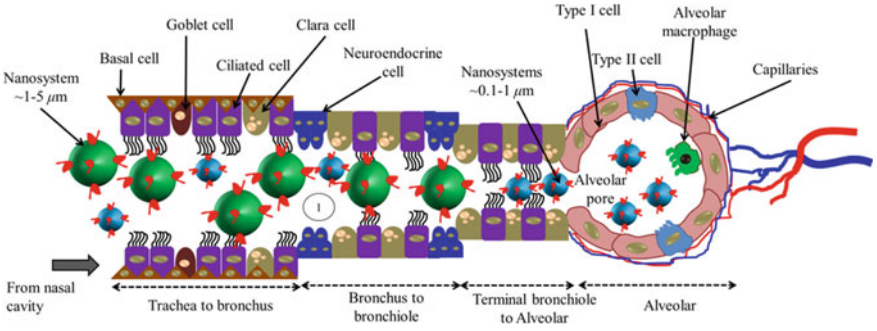


Fig. 4.6 Illustration of size differentiation of nanoparticles/systems along the pulmonary route

The translocation of nanoparticles out of the respiratory tract is crucially a function of their sizes [23–26] it was indicated that nanoparticles with dimensions larger than about 5 μm often remain in the nasal cavity, while the smaller ones of between 1 and 5 μm do not go beyond the trachea-to-bronchiole tract. Nanoparticles of very small dimensions, of the range 0.1–1 μm, can get to the alveolar region. The size differentiation of nanoparticles/systems along the pulmonary route is depicted in Fig. 4.6.

The alveolar region has high surface area and density of capillaries; hence, this is the region where the translocation of nanosystems into the blood vessels will occur. Again, just like in the GI tract, nanosystems may pass through the epithelial cells primarily by means of paracellular and transcellular transports. However, the epithelial cells of the alveoli are tightly packed such that the paracellular transport mechanism is not possible in this case, except by medicated endocytosis [24]. It has been shown in [24, 27, 28] and a great deal of other literature that nanosystems of sizes that are about 20–100 nm can translocate into the blood vessels. Therefore, to ensure that the nanosystem remains within the respiratory tract, sizes larger than 100 nm must be targeted in design.

4.2.2.2 Systemic Environment Targeting

The pulmonary route can also be used to deliver nanosystems to targeted cells in parts of the body other than the respiratory tract. To achieve this, the nanosystem has to translocate into the blood vessel network, from where it can extravasate to access the targeted sites. The fundamental goal here is to accurately understand the nasal cavity-to-targeted sites (through systemic circulatory system) route and develop ATN nanosystems that can traverse this route. Hence, aside from the challenges posed by the respiratory environment, there are the additional challenges of understanding the mechanism of translocation across the alveolar epithelial barrier and the challenges presented by the blood vessel network through which the nanosystem traverses to the targeted site.

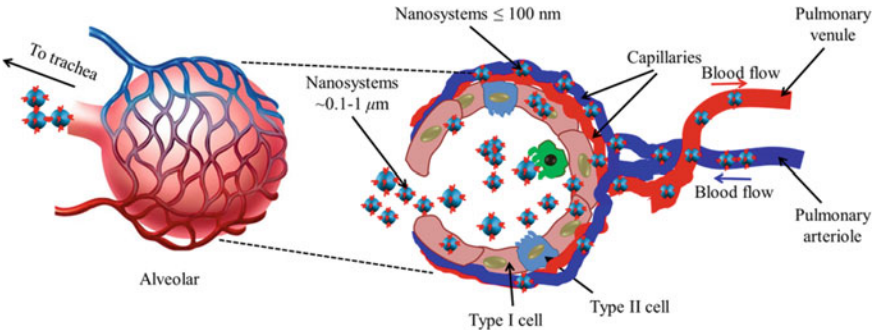


Fig. 4.7 Generalised block diagram of an ATN pre-encoded nanotransmitter

Translocation of nanoparticles into the blood vessel occurs at the alveolar environment, where the epithelial cell surface is approximately 150 m^2, thus presenting a large surface area for nanosystem translocation into the pulmonary interstitium and cardiovasculature. The alveolar epithelial barrier consists of two cell types (as shown in Fig. 4.6), namely, Type I and Type II epithelial cells. These cells are tightly packed such that translocation of nanosystems into the blood vessel by paracellular transport is not possible, except by endocytosis. It is reported in [24] that human alveolar Type I epithelial cells internalise nanoparticles by mediated endocytosis, while alveolar Type II epithelial cells do not internalise nanoparticles. Hence, the target cells for the potential translocation of nanosystems are the Type I cells, which cover over 95% of the alveolar surface [24]. The alveoli have a rich network of capillaries that makes translocation to the blood network possible.

Just like in the scenario where the delivery of the nanosystem is within the respiratory tract, targeting sites outside the respiratory environment has nanosystem size as a critical parameter. Nanosystems that are about 20–100 nm in diameter can translocate into the blood vessels. Additionally, there is the requirement that the nanosystem design considers the surface (biochemical, biophysical and physicochemical) characteristics of the nanosystem in complement to that of the Type I cells. An illustration of the journey of a nanosystem to the targeted cells outside the respiratory environment is shown in Fig. 4.7. Physical concerns such as coughing [29], mucociliary clearance and ingestion [30] may affect the delivery efficiency; hence, these should be taken into account.

Once the nanosystems are inside the blood vessel, they will propagate through the cardiovascular system and extravasate into the extracellular space to reach the targeted site. Unlike in the oral delivery route, the nanosystems that enter the bloodstream through the pulmonary route circumvent first-pass metabolism at the liver (where a large percentage may be taken out). Hence, small doses of nanotherapeutic system are administered through the pulmonary route, resulting in low systemic toxicity.

4.2.3 *Transdermal Delivery Method*

The transdermal delivery method describes the process and characteristics of nanoparticle (drugs and nanosystems) delivery to disease sites using the skin as the entry route [31]. The translocation of nanoparticles into/across the skin is not easy since the skin barrier is naturally designed to provide internal organs of the body with physical protection, immune surveillance, thermal regulation, ultraviolet light protection, and water retention capabilities [32]. A schematic diagram of the skin barrier is shown in Fig. 4.8. The schematic shows a stratified structure that primarily comprises the epidermis, dermis and hypodermis layers.

Just like in other delivery routes, nanosystem delivery into the body depends on its size. Other factors such as surface chemistry, dose, morphology and adhesiveness

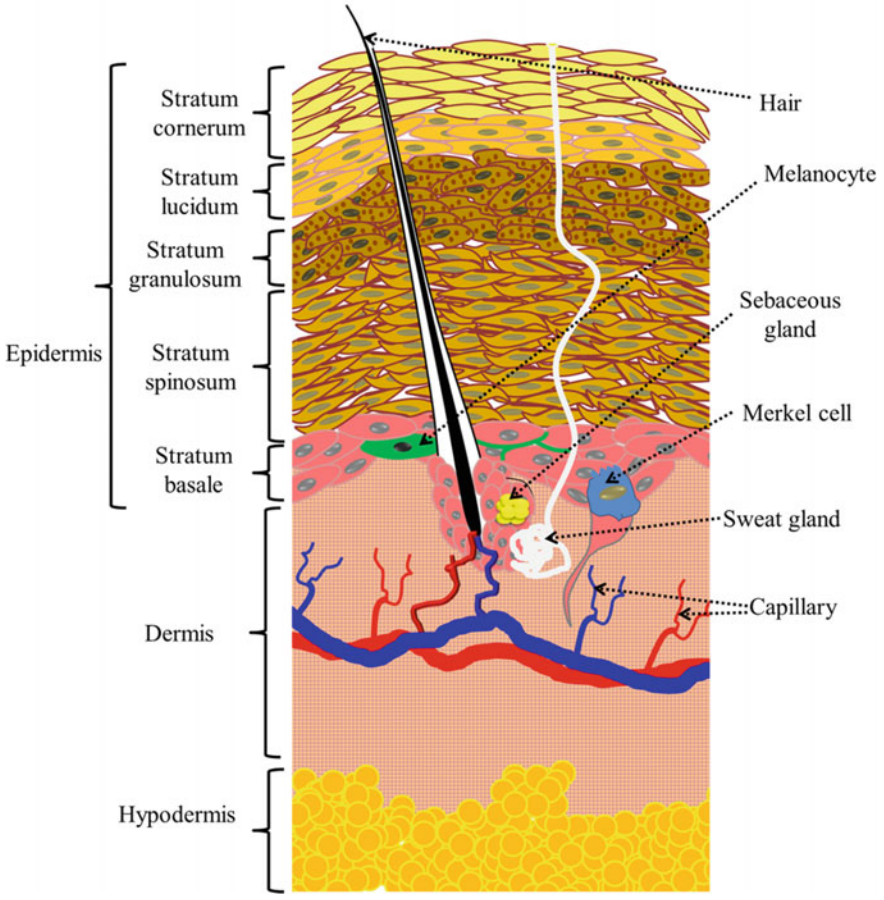


Fig. 4.8 Schematic diagram of the skin barrier

have also been found to mediate nanosystems translocation across the skin cells [33, 34]. Nanoparticles are observed to penetrate the skin through one of three pathways: intracellularly through corneocytes, intercellularly around corneocytes, or via dermal structures like hair follicles [35]. The intercellular transepidermal route involves nanosystems moving through lipid gaps of diameters in the range of about 5–75 nm. The lipid-rich path implies that the intercellular transepidermal route is regulated by lipophilicity. For larger nanoparticles, delivery through the appendageal routes, such as the sebaceous and sweat glands with orifices of 10–200 μm, can be employed.

Again, the targeted site in this method of delivery may be within the epidermis, dermis or hypodermis layers. In this case, the challenge is to design nanosystems that can penetrate the layer of interest and locate the nanosystems within the targeted environment. If, on the other hand, the targeted site is within the systemic system, the challenge will additionally include ensuring that the nanosystems translocate into the capillaries in the skin for onward journey through the cardiovascular system and beyond.

4.2.4 Intravascular Delivery Method

The intravascular method of nanoparticle delivery involves the direct administration of the particles into the blood vessel. Once inside the blood vessel, the journey of nanosystem to the point of delivery may cut across the cardiovascular system, the extracellular space, the targeted cell surfaces, the intracellular space, and the central nervous system. This journey is often primarily propelled by the diffusion/convection mechanism defined by the Fick's laws and Smoluchowski equation. In some cases, external fields, such as magnetic fields [36] or chemical gradients [37], may be incorporated into the delivery system to aid in guiding the nanosystems to the targeted site, else the journey is usually random and unaided. A schematic diagram of the typical intravascular route, indicating the propagation of nanoparticles, is shown in Fig. 4.9. The vessel network is composed of vessels such as the arteries, capillaries and veins through which blood flows in the direction indicated in Fig. 4.9.

Once the nanosystems are injected into the cardiovascular system by, say, intravenous means, they flow along with the non-oxygenated blood through the vein and into the heart. From the heart, the non-oxygenated nanosystem-rich blood is pumped through the pulmonary circulatory system, and back to the heart. Then from the heart again, the now oxygen-rich blood with the composite nanosystems is pumped through the artery to the whole-body cells. Once at the capillaries, the nanosystems will have the opportunity to either exit into the extracellular space where the cells are or get back into the vein for the next round of the journey to the heart. The movement of the nanoparticles through the blood vessels network is aided by the heart's pumping. In relation to the oral delivery route that targets cells/organs outside the GI tract, the schematics in Fig. 4.9 are appropriate with the point of introduction of the nanosystems into the cardiovascular system being through the network of capillaries connected to the portal vein. The nanosystems that translocate from the GI tracts into

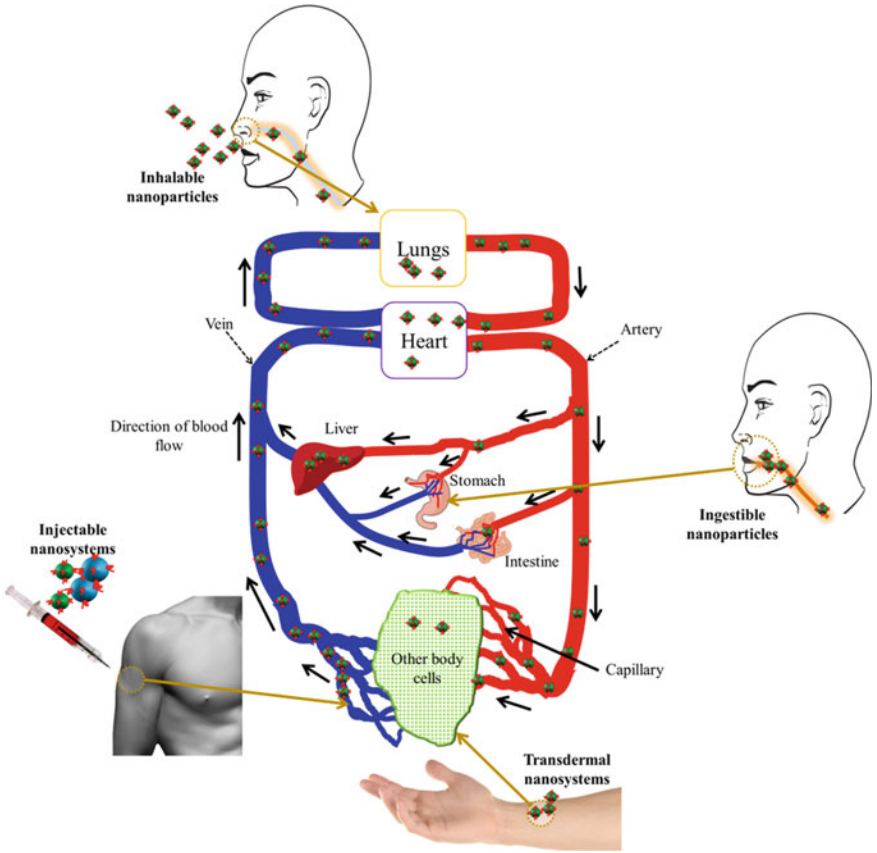


Fig. 4.9 Schematic diagram of nanoparticle routes into the intravascular route

these capillaries are conveyed through the portal vein to the liver, where they undergo first-pass metabolism before exiting the liver into the vein. Usually, a large percentage of the nutrients as well as the nanosystems is metabolised in the liver, hence reducing their bioavailability [38]. The capillaries connected to the pulmonary venule and the venule in the skin (about the location of administration) are the points of entry of the nanosystems when the route of administration is the pulmonary and transdermal routes, respectively, as depicted in Fig. 4.9. It can be observed that the liver is majorly circumvented in the delivery of nanoparticles using these two methods. Aside from this difference, the rest of the journey of the nanosystem is the same. The targeted site may be located within the vascular environment (inside blood vessel), on the surface of cells exterior to the blood vessels, or inside the cells.

4.2.4.1 Vascular Targeting

Vascular-targeted nanosystems are an attractive ATN solution for the treatment of a number of cardiovascular diseases. However, like in normal drug delivery, many factors need to be considered in designing such a system to ensure good performance. The propagation goals here are to ensure that (i) the nanosystems do not exit the blood vessel, and (ii) they locate the target sites in the vascular systems and bind/anchor on it over a predefined duration. The targeted sites may be the endothelial cell surfaces or interior, pathogens circulating in the blood, or other components of the blood vessel compartment. To achieve this goal (i), size is a crucial factor. Here, the size of the nanosystem must be greater than that of the fenestrae (gap between endothelial cells) on the endothelial barrier. The fenestration diameter of 60 nm is typical for normal endothelial cells and 240–400 nm for tumour endothelial cells [39, 40]. This implies that with nanosystems of diameters much greater than 60 and 400 nm, goal (i) can be achieved in normal and disease cells, respectively. The determination of the appropriate nanosystems size for a particular patient is addressed by the personalised aspect of the ATN delivery.

Ideally, the nanosystems propagate through the blood vessels by means of the superposition of the Brownian motion and advection phenomena [41], under which influences the goal of delivering the nanosystems to the targeted site has to be achieved. Achieving goal (ii) is influenced by factors such as the blood flow velocity, size/shape of the nanosystem, and surface chemistry of the nanosystem [42, 43]. The velocity of the blood/nanosystem is defined by the cardiac input, the dimension of the blood vessel and the viscosity of the blood. The flow generally has a laminar (streamline movement of blood) characteristic such that nanosystems near the surface of the vessel walls move with lower velocity compared to those at the centre of the vessel, as shown in Fig. 4.10. This characteristic of laminar flow profile and the physical properties of red blood cells encourages the formation of a ‘red cell core’ along the centreline of blood flow, which traps nanosystems within this core; hence, very few red cells flow close to the endothelial surface to make contacts [44]. Smaller nanoparticles are more susceptible to this effect than bigger ones. Therefore, the larger the nanoparticle is, the higher the probability of making contact with the targeted endothelial cells. Thus, researchers designing vascular-targeted carriers should be wary of the assumption that smaller particles will always perform better due to increased transmigration ability.

To bind/anchor at the targeted endothelia cell, the nanosystems must come in contact or at least within a binding distance to the cell as it flows along with the blood. At lower blood velocity profile, the probability of binding and maintaining nanosystem-target bond increases. The nanosystem’s shape also influences the probability that the propagating nanosystem binds to the targeted site, whether it is the endothelial cells or the constituents of the blood [45]. It is shown in [46] that nanosystems with nonspherical geometries are more prone to tumbling and oscillatory effects in vasculature, increasing their propensity to hit the vessel wall and subsequently bind to the

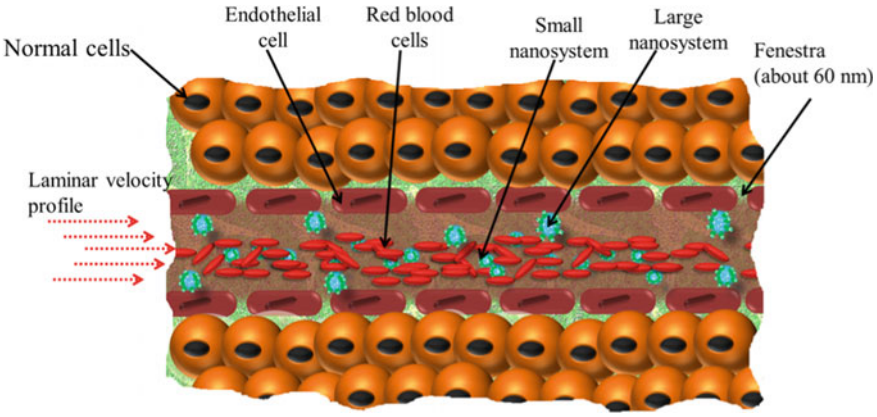


Fig. 4.10 Schematic of nanoparticle targeting of the vascular environment

endothelial cell. Moreover, with the appropriate surface chemistry and high affinity to the endothelial cell receptors, high adhesion force can be achieved.

As they propagate through the blood vessel network, the nanosystems are influenced by processes such as absorption, reaction, adhesion and elimination. Absorption is the process by which nanoparticles pass through the walls of the blood vessel. The reaction process is the biochemical interaction between a nanosystem and complimentary substrates in the blood vessel network. The adhesion process is a physical phenomenon by which the nanosystems stick to other biomolecules (including other nanosystems) in the blood vessels. The elimination process is the generalisation of the processes whereby nanoparticles are eliminated from the circulatory system by phagocytosis and the reticuloendothelial system, such as the liver and spleen [47]. All these factors influence the probability of a nanosystem locating and binding to the target sites in the vascular systems. They are basically lossy processes that reduce the number of the nanosystems that are circulating in the vessels, thereby reducing the probability of binding to the targets. However, the elimination process can be beneficial in the sense that it ensures that the redundant nanosystems are removed from the body.

It should also be noted that the nanosystems can translocate into the targeted endothelial cells by mediated passage. In this case, receptors on the endothelial cell membrane can bind to complementary ligands (nanoparticles) to mediate their differential uptake into the cells by endocytosis [48]. For instance, the uptake of the albumin nanoparticles is mediated by glycoprotein gp60 on the endothelial cells [49, 50].

4.2.4.2 Extracellular Targeting

In ATN solutions, cells in parts of the body other than the endothelial cells can be targeted using the blood vessel as route. In this case, the nanosystems are required to exit the blood vessels at some point into the extracellular space where the targeted cells are located. Hence, the propagation goals here are to ensure that (i) the nanosystems exit the blood vessel into the extracellular space where the targeted cells are located, and (ii) once inside the extracellular space, they can locate/bind/anchor at the target sites.

To achieve the first goal (i), size and shape are again crucial factors. Here the size of the nanosystem must be smaller than that of the fenestrae (gap between endothelial cells) on the endothelial barrier, as illustrated in Fig. 4.11. In normal endothelial cells, the fenestration (intercellular gap) diameter is about 60 nm [39]. But in disease cells, endothelial cells lose cellular integrity due to the activation of proinflammatory cytokines causing the gap between the endothelial cells to get wider [51]. For instance, it is about 240–400 nm for tumour endothelial cells [40]. This implies that to minimise the accumulation of nanoparticles at undesired sites, nanosystems of diameters much greater than the normal cell fenestrae and less than that of the fenestrae at the disease cell location are optimal.

The nanosystem's shape also influences the probability that the propagating nanosystem will extravasate through the endothelial intercellular gaps. As stated earlier, large nanosystems with nonspherical geometries are more prone to tumbling and oscillatory effects in vasculature, increasing their propensity of hitting the vessel wall and subsequently bringing them in proximity with the fenestrae thereby increas-

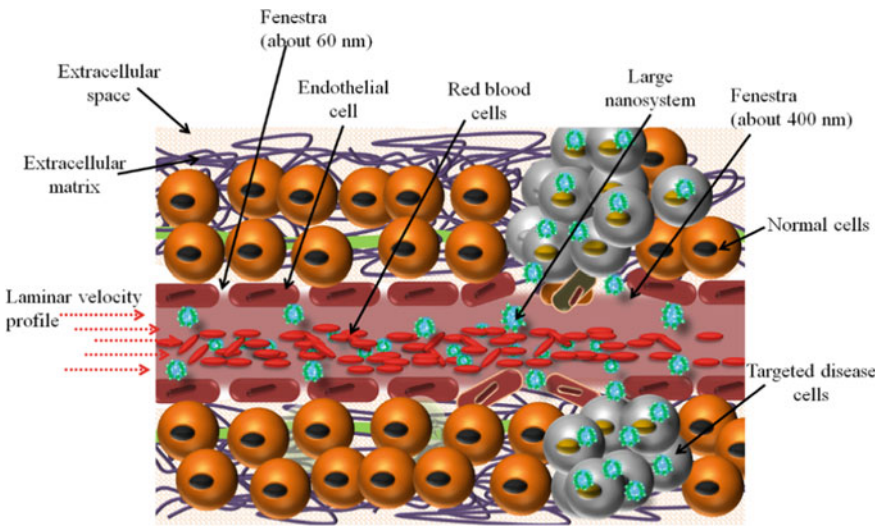


Fig. 4.11 Schematic representation of nanoparticle targeting of tissues in extracellular space

ing their chances of exiting the vascular network. Moreover, with the appropriate surface chemistry and some affinity between the nanosystem and the endothelial cell receptors, the nanosystem will likely flow along the endothelial barrier making their exit more possible.

After exiting the cardiovascular network, the nanosystem has to propagate and locate/bind/anchor on the target cells or molecules within extracellular space, which is the second goal of its journey. Goal (ii) is influenced by factors such as the size and shape of the nanosystem, the physic-chemical composition and characteristics of the extracellular space, and the surface chemistry of the nanosystem. In humans and many other multicellular organisms, the extracellular space depicted in Fig. 4.11 is composed of the extracellular matrix and the interstitial fluid, where many cells are located. The extracellular matrix is an assembly of extracellular molecules that provide structural and biochemical support to the cells within its vicinity [52]. The interstitial fluid is usually an ionic solution of mainly NaCl [53]. This ionic solution is a complex mixture of biochemical constituents such as amino acids, lipids, glucose, growth factors, hormones, metabolites, cytokines and neurotransmitters, which are necessary for the survival of the cells. Summarily, in the extracellular space, cells are anchored in tissues by the extracellular matrix, and are washed in the interstitial fluid. The volume and composition of the extracellular space generally differ between tissues and are altered upon pathological processes, factors which must be accounted for in the development of an ATN solution.

Nanosystems and other nanoparticles propagate through the extracellular space, facilitated by convection–diffusion [54] and Brownian motion [55]. Convection–diffusion phenomenon is facilitated by the dynamics of the interstitial fluid [54, 56] due to the interplay of the vascular and interstitial pressures. Factors such as blocking by the extracellular matrix [1], charge of the nanosystem [57], and the diffusion coefficient of the interstitial fluid [58] influence delivery to the extracellular space.

On getting to the targeted cells, the nanosystems bind to the targeted cells' surface receptors in a random manner by mean of high-affinity ligand-receptor binding activities, as shown in Fig. 4.12. To enable the capability of a nanosystem to target and anchor at the desired tissue surface, the nanosystem membranes must be grafted with specific ligands mounted on the tip of tether to the membrane, which binds to complimentary receptors at each of the targeted tissues. For selectivity in targeting, these target ligands must be unique to receptors found at the targeted site, which is possible based on the diverse physiological state of the diseased tissue. Examples of popular ligands for targeting include sugar, folic acid, peptide and antibody [59], as well as some corresponding complementary receptors on the disease tissue surfaces that include folate, peptide and cell surface antigen. For instance, the folate receptor is an attractive target for selective tumour delivery of liposomal doxorubicin because it is abundantly expressed in a large percentage of tumour cells [60]. The overall activity of targeting and anchoring on the targeted surface is defined by the anchor probability [61], which describes the probability that a nanosystem which enters a certain area that defined the targeted nanonetwork anchors in it. This probability depends on the number of free binding sites in the nanonetwork for the nanosystems and the strength of the associated bond that is formed [62]. A high anchor probability

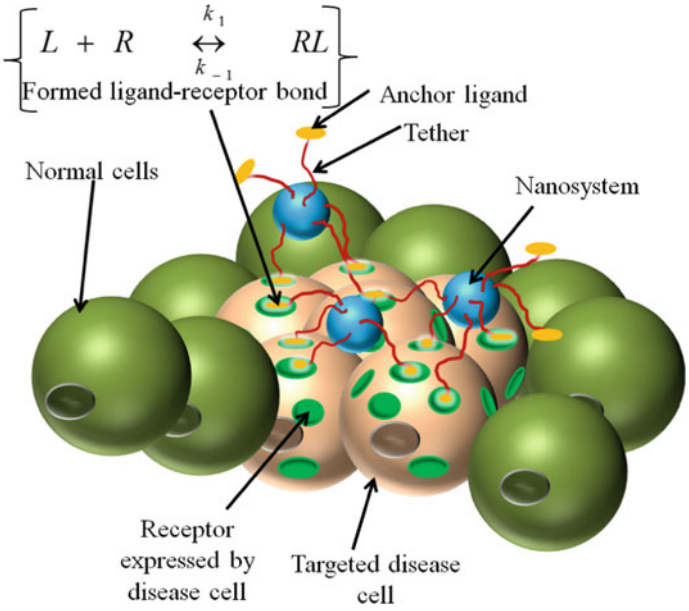


Fig. 4.12 Schematic of nanosystems binding to the targeted cells' surface receptors by mean of high-affinity ligand-receptor binding activities

is ideal. The rate at which the nanoparticles anchor at the surface will contribute in determining the rate at which nanoparticles extravasate into the extracellular space by virtue of change in concentration gradient of the nanosystems.

4.2.4.3 Intracellular Targeting

Depending on the desired targeted actions, when the nanosystems anchor on the targeted cell surface, they either operate on the cell surface or translocate into the cell. If the targeted site along the course of their operation is inside the cell, some nanosystems/nanoparticles will have to find their way into the cell by means of passive diffusion, diffusion through ion channels, facilitated diffusion and endocytosis. Cell membranes are basically lipid bilayer membrane structures with average pore sizes of about 3–5 nm [63]. Hence, only very small hydrophobic nanosystems can diffuse into the cell by passive diffusion. The ion channel is a gated channel of about 3 nm [64, 65] that allows only ions to pass through into the cells in a regulated manner under certain electrical potential gradient. Large or hydrophilic particles can enter the cell through endocytosis, which requires the participation of transmembrane proteins [66]. To do so, the nanosystem has to be equipped with clever designs (surface chemistry) that enable them to translocate across the cell membrane.

The nanosystem can either journey on through the cell cytoplasm well into/onto the targeted organelle, such as the nucleus, lysosome and mitochondria, in what is termed third-level drug targeting [67] or deliver its content (therapeutic/signalling molecules) into the cytoplasm. Once inside the cell's interior, the nanoparticles traverse the cytoplasm mainly by passive diffusion. Aside from the diffusion mechanism, information molecules can also be transported to the organelle through the cytoplasm by active transport [68–71]. In active transport, which is akin to the wired channel, the information molecules are delivered to the organelle by a family of molecular motors such as myosin and dynein. Some mathematical models for this type of wired molecular channel can be found in [68, 69, 71], and some design consideration in active cargo transport using molecular motors can be found in [70, 72]. The active nature of this form of molecular transport system implies that energy is crucial to its operation. Hence, accurate energy models have to be developed to ensure that the delivery capability of a given active transport route is predictable.

4.2.4.4 Nervous System Targeting

In some special cases, the ATN solution may require nanonetworks that operate in the nervous system, which is an organ system containing a network of specialised cells called neurons. The need for such cases will arise in the treatment of neurodegenerative diseases [73] and the after effect of some cardiovascular diseases that occur in the central nervous system. The network of these neurons in the central nervous system, depicted in Fig. 4.13, coordinates the action of the host organism and transmits signals between different parts of its body. The nerve cells, called neurons, propagate membrane-potential differences across organs. These neurons, which are considered as nanotransceivers of the nervous nanonetwork, are electrically excitable cells capable of storing, processing and transmitting information through chemical and electrical signalling mechanisms [74–76]. Hence, any disorder in these nerve cells has the potential to affect many parts of the body.

To deliver nanosystems to the part of the nervous system located in the brain region, the ATN nanosystems circulating the bloodstream will extravasate into the extracellular space where the neurons reside. However, unlike the endothelial interface between the blood and the extracellular space housing the cells in other parts of the body, the endothelial interface of the blood vessels in the brain region presents a unique barrier and challenge. This barrier, called blood–brain barrier (BBB), has made access to the brain cells by therapeutic nanoparticles difficult.

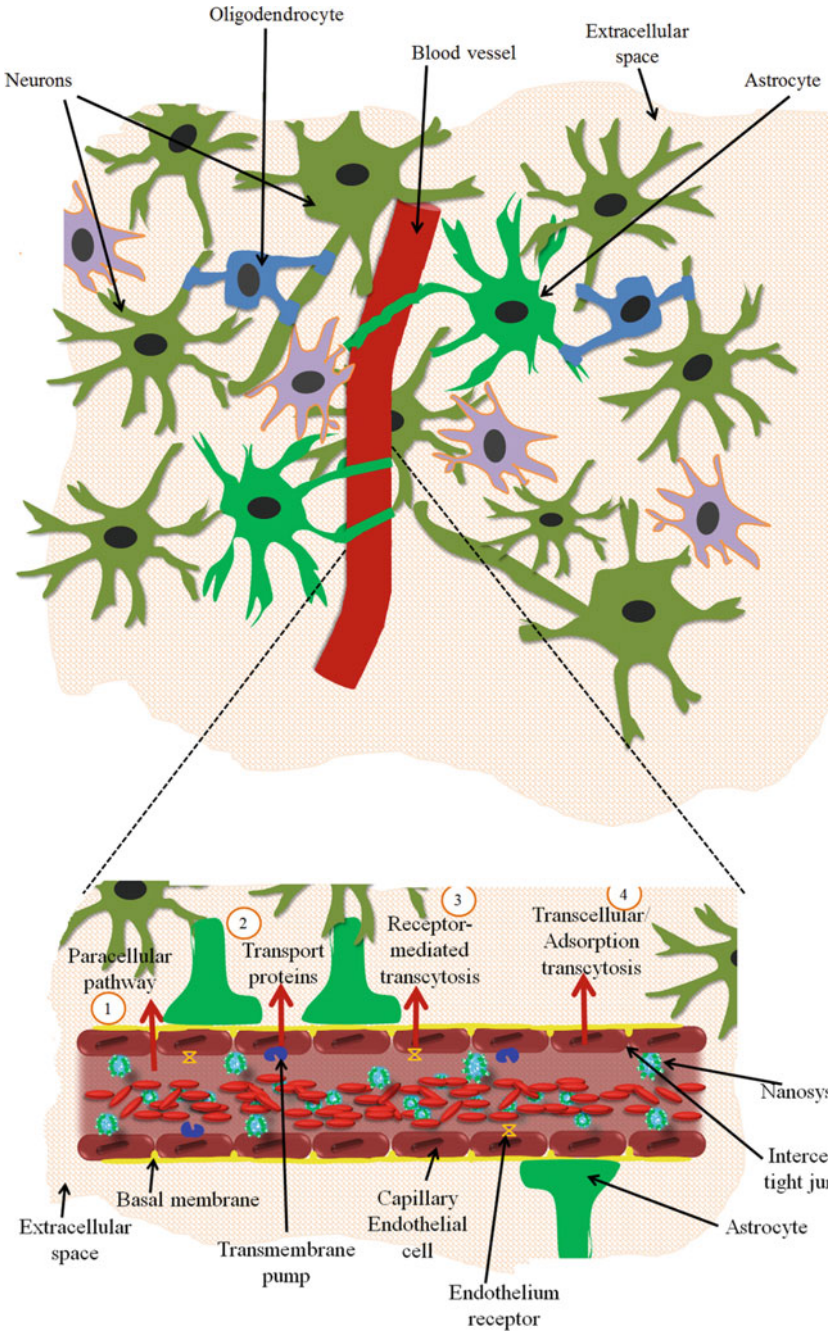


Fig. 4.13 Illustration of nervous system targeting

4.3 Operating Environment of Nanosystems in a Nanonetwork

In typical ATN solutions, a nanonetwork may comprise more than two nanosystems communicating and working cooperatively to achieve a task. The number of nanosystems may range from a few hundred to millions. From our discussion so far, it can be seen that the cell surfaces/extracellular space, and the interior of the blood vessel network are fundamentally the operating environment of the nanosystems, as illustrated in Fig. 4.14.

In the extracellular space operating environment, the mode of molecular communication signal propagation is mainly by diffusion, where factors such as the influence of the ISF viscosity and the extracellular matrix blocking on the propagating molecules should be taken into account in system modelling and evaluation. The influence of the ISF comes in the form of the properties of the propagation medium, which include the diffusion coefficient and the ISF dynamics. The stability of the anchored nanosystems is important since any unanchored nanoparticles may diffuse freely and interfere/interact with the propagating information particles. Another influencing factor is the number of nanosystems that anchor at the targeted site. The number of anchored nanoparticles is crucial in two senses; (1) the more nanoparticles there are in the targeted site, the greater their interaction/interference

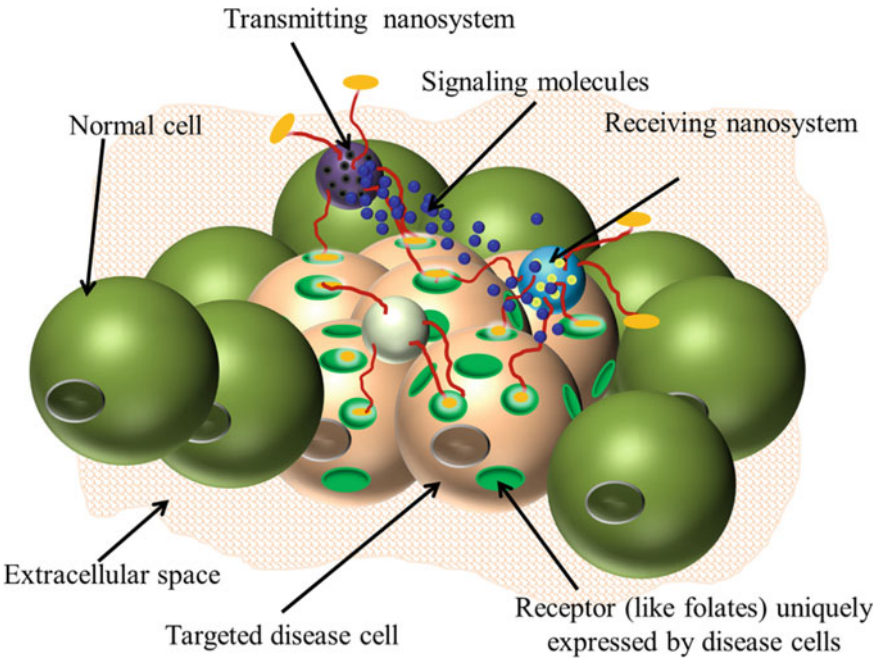


Fig. 4.14 Schematic of the basic operating environment of the nanosystems

in the information molecules' propagation process, and (2) the presence of more than one transmitting and receiving nanosystems implies the need to consider the contribution of each nanoparticle in the entire communication process.

In the blood vessel operating environment, the mode of molecular communication signal propagation is mainly by diffusion–advection. In this case, factors such as the blood flow/velocity profile, and the influence of absorption, elimination, adhesion and reaction processed on the propagating information molecules, should be taken into account in system modelling.

4.4 Communication Engineering Approach to Characterisation and Modelling of Nanosystems Delivery Routes and Operating Environments

One of the greatest challenges faced by contemporary nanomedicine, and of course ATN, is the complete mastery of the entire route of a nanosystem from the point of administration to the targeted sites in an individual. Without this knowledge, the design and effective deployment of nanosystems for the delivery of a nanomedical solution and the achievement of application merits are impossible. This understanding can be obtained by direct experimentation ('wet' experiment) or/and mathematical experimentation ('dry' experiment), as shown in Fig. 4.15. Given a specific nanosystem administration method, and based on what is known about the delivery route, the various phenomena and factors associated with the route are characterised. The characterisation provides a distinctive description of the variables, factors and attributes of the various phenomena related to the route under consideration.

Based on the characterisation results, an experimental setup that represents the delivery process is developed, and experiments conducted either in vivo, in vitro or in silico. Concurrently or differently, mathematical models that represent the delivery process can be developed. The use of mathematical models to evaluate and predict the behaviour of systems provides a more flexible approach at low resource commitment compared to experimental systems. Results from both approaches are evaluated, compared and validated to form a hypothesis. The validated results are usually fed back to the system to fine-tune the entire process until an accurate model is obtained. In the current version of this book, the mathematical modelling approach is of concern.

Several attempts have been made by various researchers to provide mathematical models for the representation of the administration and delivery processes of nanoparticles (drugs and nanosystems). Such mathematical models are given under the term physiologically based pharmacokinetic models [62, 77–80]. The physiologically based pharmacokinetic modelling approach offers good tools for describing and predicting in vivo absorption, distribution, metabolism and excretion of nanoparticles administered through the various routes described earlier.

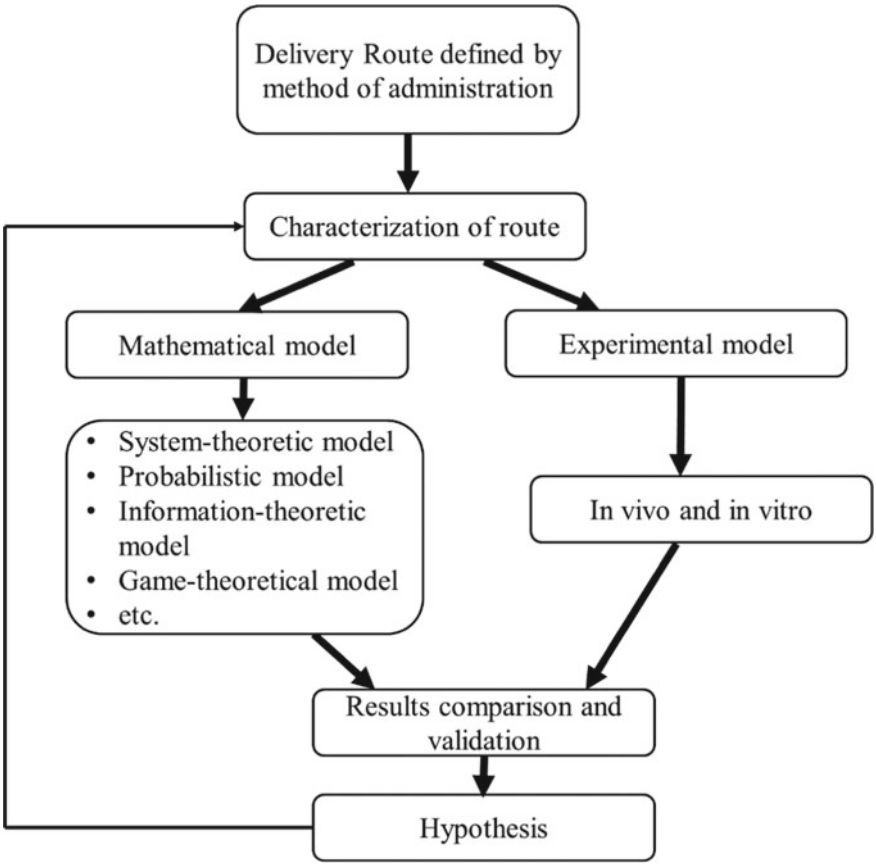


Fig. 4.15 Schematic diagram of delivery route modelling and analysis

4.4.1 Communication Engineering Platform for Nanosystems Delivery Route Modelling

Communication engineering presents an alternative but excellent platform and tools for the abstraction, characterisation and modelling of the nanoparticle delivery process. From this perspective, the system/machine that administers the nanoparticles/nanosystems is the transmitter, the nanoparticles/nanosystems are the information carriers, the delivery route is the communication channel, and the targeted sites or certain predefined locations in the body are the receivers.

Hence, the characterisation and modelling approach employed for the electronic communication channel can be extended to the nanoparticle delivery channel. In order to design communication systems, mathematical models of the channel through

Table 4.1 Equivalence among the molecular propagation channel phenomena and those of electromagnetic communication channel

Electromagnetic channel phenomena	Cardiovascular channel phenomena
Attenuation	Reaction, absorption, elimination
Delay	Viscosity, distance factor, adhesion, ECS blocking
Multipath	Bifurcation–recombination
Scattering	Collision of molecules with other constituent molecules
Depolarisation	Charge

which the communication will take place are constructed to reflect the most important characteristics of the channel. Then, the information obtained from the channel modelling is used for the design of the subsystems of the transmitter and receiver, such as channel encoder/decoder, modulator/demodulator, amplifiers, etc. Obtaining excellent knowledge of the nanoparticle delivery route will avail us with the knowledge of how to design excellent nanosystems that can deliver the promises of nanomedicine in general and ATN in particular.

Various mathematical models have been employed to model the contemporary electronic communication channels. These models include those based on system-theoretic, information-theoretic and statistical approaches. In each of these models, the main idea is to be able to estimate/predict the value of a given input that is mapped to a certain output by the channel, given that we have complete or partial knowledge of the mapping operation. Hence, the modelling approach provides us with the knowledge of the channel characteristics defined by certain channel parameters. The channel parameters include delay profile, attenuation factor, power profile, interference level, signal-to-noise ratio, channel bandwidth, Doppler spread, and so on. However, instead of considering the propagation of the electromagnetic waves across the channel, the propagation of nanoparticulate signals is considered in the delivery process. The various channel effects that are common to the intravascular route can be compared with the electromagnetic channel effects, as shown in Table 4.1; but caution must be applied as these effects cannot just be considered on the one-to-one mapping basis.

4.4.1.1 Intravascular Delivery Channel

The abstracted block diagram of the intravascular delivery channel is depicted in Fig. 4.16. It comprises the cardiovascular network and the targeted site. The focus of the channel model here is to be able to accurately predict the concentration or number of nanoparticles that eventually reach a targeted location in the body, given that we know the concentration or number that was injected at a reference location. Typically, the journey of the nanosystem takes it from the point of injection into

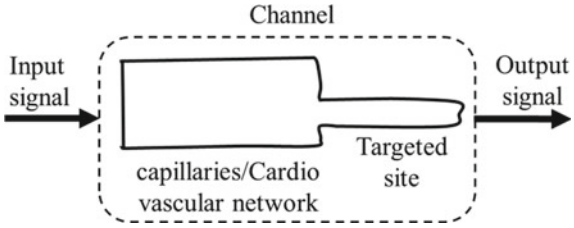


Fig. 4.16 Abstracted block diagram of the intravascular delivery channel

the blood vessel network, through the stages of circulation/distribution in the blood network, and eventual extravasation into the extracellular space, and to the targeted cells (and organelles).

The input–output mathematical relationship and model that describe this route must take into consideration and characterise the effects enumerated in Fig. 4.17. These include the geometry of the vessel and the reaction, adhesion, absorption and elimination processes that may occur while the nanoparticle is circulating in the blood vessel network [61]. Other factors that should be considered with respect to the extracellular space are the charge [57], extracellular matrix blocking (and tortuosity) [81], viscosity and degradation (by proteases). The influence of the interstitial fluid flow/pressure [82], saturation [1] and anchor probability at every instance have to also be taken into account in the channel modelling. The anchor probability influences the rate at which the nanosystems anchor at the surface of the targeted site, and directly contributes in determining the rate at which nanosystems extravasate into the extracellular space by virtue of change in concentration gradient of the nanosystems within the space.

Some exemplary mathematical models are considered in the literature. In [83], computational tools for modelling the nanoparticle delivery process and the design of nanoparticles for efficient ATN are discussed. In [41], the cardiovascular system is modelled based on the Navier–Stokes equation, and the corresponding MC-based drug propagation network is modelled as an advection–diffusion equation. In [84] a propagation model is presented, which takes into account the effect of physiochemical processes such as absorption, adhesion and adhesion in the propagation of nanoparticles through the cardiovascular network. A noise model of the drug delivery with respect to the cardiovascular system is presented in [85]. In [86], the blood vessel network is modelled for the capillary end of the system by the Hagen–Poiseuille equation, which is derivable from the Navier–Stokes equation. In [62], the compartmental pharmacokinetic model is employed to quantify the concentration of the nanosystems delivered to a targeted site. A set of differential equations is used to derive the system expression. An overview is given in [87] on the nature of barriers to free access of drugs to tumour sites within the brain and the state of the art in related theories and mathematical modelling approaches describing the physical transport processes and chemical reactions which can occur in such a scenario. Figure 4.15, it is also important to validate the models with experimental results; hence, in vivo

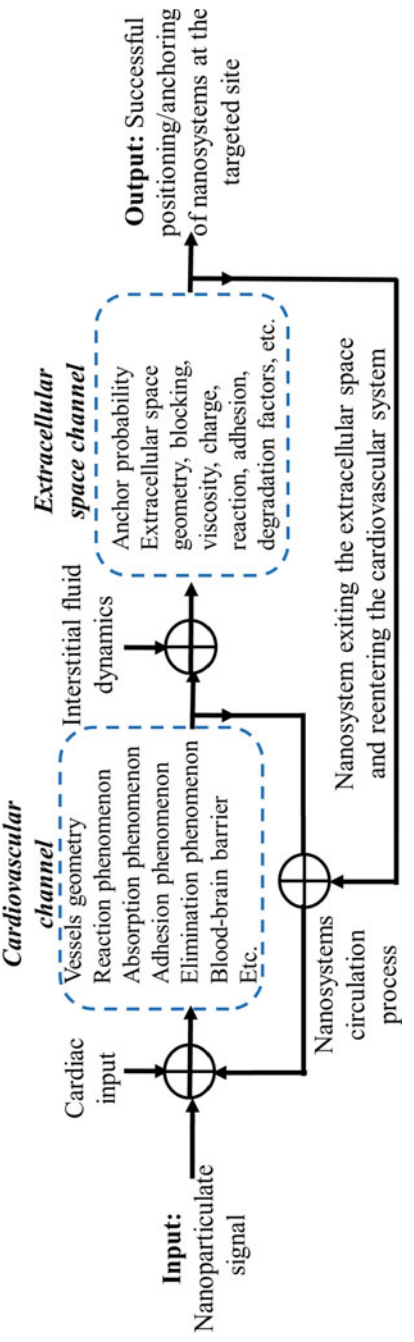


Fig. 4.17 Block diagram of the intravascular delivery channel characteristics

and in vitro experimental results are necessary. Review of experimental works on transport models for drug delivery through the cardiovascular systems can be found in [88, 89].

4.4.1.2 Oral Delivery Channel

In the case of GI tract-only route/target, the channel starts from the mouth cavity and extends through the GI tract. The channel model must take into consideration the influence of the enzymes, bacteria and food substances in the GI tract, as well as the pressure/temperature/pH of the tract. In the event that the targeted site can only be reached through the cardiovascular route, the channel extends into the GI capillaries and subsequently the liver, after which the rest is the same as in the intravascular route. Hence, in addition to characterising the channel phenomena associated with the GI tract-only route, the phenomena associated with the intravascular delivery channel must also be taken into account in the channel modelling, as is depicted in Fig. 4.18.

4.4.1.3 Pulmonary Delivery Channel

When the targeted site is within the respiratory tract, the channel model must take into consideration the influence of phenomena such as coughing, ingestion and mucociliary clearance. In the event that the targeted site can only be reached through the cardiovascular route, channel effects such as the alveolar epithelial barrier and the rest of the channel effects considered in the case of intravascular delivery channel (depicted in Fig. 4.19) must also be taken into account in the channel modelling.

4.4.1.4 Transdermal Delivery Channel

When the targeted site is within the skin layers, the channel model must take into consideration the skin barrier/layered structure of the skin, solubility process, lipophilicity and the resorption process of the nanosystems into the blood. In the event that the targeted site can only be reached through the cardiovascular route, channel effects such as the ones considered in the case of intravascular delivery channel must also be taken into account in the channel modelling. The block diagram of the transdermal delivery route that shows the characteristic channel effect is shown in Fig. 4.20.

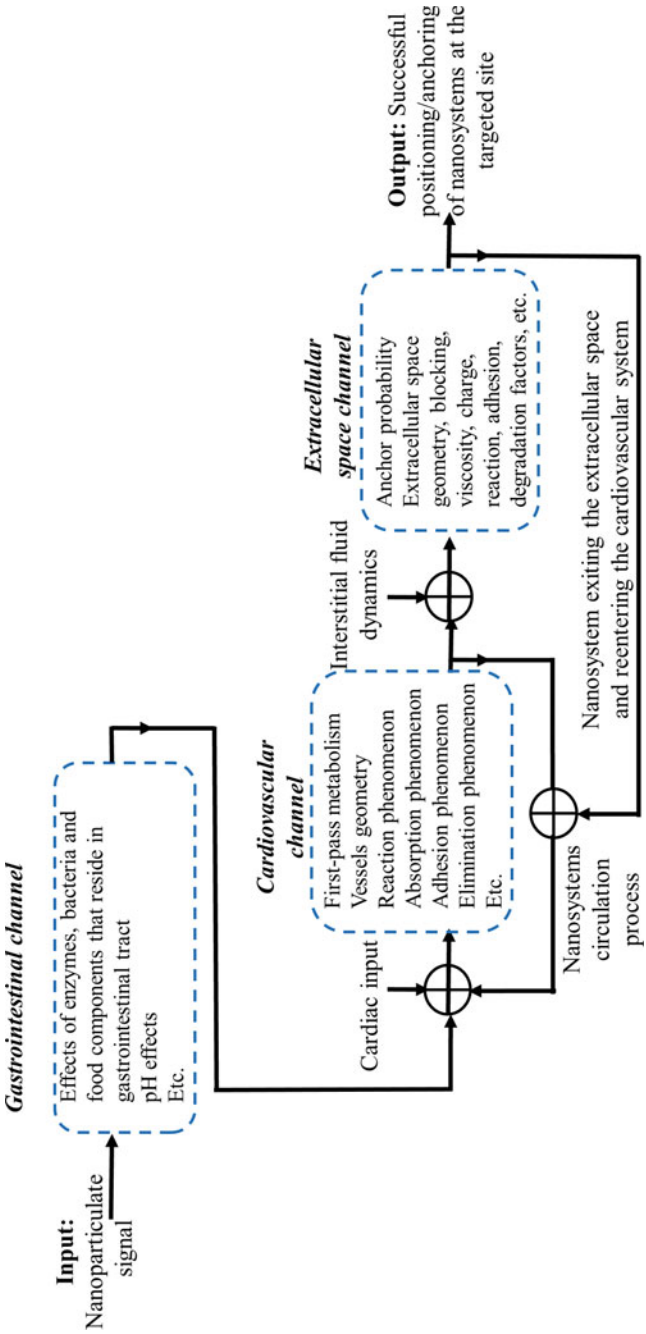


Fig. 4.18 Block diagram of the oral delivery channel characteristics

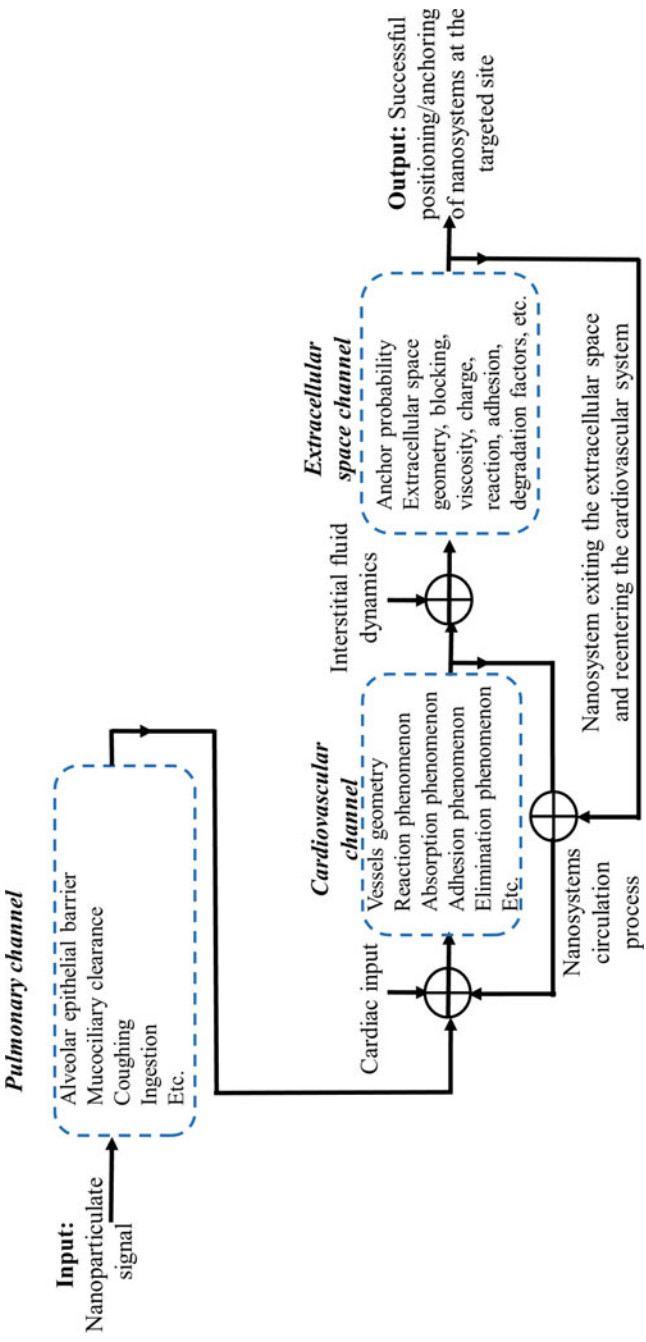


Fig. 4.19 Block diagram of the pulmonary delivery channel characteristics

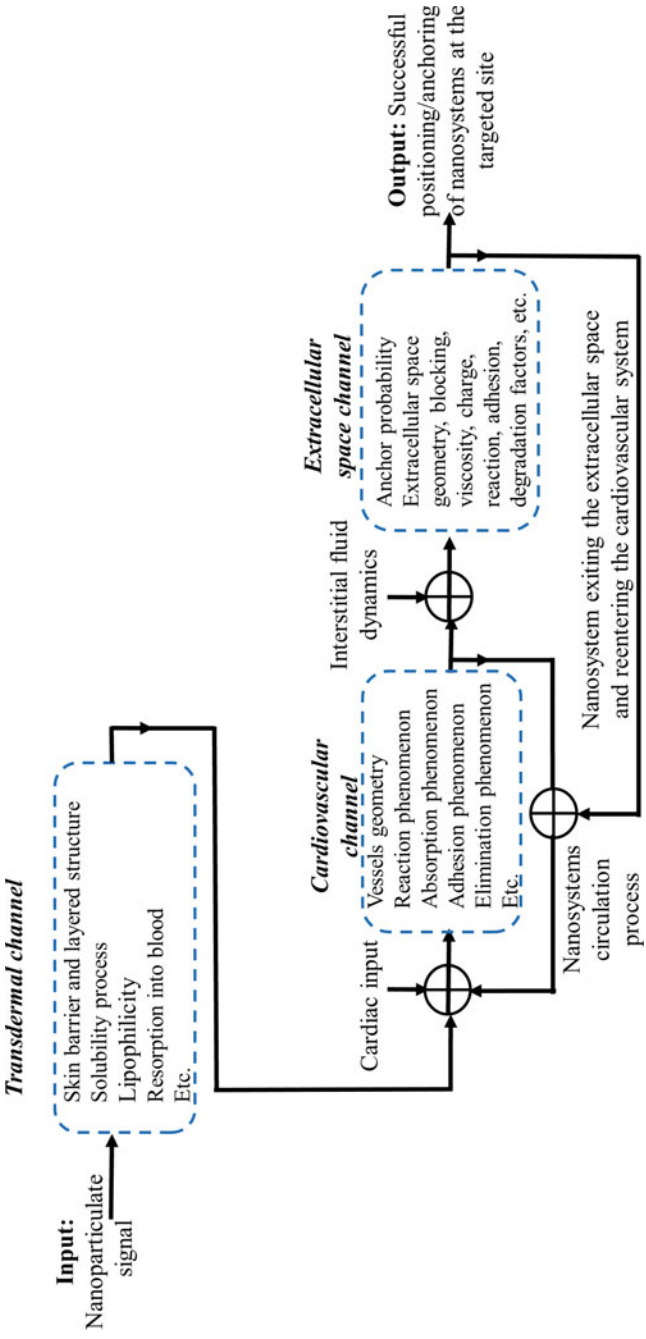


Fig. 4.20 Block diagram of the transdermal delivery channel characteristics

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Chapter 5
Classical Framework for Case-Driven Design of Advanced Targeted Nanomedical Solution

5.1 Introduction

The development and deployment of ATN solutions require relentless interdisciplinary efforts in order to bring the system and its tremendous promises to reality. The level of the interdisciplinary commitment can encompass diverse fields such as nanotechnology, communication engineering, electronics, medical biology, systems biology, computational biology, synthetic biology, genetic engineering, molecular engineering, molecular/supramolecular chemistry, atomic/molecular physics, biophysics, bioelectronics, signal processing, information theory, advanced mathematics and translational science [1]. With this knowledge spread and planning, the design and development/fabrication of an ATN solution for a particular health challenge can be effectively achieved. It is, therefore, necessary to develop a framework that will serve as a guide for researchers through the design process and the steps in achieving the ATN goal. This exercise will eventually translate the ATN from the paper-based fundamental research, through the experimental stage to clinical reality.

As can be deduced from our discussions in the previous chapters, the ATN primarily synergises concepts, tools and devices from nanomedicine and communication engineering. The nanomedical inputs provide the basis for designing and developing the nanosystems and devices, while the communication engineering inputs ensure that these nanosystems and devices communicate desirably and collaboratively to achieve the anticipated ATN objectives. While the research in ATN is still in its infancy, the pursuit of the realising its goals is reinforced by the outstanding efforts and achievements that have been made so far in nanomedicine and communication engineering separately.

In this chapter, a classical framework for the design and development of ATN solutions is presented. This presentation is devised in a case-driven way by considering an exemplary health challenge as a case for which the ATN solution is to be implemented. The health challenge considered as the case study is the one presented in [2], where a molecular communication engineering-based drug delivery model is

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proposed for simultaneously targeting cancerous tissues in multiple locations in the scenario, where some of the sites may not express significant trigger stimuli for drug release in nanocarriers.

5.2 ATN Solution Design Framework

The design and development of heterogeneous systems that involve nanosystems travelling through our bodies unnoticed, repairing damaged cells, destroying cancer cells, attacking viruses/bacteria, and communicating the outcome of their missions to each other and to external systems are at the centre of the ATN solution. This pursuit is supported by outstanding efforts and achievements that have been made so far in fields such as contemporary nanomedicine, molecular engineering, bio-nanotechnology, microelectronics and communication engineering. While the design and development of nanomedicine in general and ATN, in particular, is still at the infant stage, the translation of the associated ideas and solutions from paper-based fundamental research, through the experimental stage to clinical reality is not an easy one. Indeed, the design and development of any ATN solution is a complex exercise that takes into consideration the many component parts and stages of typical medical and pharmaceutical processes, as shown in Fig. 5.1. The framework basically involves the simultaneous or separate design and development of ideas, tools and systems such as nanonetworks, nanoparticles, body area networks and large/wide area networks. We shall discuss this framework in detail under the following sections: problem identification, initial classification and methodology development; network design; nanoparticles design and development; and ATN solution testing.

5.3 Problem Identification, Initial Classification and Methodology Development

In relation to [2], let us consider the simple scenario where a cancer patient has multiple locations in the body, say, Q, P, R and S locations, that require the targeted delivery of specific anti-cancer drugs, as is illustrated in Fig. 5.2. These locations can be within the same organ but differentiated by the stages of the disease and other conditions that imply that the different locations express relatively diverse concentrations of specific enzymes. The specific enzymes that are expressed by these disease sites are unique to particular cancer in question. The requirement is to design an ATN solution that will ensure that the disease is eliminated from the arbitrarily chosen four locations simultaneously to avoid any reoccurrence due to the metastatic phenomenon. From Fig. 5.1, it is therefore required that the problem be identified, characterised, and a set of approaches considered in addressing the medical challenge.

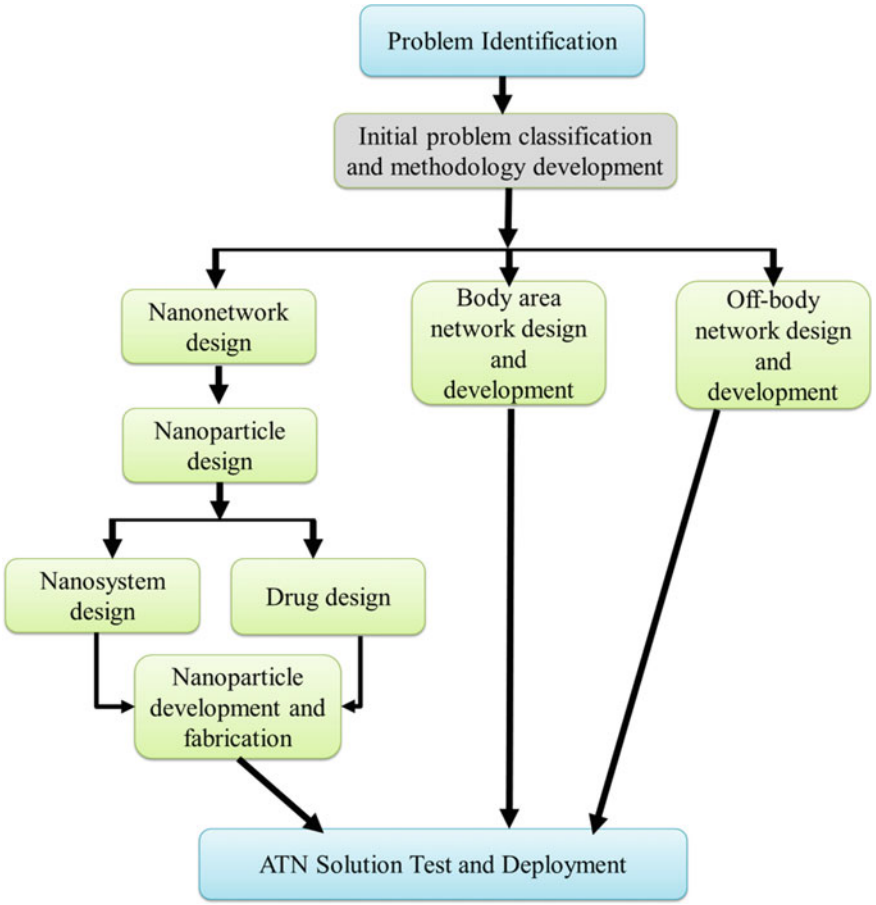

Fig. 5.1 ATN solution design and development model

5.3.1 Problem Identification

This involves finding out all that is known about the disease and the patient's history. This is where the medical biologists, pharmacologists and other related medical science specialists in the research group play vital roles. At this stage, it is assumed that propaedeutic information of the patients has been observed, diagnosis performed, biopsy conducted on the relevant tissue samples and the disease confirmed. Further, some questions that need to be answered at this stage are as follows. Where are the targeted sites located? What part of the disease cells is to be targeted—certain receptors or the organelles? What enzymes are uniquely expressed at the sites and in what quantities? What drugs prove to be efficacious in treatment? Will any of

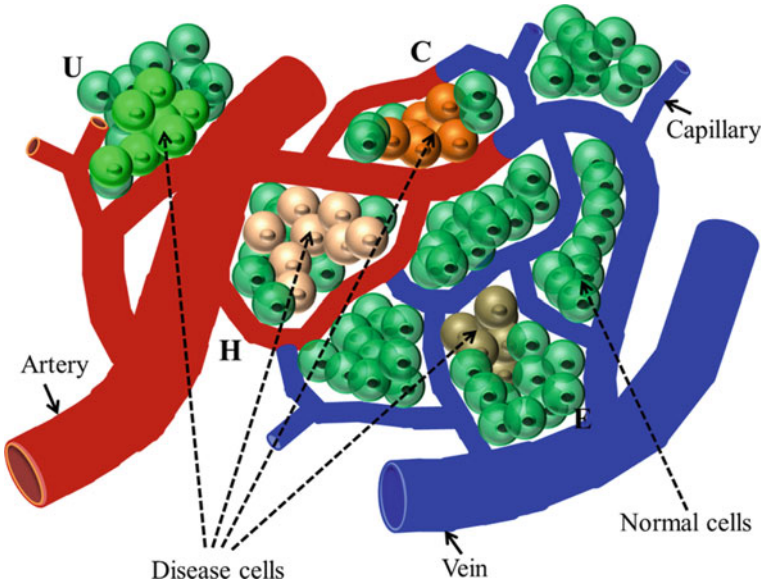

Fig. 5.2 Illustrative diagram of the multi-site delivery of nanotherapeutics

the historical or propaedeutic/diagnostic information on the patient, such as blood pressure, body temperatures, blood sugar level and age, be important factors in the treatment procedure?

5.3.2 Initial Characterisation and Framework Development

Having identified all that is known about the disease and other related factors, the next stage is to explore the initial characterisation and framework for the design and development of the ATN solution. This stage involves proffering tentative answers to the many questions generated in the problem identification stage, based on which model/framework is formed. It is important to state that the development of any framework for designing an ATN solution is built around the basic task of correcting the anomalies in the disease cells, which invariably is all about delivering nanotherapeutic particles (drug molecules) to the disease cells. Every other task associated with the ATN process, such as sensing and control, is complimentary. Hence, issues such as the identification and characterisation of the targeted cells and the therapeutic compound/drug molecules are basic to the development of the fundamental model/framework for the ATN solution. The determination of the location of the targeted sites Q, P, R and S helps define the mode of nanoparticle administration.

The model proposed in [2] is specified in an operational manner where some nanosystems are administered into the cardiovascular system via an intravascular delivery system. These nanosystems include liposome-based prodrug-carrying nanotransmitters, nanoreceivers that activate the prodrug released by the nanotransmitter, and trigger molecules for initiating the commencement of the entire operation. First, the nanotransmitter and nanoreceivers are introduced into the body and they propagate through the blood vessel network to the targeted sites, in this case Q, P, R and S. On reaching any of the targeted sites, the nanosystems anchor at the sites by binding to the cells' receptors with the complementary ligands fettered to their surfaces. With the nanosystems now anchored at the target sites, a certain concentration of trigger molecule is injected into the system to traverse the route to the targeted sites, where they prompt the start of the drug delivery process. In injecting these nanoparticles, timing is crucial to obtain good results [2]. Typically, the nanotransmitters and receivers are introduced at the same time at different concentrations, but the trigger nanoparticles are introduced after a given time has elapsed. This delay ensures that the nanosystems are already anchored at the targeted sites with an insignificant number still in the blood vessel network.

Based on the above knowledge, the initial characterisation of the nanosystems and the nanonetwork for the ATN solution can be defined. The nanosystems will include a set of nanotransmitters that will deliver therapeutic molecules (prodrug) to the targeted cells; a set of nanoreceivers to activate the prodrug released by the nanotransmitter; and nanosensors that will diagnose, monitor and control the process. Let us assume that the therapeutic molecule is a chemotherapy drug arbitrarily called *ChemA*, which have to be encapsulated inside a nanotransmitter as a prodrug. Depending on the choice of nanosystem design, the candidate nanocarrier will encapsulate, encapsidate or entrap the drug molecules that will be delivered to the targeted site. For a given dosage of *ChemA*, the size/volume of the nanotransmitter determines the number of the nanotransmitters that can be used to deliver the appropriate drugs dose to the targeted sites. We shall assume that the candidate nanotransmitter shown in Fig. 5.3 is essentially composed of a lipid membrane structure equipped with synthetic nanopores [3–5] and membrane-bound receptor proteins for triggering the transmission process. It has *ChemA*-carrying liposomes entrapped inside it. When triggered, the nanotransmitter releases the *ChemA* molecules through the nanopores. The nanoreceiver shown in Fig. 5.3 is basically composed of lipopeptide membrane covered with enzymes for activating the prodrug (*ChemA*) emitted by the nanotransmitter. The nanosensors capture the status of the processes and variations in the microenvironment (extracellular space) of the nanonetwork. In this scenario, the nanosensors are introduced to the model in [2] to aid in defining the timing in injecting the nanoparticles and synchronising the nanonetwork operation.

The nanosystems have contrast agents tethered to their surfaces, which can be used to monitor the accumulation of nanosystems at the targeted sites and ascertain the concentrations of each set of nanosystems that are able to anchor at the sites. Each type of nanosystem may be equipped with a specific contrast agent with specific visual characteristics. Examples of contrast agents that have been considered in research include those made from iodine, barium, gadolinium, manganese, iron

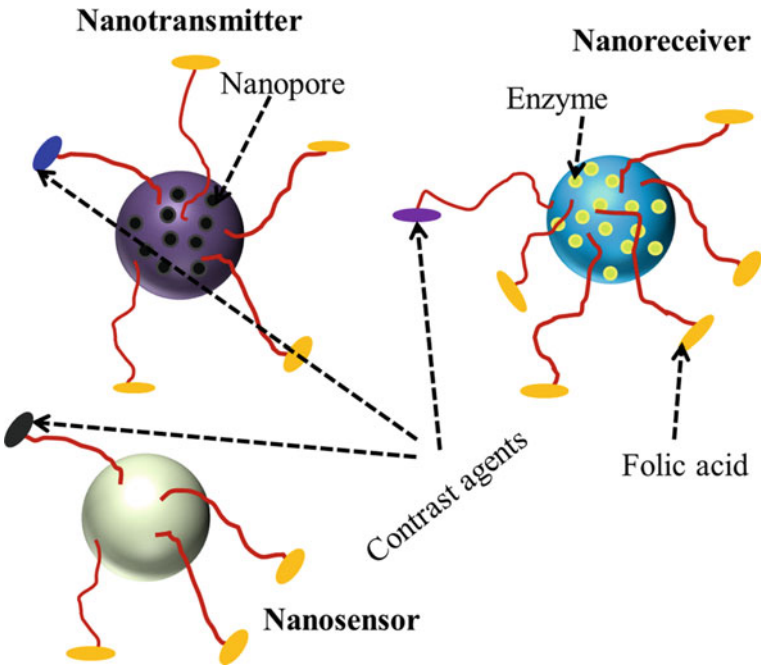

Fig. 5.3 Illustrative diagram of the multi-site delivery of nanotherapeutics

oxide, gold particles, quantum dots and microbubbles [6–8]. This implies that the external network (on-body and off-body) must include systems such as X-ray, computer tomography scanning, magnetic resonance imaging and ultrasound imaging.

And for the nanosystems to anchor at each of the tissue sites, their membranes are also grafted with specific ligands mounted on the tip of the tether linked to the membrane, which binds to complimentary receptors at each of the targeted tissues. These target ligands are assumed unique to receptors found at each tissue site. In the targeted cancerous sites Q, P, R and S, we assume that, as is typical for cancer cells, these sites uniquely express abundant concentration of folate receptors, as shown in Fig. 5.4. Hence, the corresponding complementary ligands that are to be mounted on the tip of the tether are folic acids.

Following the discussions in Chap. 4 and with respect to the challenges in the cardiovascular delivery route that is assumed in this case, the choice of the characteristics of the nanosystems must ensure that they overcome various challenges as they traverse the route. Such characteristics will enable the nanoparticles to circulate the blood network within considerable time to enable them extravasate into the extracellular space where the targeted cells are, and anchor on the cancer as illustrated in Fig. 5.5. The challenges in the cardiovascular route include phenomena and factors such as reaction, adhesion, absorption, elimination, surface charge, extracellular matrix blocking, viscosity, degradation, interstitial fluid flow/pressure and anchor

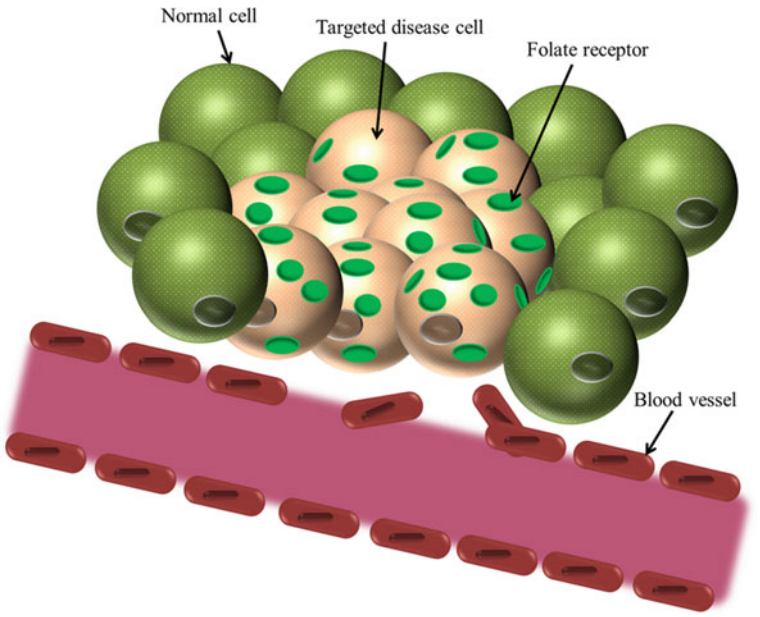

Fig. 5.4 Illustration of the unique expression of folate receptors by cancer cells

probability [9]. The factors that may influence the operation of the nanosystems, especially in terms of the release of the prodrug by the nanotransmitter (Fig. 5.6) and the activation of the prodrug by the transmitter (Fig. 5.7), have to be considered in the system modelling and analysis.

The devices for modelling the body area network and the off-body network have to also be considered. Here, we consider the physiological data such as blood pressure, body electrocardiograph and blood sugar level. The imagining systems such as the X-ray, computer tomography scan, magnetic resonance imaging and ultrasound imaging devices have to be included in the models. Off-body devices such as the network that connects the ATN networks to a remote station may also be needed. The interface unit between in-body nanonetwork and the body area/off-body network should also be considered.

Having addressed the initial characterisation of the issues, challenges and solutions, the extensive modelling of the system is required to test the typical scenarios and evaluate the performances of the framework. The models must be event-driven and accurately abstract the entire journey of the nanoparticles and every significant process from the point of the nanoparticles' delivery into the blood network until they anchor at the sites. Examples of the questions that the models will answer include (1) Given a specific number of nanotransmitter, nanoreceiver and nanosensors, what is the probability that a certain number will anchor at the sites? (2) Given a particular number/ratio of nanosystems in the targeted sites, how efficient is the process at delivering the appropriate drug concentration? The entire ATN processes of therapy,

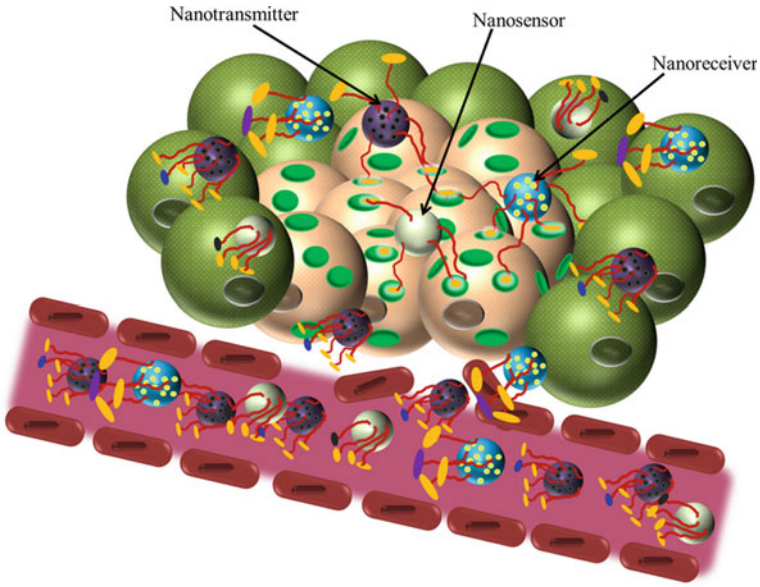

Fig. 5.5 Illustration of nanosystems anchoring on the cells by means of folate-folic acid high affinity binding

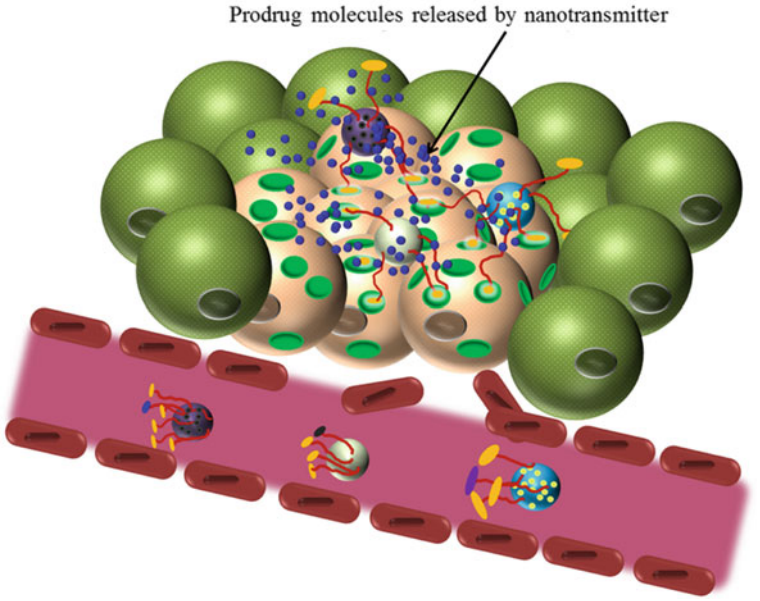

Fig. 5.6 Illustration of nanotransmitter releasing prodrug at the targeted site

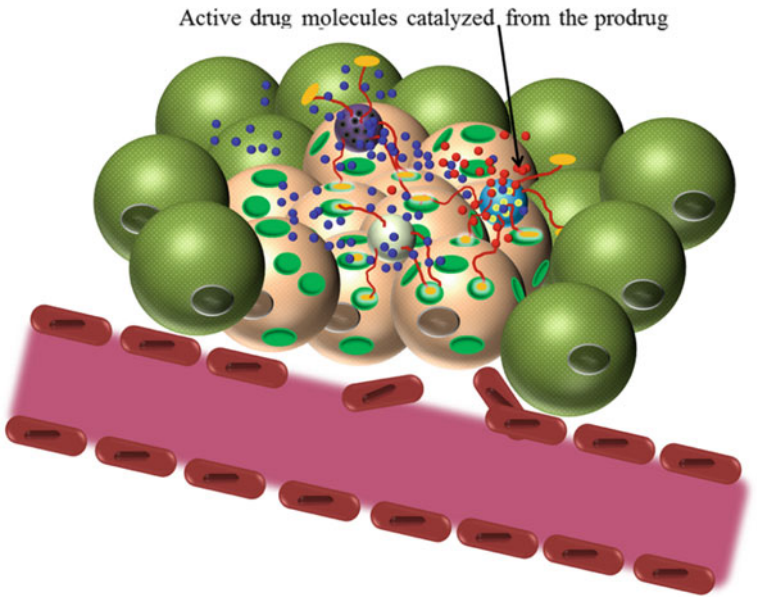

Fig. 5.7 Illustration of nanoreceiver catalysing the released prodrug into active drug molecules

monitoring and control must be accounted for in the models. At this stage, researchers in the group with strong backgrounds in areas such as communication engineering, computer science, systems biology, mathematics and physics play vital roles. The models can be mathematically and/or graphically presented, where known communication modelling approaches such as system-theoretic, information-theoretic, graph-theoretic and game-theoretic can be employed. Modelling approaches such as the deterministic methods, where differential/difference equations [10–12] and/or cellular automata [13] are often considered, can be used. On the other hand, the models can be probabilistic [14–16], where Markovian/non-Markovian processes or/and spatial modelling [17] suffice, can be employed. Examples of simulation tools that can be used at this stage are shown in Table 5.1. Moreover, access to databases comprising resources generated from various works by scientists and technologists around the globe is crucial. Table 5.2 presents some databases that can be of benefit with respect to the case at hand.

Table 5.1 List of some simulation tools that can be used in ATN research

Name	Information content	Website
Matlab	Software tool for fundamental systems design and analysis	www.mathworks.com
Mathematica	A symbolic mathematical computation software tool	www.wolfram.com
COMSOL Multiphysics	Multipurpose software platform for simulating physics-based problems	www.comsol.com/comsol-multiphysics
NS-3	A discrete-event network simulator for Internet systems, targeted primarily at research/educational use	www.nsnam.org
Cellerator	A biological modelling software tool based on automated equation generation	www.cellerator.info
CellDesigner	A diagram editor for drawing gene-regulatory and biochemical networks	www.celldesigner.org
E-Cell	Software tool for large-scale (whole-cell level) simulation	www.e-cell.org
Discovery Studio	Commercial software packages for drug design	www.accelrys.com
PathVisio	Open-source pathway analysis software that allows you to draw, edit and analyse biological pathways	www.pathvisio.org

Table 5.2 Some nanoinformatics databases for ATN research

Name	Information content	Website
NanoParticle Ontology	Ontology resource developed to provide knowledge regarding description, preparation, and characterisation of nanomaterials in cancer nanotechnology research	www.nano-ontology.org
CrownBio	Oncology databases	www.crownbio.com/oncology/oncology-databases
Cancer Open Biomedical Resource	A tool for indexing cancer nanotechnology informatics knowledge with open biomedical resources	www.bioontology.org/caOBR
Chemical Entities of Biological Interest	A database and ontology of chemical entities of biological interest	www.ebi.ac.uk/chebi

(continued)

Table 5.2 (continued)

Name	Information content	Website
LGICdb	This stands for ligand-gated ion channel database	www.ebi.ac.uk/compneur-srv/LGICdb
KinG	Protein kinase database	www.hodgkin.mbu.iisc.ernet.in/~king/
BIND	Biomolecular interaction database	www.blueprint.org/bind.php
LIGAND	Database of chemical compounds in biological pathways	www.genome.ad.jp/ligand
TRMP	Therapeutically relevant multiple pathways database	www.xin.cz3.nus.edu.sg/group/trmp/trmp.asp

5.4 ATN Network Design

The design and development of the various networks that form the ATN communication system are briefly discussed here. These networks include the nanonetwork comprising the nanosystems, the body area networks comprising the devices for measuring blood pressure, blood sugar and electrocardiograph, and the off-body electronic communication networks that comprise conventional communication devices. Only the designs of nanonetworks and body area networks are considered here as the off-body networks (local area network and the Internet) have been widely discussed in the communication engineering literature. Researchers in the group with strong backgrounds in areas such as communication engineering, computer science, systems biology and mathematics play vital roles.

5.4.1 Nanonetwork Design

Based on the four targeted sites, Q, P, R and S, there will be four different nanonetwork environments. In a practical scenario, the nanosystems injected into the blood system will arrive at the targeted sites and anchor on cells by means of the folate-folic acid high-affinity bond. First, it is important to determine the size of the targeted sites and the probable maximum number of nanosystems that can anchor at the site. To obtain this number, the number of cancer cells in each targeted site must be estimated. This can be done by estimating the average number of the folate receptors on each disease cell surface. Hence, assuming the same cell size and type, the number of folate receptors on a cell surface multiplied by the number of the disease cells in a targeted site and divided by the average number of folic acids tethered on each cell determines the number of anchorable nanosystems.

Having determined the number of anchorable nanosystems, the next objective is to define the quantity/concentration of drug molecules that each nanotransmitter can hold. This depends on its size and the size/number of the drug-encapsulating liposomes enclosed in the nanotransmitter. Of course, in choosing the size of the nanotransmitter or any other nanosystem, the effect of the channel (route) must be considered. Given that we choose R_T as the approximate radius of the nanotransmitter, its volumetric capacity can be calculated with this radius [2]. Hence, if we know the concentration of the anti-cancer prodrug that is required for effective therapy in each of the targeted sites, then the number of nanotransmitters required to deliver the doses can be estimated given that we know the number of anchorable nanosystems and R_T.

In the design of the nanoreceiver, the size and concentration of the surface enzymes are important parameters. A large surface area allows for more enzymes to be incorporated, thereby increasing the number of prodrug molecules activated per unit time [2, 12]. However, like in the case of all other nanosystems, the channel effects define the size limit of the nanoreceiver. Again, for a given nanoreceiver radius and enzyme concentration on its surface, the number of nanoreceivers required to activate the required doses can be estimated, given that we know the number of anchorable nanosystems. In the design of the nanosensors, the size and concentration/distribution of the sensing interfaces, such as probes, receptors and nanopores, are also important parameters.

It is important to note that these nanosystems will anchor randomly on the targeted sites; hence, design and deployment approaches must ensure that the desired number of each set of the nanosystems anchor at the targeted sites.

5.4.2 Body Area Network

The body area network comprises the sensors and devices for acquiring, transmitting and processing biosignals such as blood pressure, blood sugar and electrocardiogram readings within the ATN solution. The design of this network centres on the positioning of the sensors, how information is relayed, and virtual backbone topology. Other design considerations include the software and firmware development for the network.

In terms of sensor positioning, the sensor will usually be placed at a fixed location determined by the biosignal it is meant to capture. For instance, the electrocardiograph sensor and blood sugar sensor are placed at the positions shown in Figs. 3.12 and 3.14, respectively. Data collected by the sensors are usually sent to a central (or distributed) sink node for processing. Due to the time-varying nature of the body area channel caused by the presence of postural mobility related to body physical movement, relays may be needed to ensure that communication is relatively stable and reliable. Hence, relay devices will be needed, and the identification of the potential relay locations based on contextual knowledge obtained from dynamic patient body position and motion is required. To guarantee reliable communication between sen-

sors, relays and sink node, optimal virtual transport backbone topology is required. The optimal topology ensures that posture and movement minimally affect the communication link between any two nodes. Link adaptation can also be implemented to achieve optimal topology. The software and firmware, which maintain network connectivity, should be reliable, robust to failure and very responsive. Ideas for the design of the body area network can be obtained from [18–20].

The design of the interfacing system between the nanonetwork and the body area/off-body networks is very crucial. The choice of an architecture for the system will depend on the nature of the signal, the channel through which the signal is propagated and the task at hand. Some proposals for addressing the interface issue have been presented in [21–23]. The architecture and model of a bio-cyber interface for connecting the conventional electromagnetic network to the biochemical signalling-based nanonetwork are presented in [24]. This work used inspiration from biological concepts such as the responsiveness of certain biomolecules to thermal and light stimuli, and the bioluminescence phenomenon of some biochemical reactions to model the interfacing device.

5.5 Nanosystem Design and Development

The site-specific delivery of nanosystems and the promises of ATN will not be realised unless the nanosystems are properly designed, taking into account all the issues raised in Chap. 4 concerning the influence of route factors. In general, the different types of nanosystems to be used to imply different functions to execute. Hence, the design of each of these nanosystems requires the definition of specific characteristics that will enable each of the nanosystems to execute the designated task. In general, the size, shape and surface characteristics of the nanosystems are important in ensuring that they are robust against the influence of the route factors. These parameters are also crucial to accumulating/anchoring at the targeted sites and, as the case may be, internalising at the targeted cells. In the case under consideration, there are three different types of nanosystems, namely, the nanotransmitter, nanoreceiver and nanosensor. As their operations require, all the nanosystems are to anchor on the targeted cells and operate only at the surface. The fundamental characteristics of the nanosystems in the case at hand are illustrated in Figs. 5.8, 5.9 and 5.10 for the nanotransmitter, nanoreceiver and nanosensor, respectively.

5.5.1 Nanosystem Development

Having determined the required size and shapes of the nanosystems, computer design and simulation of their journey to the targeted site and their anchoring/operation at the targeted site, we get to the physical development of the nanosystems. At this stage, researchers in the group with strong backgrounds in areas such as nanoparticle

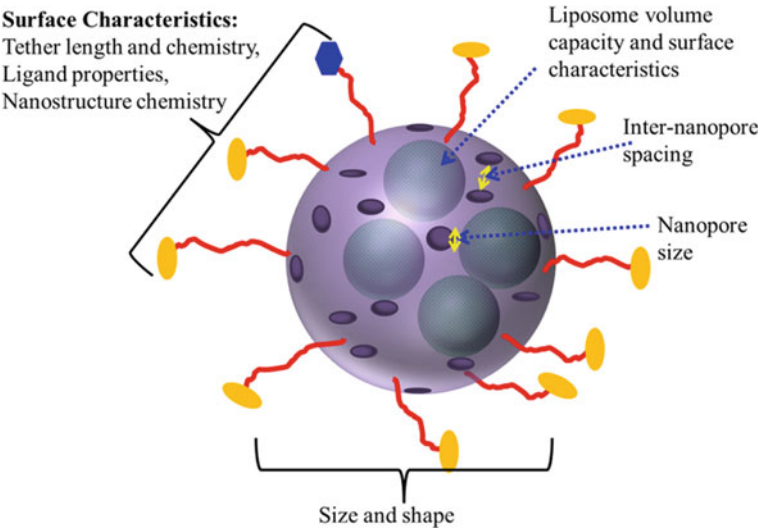

Fig. 5.8 Illustration of fundamental characteristics of the nanotransmitter

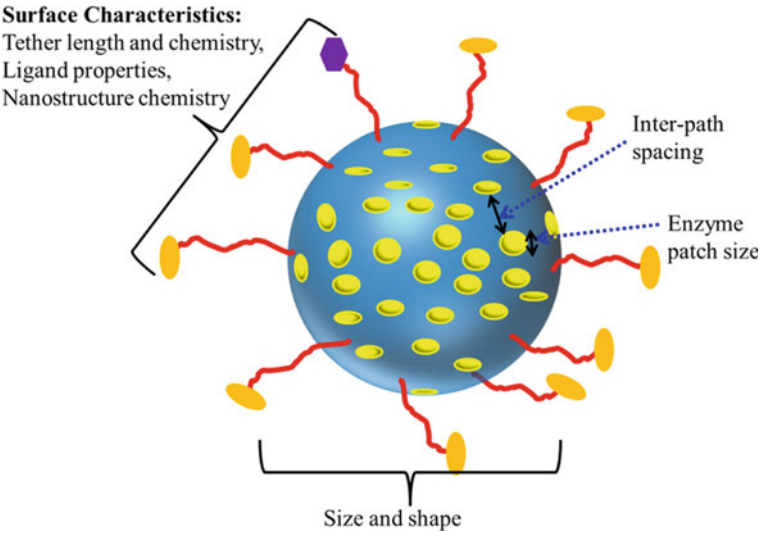

Fig. 5.9 Illustration of fundamental characteristics of the nanoreceiver

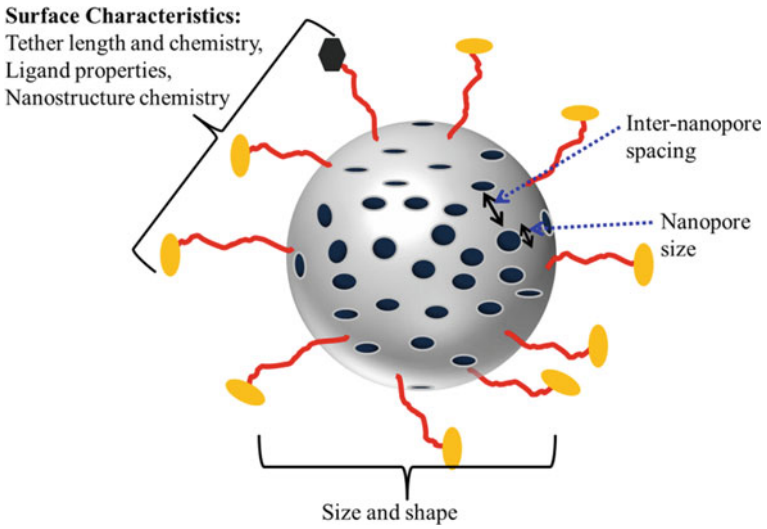

Fig. 5.10 Illustration of fundamental characteristics of the nanosensor

engineering, molecular biology, systems biology and computer science play vital roles. The workflow for the development of the nanosystems is typical of drug development, as shown in Fig. 5.11.

Given that we already identified the optimum physical parameters for the nanosystems, the main objective here is to identify the candidate nanomaterials for the design of the nanosystems. This identification is achieved by means of a deep curation process, which creates a detailed molecular interaction map of candidate nanomaterials. The deep curation process is done by integrating available knowledge of the materials from various databases, publications and other information sources. The molecular interaction mapping should also include interaction with the candidate drug molecules. The deep curation process results in the identification of hypothesised candidate nanomaterials for the design of the nanosystems.

5.5.2 Nanosystem Fabrication

The fabrication technologies for nanosystems, like in the general context of nanotechnology, can be categorised into top-down and bottom-up approaches [25, 26]. In the top-down approach, nanoparticles are generally designed by carving them out from larger blocks. The bottom-up approach considers starting with components such as molecules and atoms and placing them into position one by one to create the desired nanoparticle.

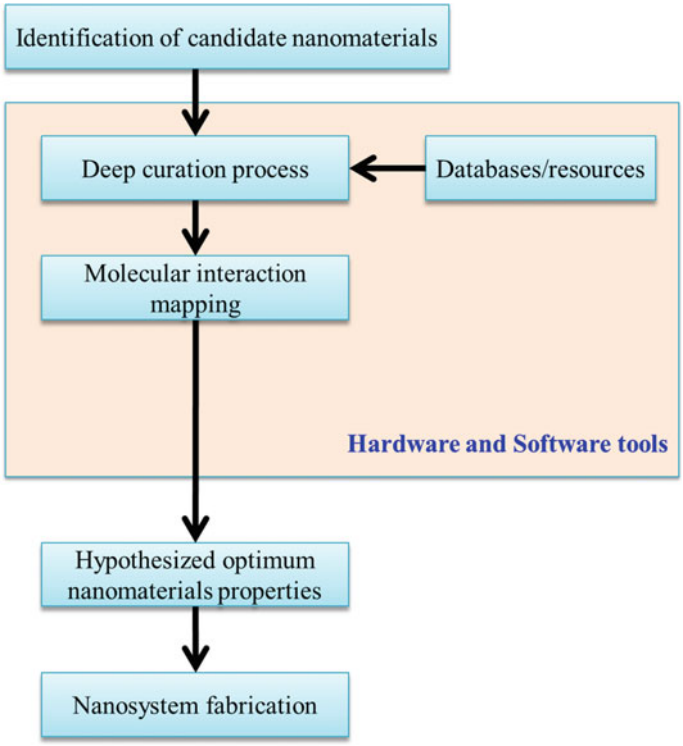

Fig. 5.11 A workflow for nanosystem development

From the results of the deep curation and molecular interaction mapping, we are now in a position to use the optimum parameters of the candidate nanosystems to fabricate the system. Contemporarily, the fabrication of almost all nanosystems follows the bottom-top approach. Some of the bottom-top fabrication methods that can be used to develop the nanosystems in this case study include the particle film stretching method [27], the self-assembly method [28], the particle replication in nonwetting templates technique [29] and the emulsion method [30].

5.6 ATN Solution Assembly and Testing

With the nanoparticles, the body area sensor/devices, and off-body devices and networks ready, the assembly (shown in Fig. 5.12) and testing of the solution can begin. After the assembly, the practical experiment and system testing can be conducted on animals, where the use of animals whose internal systems are close enough to that of the target species is ideal [31–33]. In the case of humans, the pig and mouse have internal systems that are close to that of the humans. Such experimentation gives

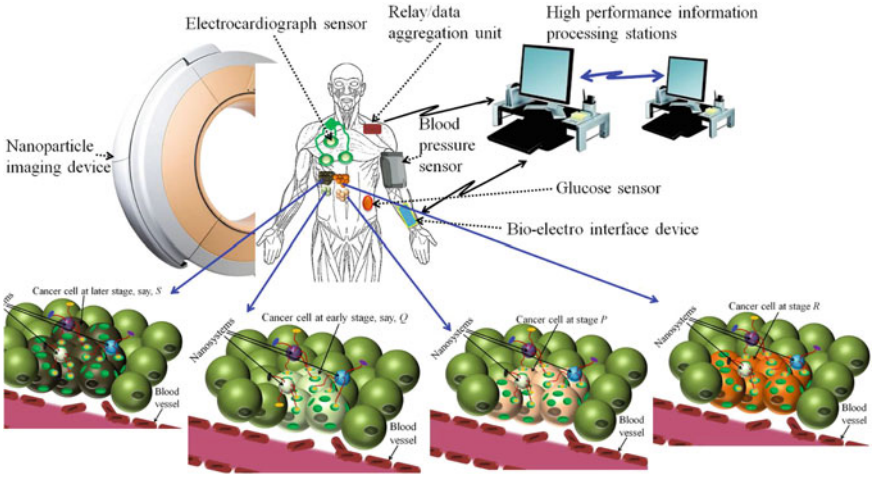

Fig. 5.12 A framework of advanced targeted nanomedicine solution

us a more definite estimation of the ATN solution's performance if it were to be administered to a human target. Successful tests and results set the stage for clinical trials and assessments.

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Chapter 6
Internet of Things for Advanced Targeted Nanomedical Applications

6.1 Introduction

The fundamental idea behind nanomedicine is to improve the efficiency of medical and healthcare systems using nanotechnology concepts, devices, tools, technologies and techniques. On the other hand, another nanotechnology offshoot, molecular communication engineering, considers the design and development of nano-scale devices and machines that can communicate by means of biochemical information exchange. By integrating the concept of molecular communication into nanomedicine [1], the coordination of activities and information sharing among several nanomedical devices and machines can be achieved, which results in expanded potentials in the medical and healthcare systems. The concept of ATN takes advantages of the MC-nanomedicine synergy by incorporating historical information of the patient as well as real-time biosignal information to personalise disease treatment, as well as monitor/control the therapeutic process. The interconnection of the network of nanosystems and the body area network of biosignal sensors [2], as well as the off-body processing unit, forms the basic heterogeneous network of an ATN solution.

With the rise in global population, coupled with the low number and uneven distribution of medical personnel, the need for a new approach to global healthcare delivery that will ensure that medical aids get to wherever and whenever it is needed, is necessary. Over the years, the concept of the Internet of Things (IoT) [3, 4], which enables the connection and communication of physical objects with anything, anywhere, at any time using embedded wireless capabilities [5], has become the focus of research and industrial interest. It has been predicted that the IoT will create opportunities for more direct integration of the physical world into computer-based systems, resulting in improvements in many facets of life, economic benefits and reduced human intervention. With regard to nanotechnology and healthcare delivery, the concept of the IoT has ushered in related concepts such as the Internet of NanoThings (IoNT) [6], the Internet of Bio-NanoThings (IoBNT) [7], and Internet of Bio-NanoThings for Ambient Assisted Living (IoBNTAAL) [8] into the research and industrial domain. The IoNT considers the potential of making nanomachines

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to communicate using the Internet platform. The IoBNT projects the prospective application domain where the activities of nanosystems operating in an in-body nanonetwork can be monitored and controlled through the Internet. The IoBNTAAL specialises the IoBNT to ambient assisted living. By synergising nanotechnology and the Internet on a platform, these technologies aim at ensuring that medical aids get to people wherever and whenever they are needed. These technologies have the potential to also offer remote fitness programmes, epidemic control and elderly care.

The ATN can greatly benefit from the promises of the IoT. In this sense, the IoT-ATN synergy, which is simply referred in this book as IoT-ATN, taps into the benefits of the IoNT, IoBNT and IoBNTAAL to provide personalised nanomedical therapy, monitoring and control anywhere, anytime and for anyone. The resources, knowledge and expertise that are not available at the patient's physical location can be accessed through the Internet by the ATN solution.

6.2 Layered Architecture and Essential Components of IoT-ATN Solution

In the IoT-ATN system, ATN considers tapping into the capabilities of the IoT to query the states of a set of living and non-living systems and to change their states as required in order to tackle medical challenges in an unprecedented way. To be able to query and alter the states of the living and non-living systems in the network, there is a need for embedded sensors, actuators, processors and transceivers, which have to work in harmony. In this chapter, the conceptual layered architecture of the IoT-ATN solution that ensures effective connectivity among the IoT-ATN devices and services is introduced. This layered architecture will facilitate the identification of opportunities in each layer and across the layers.

6.2.1 Layered Architecture

Just like for the IoT [10], the devices, nodes and firmware/software applications that are connected together in an IoT-ATN system require a de facto standard to ensure seamless interoperation. A layered architecture for the IoT-ATN application is presented in Fig. 6.1.

6.2.1.1 Environment of Things Layer

This layer comprises the objects or places where the observations and activities of the nanosystems and sensors take place. The basic object is the patient or patients (in the case where multi-patient response is required) in whose body the nanosystems and

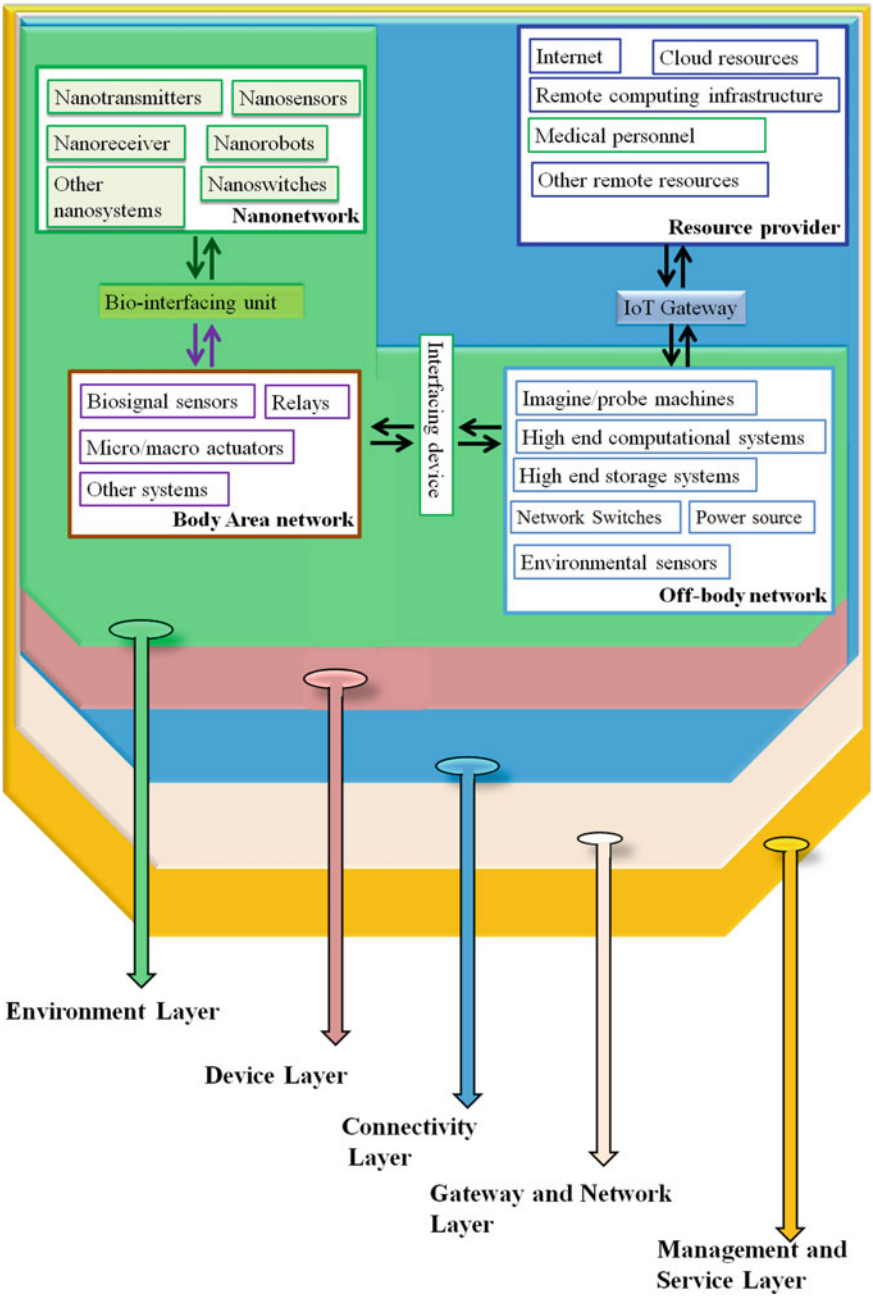

Fig. 6.1 IoT-ATN layered architecture

sensors/other devices work. The 'places' can be the immediate environment where the patient is at the time of observation.

6.2.1.2 Device Layer

This is a physical layer where hardware such as nanosystems, body area sensors, relays, environmental sensors, tags, readers and embedded systems are considered. In the IoT-ATN, the nanosystems form an in-body nanonetwork, while the body area sensors/actuators and other devices form the body area network. The nanosensors in the nanonetwork work inside the body to acquire information on the various states of the patient's internal environment, cells, tissues and organs, as well as of the activities of other nanosystems in the nanonetwork. The body area sensors/actuators and other devices form the body area network in the IoT-ATN and acquire some biosignal information of the patient, externally. Sensory information on environmental conditions like temperature, humidity, air quality and movement can also be acquired using environmental sensors that are resident in the off-body network. Tags may be located in the body area network or off-body network for information storage. And embedded edge processors (centralised or distributed) will usually be employed to process acquired information.

6.2.1.3 Connectivity and Data Processing Layer

This layer takes care of the communication connectivity and data processing among the various nanosystems in the nanonetwork, the devices in the body area network and those in the off-body networks. The diversity in the communication formats among the different networks necessitates that this layer be separate from the gateway and network layer discussed below. Concerns at this layer include the physical placement and configuration of the network devices to achieve the desired goals. The achievement of good connectivity among the nanonetwork nanosystems requires the development of network technologies that depend on biological signalling and other appropriate signalling functions for information exchange in an in-body nanonetwork. For the body area and off-body networks, technologies such as Wi-Fi, ZigBee, ultrawideband (UWB) and Bluetooth can be used to connect the devices. Furthermore, this layer takes care of the processing of the information that is passed around the respective networks in a way that enables real-time information collection and processing as may be required.

6.2.1.4 Gateway and Network Layer

This layer performs the basic role of connecting the nanonetwork, body area network, off-body network and the Internet together. Issues such as routing and addressing, network/transport capabilities and error detection/correction are considered in this layer.

These functions will be handled by some kinds of nanogateways, microgateways and macrogateways [11]. Due to the diversity in the various constituent networks in the IoT-ATN environment, which entails the availability of many different networking technologies and access protocols, this layer should be able to handle connectivity in a heterogeneous network.

6.2.1.5 Management and Service Layer

This layer coordinates and manages the diverse network service providers within the IoT-ATN setting. Its functions include data and application management, control, security, monitoring, storage, organisation and visualisation across various services. In this layer, different policies such as quality of service management, traffic management, device management, traffic engineering, business process modelling/execution, packet inspection, identity management, access authorisation and functions that can be applied to better manage the information generated by all the devices and network constituents are considered.

6.2.1.6 Application Layer

This layer is responsible for delivering various applications that provide user interface within the IoT-ATN environment. It defines the applications in which the IoT-ATN can be deployed, which in this case is the personalised medical care delivery.

6.2.1.7 Essential Components of IoT-ATN Solution

An IoT-ATN application system comprises primary components such as sensing, actuation, communicating, firmware/software, virtual resources and energy components.

6.2.2 Sensing Components

The sensing components gather information from the points of activities in the IoT-ATN system. This can be the information captured by the in-body nanosensors, implants, on-body sensors, off-body sensors and other wearable devices. The diversity in the sensing methods of these heterogeneous components could be a challenge to information processing and analysis.

6.2.2.1 Actuation/Moving Components

These components include nano-, micro- or macro-machines such as molecular motors, nanorobots, micro-robots and moving parts that are involved at any point of activity in the IoT-ATN system. Usually, information gathered from the sensing components is used to activate these components to act in a desired manner in order to achieve an effectively controlled ATN process.

6.2.2.2 Communication Components

The communication components are the devices whose function in the IoT-ATN system is to ensure optimal communication between the various components, systems and networks. These include the nano-, micro- and macro-transmitters, receivers, switches and routers; local area network (such as Wi-Fi, Bluetooth, ZigBee); the Internet; and virtual systems like the cloud (for big data storage). The importance of the cloud can be seen in the need to access or store massive information during the deep curation process of designing and developing nanosystems for the application.

6.2.3 Firmware and Software Components

To make information such as data, graphs, images, and audio available to the users in a simple and transparent format for the IoT-ATN process, various firmware and software are required. This necessitates the design and development of robust and accurate user interfaces that provide an optimised experience across multiple communicating device platforms.

6.2.3.1 Virtual Resources

Due to the crucial requirement for processing and storing data generated in the various networks within the IoT-ATN system, there is a need for efficient computational and storage systems. These systems can be some high-end processing mobile systems, or supercomputers with high computational and storage capabilities.

6.2.3.2 Energy Components

To be able to power the devices and networks in the IoT-ATN system, there is a need for energy sources. Unlike the conventional IoT, the IoT-ATN requires different types of energy sources to power the different systems in the network. For instance, while most electronic devices will be powered by batteries and other conventional power sources, the in-body bio-nanosystems will be powered by

biological/biochemical sources that may mimic the mechanisms of the adenosine triphosphate (ATP) synthase in natural cells. The ATP synthase is an enzyme that creates the energy molecules called ATP in the cells [12]. The ATP synthase working involves the accumulation of torque by twisting a rod-shaped structure composite. The discharging of this torque by the rotation of the structure provides the energy for the synthesis of the ATP molecules.

6.3 Characteristics of IoT-ATN Applications

The fundamental characteristics of the IoT-ATN are as follows.

6.3.1 Diverse Network Devices

The devices and nodes that can be connected to the IoT-ATN systems are very diverse in composition and dimension. They could range from macro-size to nano-size in dimension, and from living to non-living in composition. In the IoT-ATN scenarios, usually, there may be so many nanosystems operating in the nanonetwork and a handful of body area sensors and other important on- and off-body devices. Hence, timely and efficient processing of the sensor data and the resultant control activity are needed.

6.3.2 Heterogeneity of Signalling

Unlike the signalling among devices in the conventional IoT, whose nature is mainly electromagnetic, signalling in the IoT-ATN systems is typically diverse. Truly, signalling in the IoT-ATN is usually the combination of all the signalling formats discussed in Chap. 2, namely, electromagnetic, biological, chemical, electrical, magnetic, optical, acoustic, and so on. With each of these signalling formats having different characteristics, the design and development of the IoT-ATN solution will be very challenging.

6.3.3 Diverse Timescale of Communication Processes

Dissimilar to the conventional electromagnetic-based IoT, whose communication processes are physical in nature, IoT-ATN communication processes are typically a combination of physical and biological (biochemical) processes. For instance, within the in-body nanonetwork, it is known that the process of molecular diffusion that

mainly governs communication between nanosystems is a physical process; the interactions between the transmitted molecules and the nanoreceiver surface receptors involve biophysical processes; and the intracellular processing of received signals is basically biological in nature. These different types of nanonetwork communication processes usually operate on different timescales, which can range from nanoseconds to years. For example, the diffusion time step can occur in nanoseconds [13] with diffusion over 1 μm occurring in about 10–100 ms [14]; protein–protein interaction can occur in seconds [15]; ligand–receptor residence time can be in milliseconds [16]; and enzyme turnover time can be in microseconds [14]. On the other hand, the timescale of the electronic communication processes of the core IoT can occur at the speed of light. This diversity will make the design and development of the IoT-ATN solution very challenging.

6.3.4 Dynamism

The states of the devices and functions in the IoT-ATN system change as functions of space, time and composition. For instance, the position of nanosystems in a nanonetwork may change inadvertently or not in the course of the process. On the other hand, the position of the body area sensors may change due to variations in the patient's orientation (position change). These dynamic processes can influence the working of the entire IoT-ATN system.

6.3.5 Heterogeneity in Energy Source and Forms

Coupled with the huge data demand of the IoT, the heterogeneity in the type and characteristics of the devices in the IoT-ATN implies diverse forms and amount of energy required in the network. For instance, energy sources for the off-body and on-body systems will mostly be batteries and other conventional power sources, and the in-body nanosystems will be powered by biological/biochemical sources. Such sources may mimic the mechanisms of the ATP synthase in natural cells as mentioned earlier.

6.4 Challenges of IoT-ATN

The IoT-ATN process involves interaction among living and non-living systems in the multiple networks. In comparison to the conventional IoT, while the design, development and configuration of the various composite devices for IoT applications are well-established, the IoT-ATN and its umbrella technologies are still at the infant stage. As an offspring technology of the IoT, most of the challenges in IoT [17, 18]

abound in IoT-ATN. Here, we highlight some of the unique challenges of designing and implementing the IoT-ATN. These challenges include nanonetwork interface, data fusion and analysis, nanonetwork energy management and conservation, security, privacy and standards/policy.

6.4.1 Nanonetwork Interface

A very crucial challenge that is unique to the IoT-ATN is the design and development of effective units that can be used to interface between two nanonetworks, or between a nanonetwork and a body area network/off-body network. The nanonetwork–nanonetwork interface requires what may be termed a nanogateway or microgateway, depending on the size of the gateway. The gateway/interface for the nanonetwork-body area network/off-body network will most likely be a microgateway or macrogateway depending on the size of the gateway. The architecture and working principle of these gateways, which typically resides in the gateway and network layer of the IoT-ATN protocol, depends on nature/format of the communication signals, the channel through which the signal will be propagated and the transmit/receive requirements of the communicating network access points. Unlike the gateway devices in the conventional IoT, whose nature is mainly electromagnetic, signalling in the IoT-ATN systems is typically the combination of diverse signalling. Hence, the design of protocols to manage the multiple signalling formats of the IoT-ATN implies that the gateway should be able to handle such a challenge. In such design, one is compelled to ask whether the biological nanonetworks are suitable for the transmission of the 'traditional' types of traffic such as video, images and audio. The answer is most likely no. Even when the transmission of such traditional traffic is required, achieving it with say, biochemical signalling will be challenging.

In the design of the IoT-ATN gateways, inspiration from natural biological systems and phenomena will be very helpful [19]. Some proposals for addressing the interface issue have been presented in [20, 21]. More recently, the architecture and model of a bio-cyber interface for connecting the conventional electromagnetic-based Internet to the biochemical signalling-based bio-nanonetwork is presented in [9, 22].

6.4.2 Information Fusion and Analysis

Information fusion and analysis in the IoT-ATN fundamentally focus on the combination of information from sensors, databases and other related sources in the network. This information is processed and explored in the most optimal manner possible to obtain estimates of some unique characteristics of the process. In the IoT-ATN, there are sensors of different kinds producing diverse information formats of diverse signal strength/complexity, and with different delay, bandwidth and throughput requirements. Examples of the IoT-ATN sensor information and other

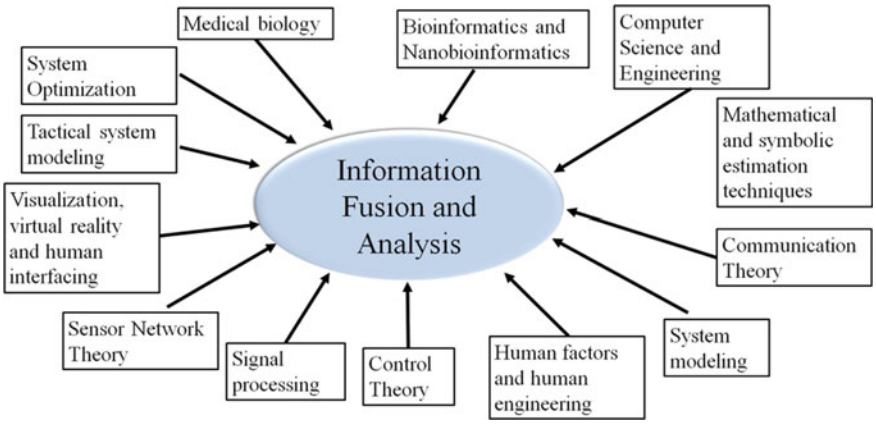

Fig. 6.2 Multidisciplinary design model of information fusion and analysis

information sources include biosignals such as electromagnetic signals, electric signals, hormonal signals, blood glucose variation, blood pressure, neuronal signals, electrical signals (from electroencephalograph, electrocardiograph, electromyography, etc. sensors), and other closely associated signals and sources such as bioluminescence, fluoresces and databases. Issues and challenges, such as whether to consider centralised, distributed [23, 24] or hybrid processing, also arise.

To deliver the promises of ATN, the information from these diverse multisources has to be fused and processed to obtain the desired results, which are challenging tasks. The process requires the design and implementation of a heterogeneous multisource information fusion and processing system based on a multidisciplinary approach, as depicted in Fig. 6.2. The sub-disciplines mentioned in Fig. 6.2 work together to refine observed information in order to make informed decisions in real time, and possibly to modify the course of the ATN process if desired.

6.4.3 Security Concern

Securing the IoT-ATN devices and networks is an important consideration for allowing multiple devices, vendors and users to participate in a single platform. For example, a set of devices may be associated with a particular service provider; therefore, the control of such devices should only be accessible to the authorised service provider. Also, the issue of unwanted malicious interference in the working of the entire system is an important and challenging concern. Securing the system requires that (i) communication between entities is genuine, (ii) only authorised sources can provide information to the network, (iii) only the desired destination systems can understand given information, and (iv) information cannot be modified by a malicious intruder. The existing methods for securing traditional wireless

communication systems cannot be applied to the entire IoT-ATN system for reasons such as low computational capability and large technology variance. For instance, in conventional practice, coding, encryption and steganography are some of the methods used to secure traditional wireless communication systems. In the context of IoT-ATN, some coding schemes have been discussed [25, 26]; however, how these schemes can be practically implemented in a real IoT-ATN nanosystem is unclear, with size and complexity of the nanosystem being defining factors.

Concurrently, privacy will be a major issue to the users present in the network. Due to the integration of multiple devices into a single platform, multiple authorities may have information about who is doing what, which in turn violates the privacy of the users. Consequently, researchers need to consider such cases in order to preserve the privacy of the users while integrating multiple devices into a single platform. The fine-grained control of flows using a software-defined network may be employed to enhance the security and privacy of network traffic [27].

6.4.4 Standards

Within the scope of the IoT, several technologies are typically connected together, and different participating industries and parties define different IoT solutions. Hence, the need to define a standard for IoT to perform common backend tasks in order to guarantee levels of interoperability, manageability and portability across various platforms is important. The same need for standardisation extends to the IoT-ATN, but with the added requirement that the concerns of parties from the medical science sector be integrated. Hence, efforts have to be made to harmonise the regulatory framework for IoT and medical science, specifically, nanomedicine. The Food and Drug Administration regulations/standards and the IEEE Standards Association project, the IEEE P1906.1 [28], can provide some recommended practice that can be employed in defining the IoT-ATN standards. The FDA is a federal agency of the United States of America Department of Health and Human Services responsible for protecting public health by assuring the safety, security and efficacy of human and veterinary drugs and medical products/devices. The IEEE P1906.1 presents guidelines for developing clear, common definitions and a conceptual framework needed to accelerate, solidify and guide nanocommunication research towards practical implementation.

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Chapter 7
Discussion on Advanced Targeted Nanomedical Application Scenarios for Treatment of Some Chronic Diseases

7.1 Introduction

In this chapter, classical discussions on the possible application of the ATN solution to the treatment of some chronic diseases are provided. The diseases discussed include cancer, Alzheimer's disease, acquired immunodeficiency syndrome (AIDS) and cardiovascular diseases. For each disease, discussion trails the pathophysiology and pathways of its occurrence. How the abnormalities in cell death regulation (apoptosis) significantly mediate the occurrence of some of these diseases is highlighted. Indeed, the inappropriate response of a cell to undergo apoptosis is a factor in many human conditions including cancer, AIDS, ischemia and neurodegenerative diseases [1]. The exposure in this chapter, like the rest of this work, is structured in a way that makes it accessible to readers with little or no background in medical science. Exemplary suggestions for defining possible ATN solutions to the various medical challenges mentioned above are given.

7.2 ATN Application to Cancer Treatment

7.2.1 Cancer Pathophysiology and Pathways

Cancer refers to a group of diseases that result from the uncontrolled growth of abnormal cells anywhere in a body (for example, breast, colon, lung and skin). A key driver of cancer is the impairment of a vital cellular function called apoptosis or programmed cell death. Apoptosis is generally crucial for processes such as proper embryonic development, regular cell turnover and accurate functioning of the immune system [2]. Hence, in response to damage to a cell's DNA and other cellular

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stresses, a normal cell will usually try to repair the damage [3]. But when the repair fails or if the damage (like the error in the DNA) or stress is great, the cell will initiate apoptosis.

Apoptosis is generally characterised by distinct morphological characteristics and energy-dependent biochemical mechanisms that result in the self-annihilation of the associated cells. It can occur through two pathways, namely the mitochondrial/intrinsic pathway [4] and the death receptor/extrinsic pathways [5]. The mitochondrial pathway is often initiated by intracellular stresses, while the death receptor pathway is initiated by the recruitment of cell surface receptors with specific ligands.

The mitochondrial pathway is tightly regulated by a group of structurally related proteins called the BCL-2 family [6]. These proteins are of two types, pro-apoptotic and anti-apoptotic, which regulate the permeability of the mitochondrial membrane. Under the influence of stress stimuli, such as the deprivation of growth factor, DNA damage, heat shock and genomic instability, the pro-apoptotic BCL-2 proteins alter the outer mitochondrial membrane by forming mitochondrial apoptosis-induced channels/pores in it [7]. These membrane channels allow the release of *cytochrome c* and other cytotoxic proteins into the cytosol. The *cytochrome c* interacts with the cytosolic adapter protein *Apaf-1* to activate a group of cysteine aspartic acid-specific proteases known as caspases, whose activation is central to apoptosis [8]. Several proteins are degraded by the caspases culminating in eventual cell death.

The extrinsic pathway is activated through diverse external signals from other cells in the body. For this pathway to be activated, the extrinsic signal may come from other cells such as the T lymphocytes [9]. The death ligands, often referred to as the FAS (also called *Apo-1* or *CD95*) ligands, bind to the death (FAS) receptors causing the oligomerisation of the receptors. This ligand–receptor complex initiates the clustering of adaptor proteins called FAS-associated death domain (FADD). The FADD protein then binds to a protein interaction domain termed death-effector domain (DED). The DED binds to a homologous motif in Procaspase-8. Upon recruitment by DED motif, Procaspase-8 oligomerisation drives its activation through self-cleavage. Active Caspase-8 then activates downstream Caspase-3, thereby committing the cell to apoptosis [10]. Just like in the case of the intrinsic pathway, several proteins including DNA fragmentation factor inhibitor are then degraded by the caspases culminating in eventual cell death.

In contrast to normal cells, cancer cells are generally less sensitive to similar stresses and tend to avoid apoptosis. The inappropriate response of a cell to undergo apoptosis is a factor in oncogenesis (cancer development) as well as other human conditions. Both the mitochondrial and the extrinsic apoptotic pathways are evaded by cancerous cells. The intrinsic pathway may be more sensitive in cancer formation than the extrinsic pathway, as many of the cellular stresses encountered by cancer cells are activators of this pathway [11]. In the mitochondrial pathway, a very common cause of oncogenesis is mutation of the p53 protein. The p53 protein is a nuclear transcription factor with a pro-apoptotic function for the regulation of the cell cycle. It is believed that the mutation of this gene alters its ability to regulate cell apoptosis, the checkpoints in the cell cycle, DNA repair, senescence and genomic integrity [12]. Hence, any mutation that causes p53 to lose any of its function will let the cell grow

indefinitely without control. Another important factor is the balance between the pro-apoptotic and anti-apoptotic members of BCL-2 proteins. Many cancers are able to evade apoptosis through the downregulation of pro-apoptotic proteins, or an increase in BCL-2 expression, thereby dysregulating the BCL-2 family members. Specifically, in cancer cells, a mutation of the BCL-2 gene that results in increased expression will suppress the normal function of the pro-apoptotic proteins. Conversely, if a mutation on the pro-apoptotic genes causes a downregulation of expression, the cell will also lose its ability to regulate apoptosis, again causing oncogenesis [12].

7.2.2 Exemplary Perspective of ATN Approach to Cancer Treatment

The discussion so far indicates that cancer cells result from a combination of factors that may have altered the cells' integrity, mechanism and structure in many different and probably random ways. Indeed, cancer cells express colossal individuality and heterogeneity, each with its own unique characteristics and highly variable and unpredictable responses. Consequently, there are no unique and uniform drugs for the treatment of cancer. Moreover, cancer cells are known to have the capability of adapting to new targeted therapies and developing drug resistance [13, 14]. Hence, a broad spectrum of therapeutic approaches may be required for cancer treatment. There are various contemporary approaches to the treatment of cancer. The particular approach or set of approaches employed will depend on the type/stage of cancer and other personalised physiological and molecular information relating to the patient. Examples of cancer treatment modalities include surgery, chemotherapy, radiation therapy, immunotherapy and hormone therapy.

7.2.3 Contemporary Modalities for Cancer Treatment

Surgery modality involves the removal of the cancer cells and probably, the surrounding tissues and lymph nodes. This approach is most effective when the cancer is still localised within its original site, which must also be accessible. There may be the rare possibility that the surgery might aid in the spread of cancer.

Chemotherapy modality [15] is a popular approach to cancer treatment, where specialised drugs such as *doxorubicin*, *methotrexate* and *cisplatin* are injected into the body to kill cancer cells. It is a systemic treatment, meaning that the drugs flow through the bloodstream to nearly every part of the body. Unlike surgery, which targets a specific location, chemotherapy targets all body locations that are accessible to blood flow. Chemotherapy primarily works by acting in many inhibitive ways to disrupt the division of cancer cells. It is good at killing cells that are dividing rapidly like the cancer cells and other cells in the body. As a result, the unintended damaging

of other healthy cells in the body gives rise to side effects such as loss of hair, poor appetite, nausea and vomiting, diarrhoea or mouth and lip sores [16].

Like the surgery modality, the radiation modality [17] targets cancers localised in the body. Radiation uses a directed high dose of X-ray beam to destroy cancer cells by inflicting overwhelming damage to their DNA, which causes the cells to stop dividing and die. The side effects of radiation are usually mild and depend on the amount of radiation given (the dose), the part of the body that is treated and the individual patient's response [18].

Immunotherapy modality [19] aids the body's natural ability to fight diseases to destroy cancer cells. Monoclonal antibodies, interferon, interleukin-2 and colony-stimulating factors are some types of biological therapies. The side effects caused by biological therapy vary with the specific mode of treatment. In general, these treatments tend to cause flu-like symptoms, such as fever, chills, muscle aches, loss of appetite, weakness, nausea, vomiting, diarrhoea and swelling [20].

In the use of hormone therapy [21] to treat cancer, certain cancers that depend on hormones for their growth are targeted. Oncogenesis associated with certain categories of cancer such as breast and prostate cancers depend on hormones to develop. This therapy may involve the removal of certain organs that produce some of the hormones that promote cancerous growth or using drugs to stop the secretion of such hormones. Some of the side effects include fluid retention, tiredness, weight gain, vomiting, nausea and loss of appetite [22]. Other effects include the loss of the functionalities associated with the affected hormones.

7.2.4 Hallmarks of Cancer Diseases

In [23], the hallmarks of cancer are illustrated (see Fig. 7.1). These include biological capabilities such as evading apoptosis, evading destruction by the immune system, evading cell growth suppressors, programming energy metabolising, promoting angiogenesis, facilitating endless replicative potential, sustaining proliferative signalling and triggering metastasis. These capabilities are underlined by genome instability, mutations and tumour-promoting inflammation. An understanding of these hallmarks is crucial to providing a solid foundation for understanding the biology of cancer and projecting novel and effective therapeutic approaches to the disease.

7.2.5 Possible Directions of ATN Solution to Cancer Treatment

While there have been many solutions and treatments proposed and applied to cancer treatment, the disease has remained elusive to any permanent and unified treatment. This is basically as a result of the complexity and heterogeneity of cancer biology

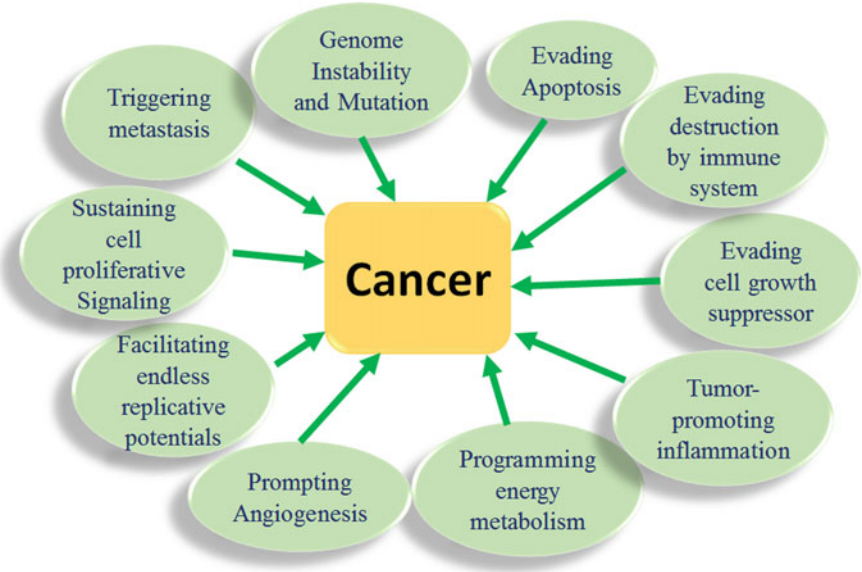

Fig. 7.1 Therapeutic targeting of the hallmarks of cancer

as well as the incomplete understanding and unpredictability of the disease. The nature of cancer, summarised in the hallmarks depicted in Fig. 7.1, is rooted in fundamentally entangled molecular mechanisms of cell operation, which equip it with very resilient capabilities and incredible survival strategies. Therefore, there is the need to explore more options in the frontier of the war against cancer. For the fact that cancer manifest as a result of fundamental mechanisms of cell operation, a multi-facet approach to cancer research and treatment is a promising option. Such effort that would unite ideas and experts from a broad cross section of related and unrelated fields could help in tackling this difficult health challenge and enable the development of a permanent cure.

One such option is rooted in the principle of nanomedicine and ATN in particular, which are purely interdisciplinary medical solutions. Indeed, modalities such as chemotherapy, radiation therapy, immunotherapy, hormone therapy and even surgery, can be offered on the platform of the ATN solution in a more effective way. This can be achieved by using various techniques/principles from the nanomedical arsenal such as targeted drug/agent delivery, nanorobotics, molecular communication, systems biology and other ATN subsystems and concepts.

The ATN solution promises to treat the cancer problem as a communication problem with a communication engineering solution. In this sense, cancer is considered in part as a breakdown of intercellular regulation for which systems biology ideas and tools built upon the principles of communication engineering can be employed

to acquire an in-depth, unified understanding of the cancer phenomena and characteristics. This will promote the discovery of new drugs and approaches for the development of vaccines. The ATN tool of targeted drug delivery can help to improve drug therapeutic index by ensuring efficacious bioavailability of cancer therapeutic nanoparticles at the targeted sites at reduced toxicity. In vivo real-time molecular sensing can be used to achieve more sensitive and early cancer diagnosis. Particulate imaging agents can be employed to achieve deep tissue visualisation of cancer cells and the therapeutic process. The ATN solution can also address the heterogeneity challenge in cancer occurrence by employing a personalised approach to treatment. For instance, it is known that if the human epidermal growth factor receptor 2 (Her2) is present in breast cancer cells, certain cancer drugs that specifically target this growth factor receptor can be used to kill those cancer cells. However, if Her2 is not present, then such drugs will be ineffective [24]. Moreover, with the real-time monitoring of the therapeutic process, challenges such as drug resistance and behavioural change in the disease pathology can be observed and addressed.

7.3 ATN Application to Alzheimer's Disease

7.3.1 Alzheimer Disease Pathophysiology and Pathways

Alzheimer's disease is an irreversible neurodegenerative disorder with a long preclinical progressive course, and is the leading cause of dementia, which is prevalent among senior citizens. It is presently incurable and marked by reasoning and interactive impairment that considerably interfere with social and occupational capability of the patient. It affects over 35 million people worldwide, and one in nine over the age of 69 [25].

The brain is basically composed of neurons, which are interconnected to form a vast network of neuro-signalling highways and tracks. Each neuron is connected to another through the synapse, which enables the transmission of information from one neuron to another as the signal propagates through the neuronal network. First described in 1906 by Dr. Alois Alzheimer when he was performing a histopathological examination for one of his patients, Alzheimer's disease is pathologically characterised by the formation of two lesions, namely the extracellular senile plaques and intracellular neurofibrillary tangles [26, 27] depicted in Figs. 7.2 and 7.3. The formation of these lesions starts long before the symptoms of the disease begin to manifest. The senile plaque is composed of the beta-amyloidal protein [26], while the neurofibrillary tangles are composed of modified tau proteins [27]. The formation of the plaques and tangles alters/disrupts neuron-to-neuron signalling, which impairs brain function.

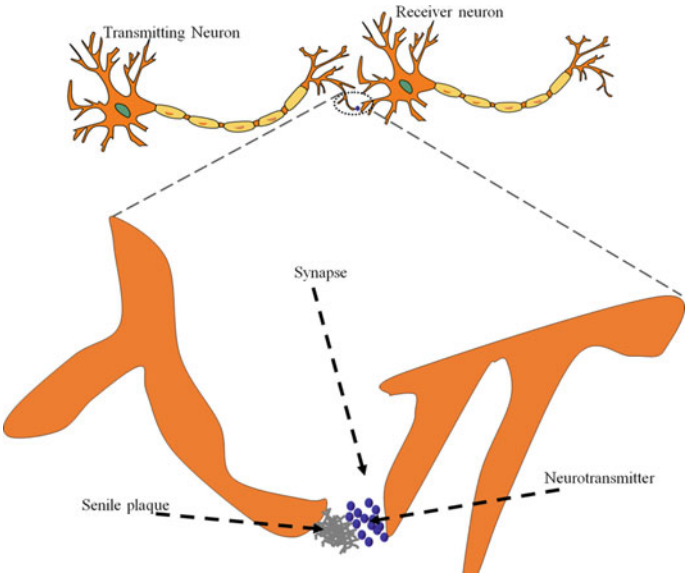

Fig. 7.2 Formation of extracellular senile plaques

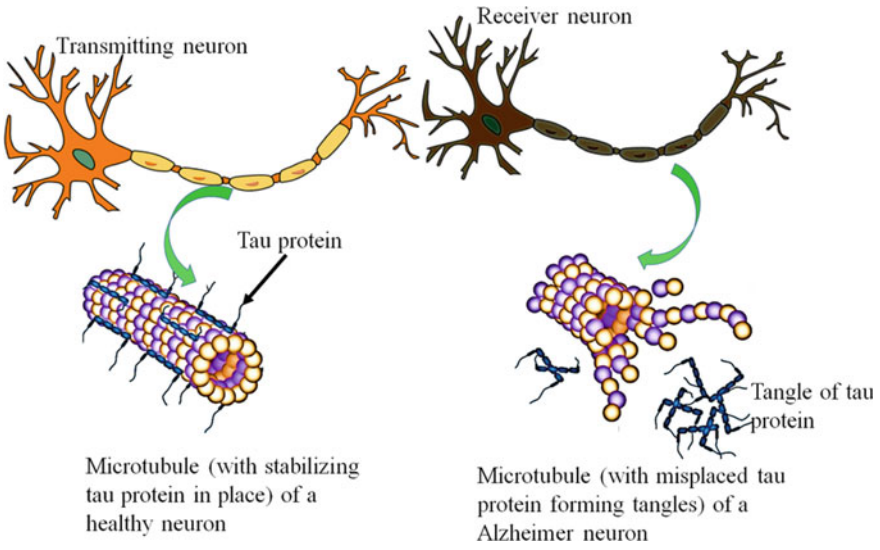

Fig. 7.3 Formation of intracellular neurofibrillary tangles

To address the Alzheimer's disease challenge, advances in the field of pathogenesis have inspired researchers to investigate and develop pharmacological therapeutics aligned towards the pathophysiological events of the disease. However, the complete understanding of the factors, mechanism, sequence of events and phenomena that result in the formation of the plaques and tangles (pathogenic process) is still elusive. Hence, contemporary treatment approaches have minimal impact on the disease. These current therapeutics only slow down disease progression and offer symptomatic relief.

7.3.2 Exemplary ATN Solution Perspective to Alzheimer's Disease Treatment

Despite the large amount of scientific research and invested financial resources, prevention strategies and effective therapy for Alzheimer's disease are yet to be achieved, which is basically due to the fact that the disease is still not well understood. The fundamentally accepted hallmarks of Alzheimer's disease pathology are the build-up of amyloid plaques, the formation of neurofibrillary tangles and eventual neuronal degeneration. However, numerous questions are yet to be answered. For instance, what is the exact sequence of the molecular mechanisms that lead to the formation of the senile plaques and the tangles? Which of the phenomena occur to trigger the occurrence of the other? What is the role of genetic (family history) and environmental risk factors (such as injury and climate) in the occurrence of the disease? And, how can the disease be accurately diagnosed much earlier?

As is always suggested, and rightly so, for many life challenges that have no known solution, the diagnostic and therapeutic challenges of the Alzheimer's disease require interdisciplinary research efforts. Again, nanomedicine certainly bears promising new approaches for addressing the Alzheimer's disease challenges [28, 29]. Nanomedicine tools such as the use of nanosystems with highly precise and sensitive capabilities for early diagnosis, and nanovectors for precise and effective delivery of diagnostic/therapeutic/monitoring agents, can provide more effective ways of addressing the disease challenges. For instance, like for any disease but especially in the case of the Alzheimer's, early diagnosis is vital for effective treatment and the prevention of further neurodegeneration. Since, the degeneration starts long before symptoms appear, early detection is possible when the right tools are available. The currently used diagnostic tools, such as clinical assessments, neuroimaging, neuropsychological testing and the detection of cerebrospinal fluid biomarkers [3], cannot be used to achieve early detection. Nanosystems with high-molecular level sensitivity that are delivered directly into the brain tissues bear great potential in achieving early detection of disease pathology [30]. Also, the delivery of drugs/agents to the defective neurons requires that the drugs/agents be able to cross the blood–brain barrier (BBB) and reach pharmacologically relevant levels. Nanosystems with specialised surface chemistry can handle such task [31, 32].

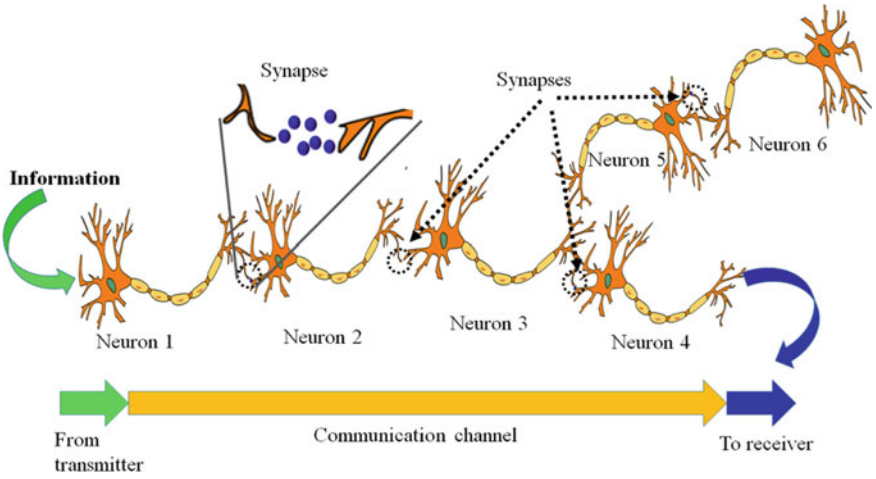

Fig. 7.4 Simple neuronal circuit

However, any curative measure for the disease requires complete understanding of its molecular mechanism. One of the approaches to achieving this understanding is to model and analyse the entire neuronal signal propagation from the perspective of communication engineering. Indeed, all neurological disorders are due to disruption of the communication channel between one neuron and another, such as in the circuit depicted in Fig. 7.4. Molecular communication, which is part of the fabric of the ATN solution, can enable the systems biology theoretic modelling and promote a deeper understanding of the Alzheimer's disease in a new way. This approach will also provide the capability to analyse pathological conditions on an individual basis in order to personalise treatment. Moreover, molecular communication engineering can provide specialised nanosystems in the form of synthetic neurons to replace degenerated neurons or reconfigure damaged signalling pathways to re-establish communication, thereby delivering neuro-regeneration and neuro-protection capabilities in the disease treatment.

Further, the integration of ATN tools such as body area networks and off-body networks will provide extended capability for more efficient real-time monitoring and control of the treatment process.

7.4 ATN Application to HIV Treatment

7.4.1 HIV Pathophysiology and Pathways

The human immunodeficiency virus (HIV) is a virus that attacks the immune system, thereby causing the disease called acquired immunodeficiency syndrome (AIDS). The virus acts by attacking the immune cells, thereby preventing them from fighting

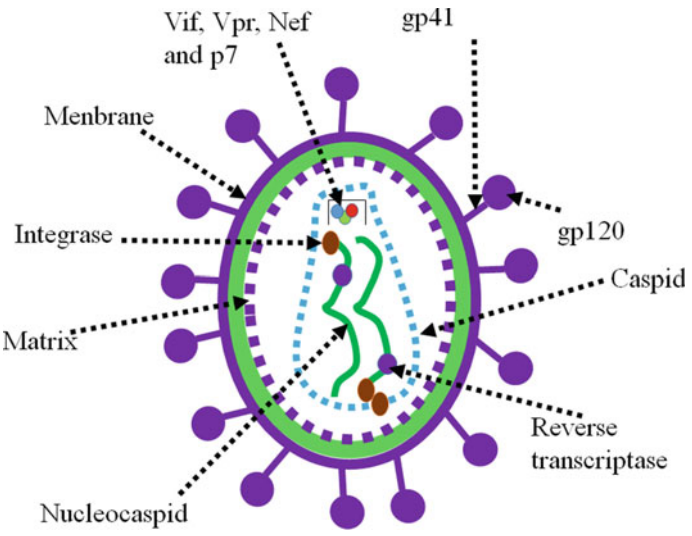

Fig. 7.5 Schematic of the HIV lentivirus

other infections that may arise in the body, which will ultimately kill the patient. The immune system protects the body by identifying invading antigens on pathogens such as bacteria and viruses and attacking them. The interaction between the immune cells/antibodies and the antigens on the pathogens induces a state of sensitivity and immune responsiveness, which ultimately destroys the antigen, allowing the body to be free of infections.

The immune system basically consists of systems such as the blood, lymph nodes/lymphatic vessels, adenoids, spleen, bone marrow, tonsils, thymus gland and appendix [33]. These components are vital in the production and development of lymphocytes, namely T lymphocytes (or T cells) or white blood cells and B lymphocytes (or B cells). The T lymphocytes basically regulate the immune system and kill cells that bear specific target antigens. On the other hand, the B lymphocytes provide antibody immunity and can recognise specific antigen targets and secrete specific antibodies, which are highly specialised serum protein molecules. These antibodies then coat antigens, thereby making the antigens more vulnerable to phagocytosis, or trigger a complement system that informs an inflammatory response.

The specific attack on the T lymphocytes (T helper cells) by the HIV destroys these cells, and the resultant replication of the virus weakens the immune system in general, leaving the body vulnerable to infections. The schematic of the HIV lentivirus, which is about 100 nm in diameter, is shown in Fig. 7.5. It consists of a cylindrical centre enclosed by a sphere-shaped lipid bilayer envelope. On the surface membrane are two viral glycoproteins, gp120 and gp41, which play an important role in the virus attack mechanism. To enter and attack the cell, the gp120 and gp41 mediate the recognition of the surface receptors (CD4 and CCR5) specifically expressed on the

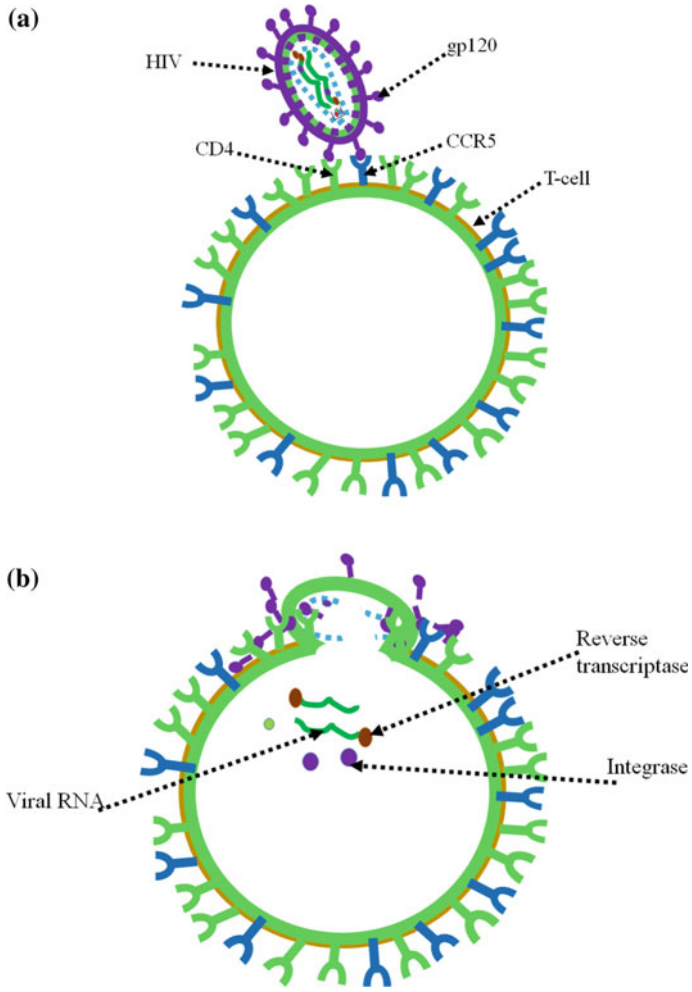

Fig. 7.6 Schematic of the HIV invasion of the T cell: **a** The virus approaches the T cell and binds to its CD4 and CCR5 receptors. **b** The bond enables it to fuse to the membrane of the T cell and empty its genetic material into the T cell's cytoplasm

surface of the T cell of the host [34]. This enables the virus to attach itself to the receptors, fuse to the cell membrane, and empty its genetic material into the host cell to invade it, as illustrated in Fig. 7.6. The viral capsid encloses two single-stranded copies of the viral RNA, as well as multiple proteins and enzymes necessary for HIV replication and maturation, which include reverse transcriptase and integrase. Various accessory regulatory proteins such as the viral infectivity factor (Vif), viral protein *R* (vpr), negative regulatory factor (Nef) and the viral structural proteins like the nucleocapsid protein p7, are important in the viral replication and for increasing

HIVs contagion rate. Once the viral RNA, the accessory regulatory proteins and the structural proteins are emptied inside the host T cell, the cell's machinery can replicate the virus using these viral materials, and go on to infect more T cells.

7.4.2 Exemplary ATN Solution Perspective on HIV Treatment

HIV infection has become one of the most devastating diseases in the contemporary world and has remained largely incurable despite the enormous scientific and financial resources having been dedicated to finding a cure. The hallmark of HIV infection is characterised by progressively profound immunodeficiency, a long clinical latency period and opportunistic infections [35–37]. Typically, the replication of the virus within the T lymphocytes that express CD4 cells results in the qualitative and quantitative depletion of the CD4 cell counts, a phenomenon on which contemporary diagnostic steps depend [38].

From the time the virus was identified as the cause of the disease until now, enormous research efforts have been intensely channelled into finding prevention and curative strategies for the disease. The contemporary efforts have resulted in the development of highly active antiretroviral therapy, which involves a combination of antiretroviral drugs. These drugs have been able to act on the disease in a way that aids in extending the lifespan of the HIV-infected patient. The goal of the contemporary treatment is to prevent the immune system from deteriorating to the point that opportunistic infections become more likely. The challenges with this therapeutic approach are schematically illustrated in Fig. 7.7.

Ideally, contemporary HIV disease therapy works by inhibiting the various viral enzymes critical to the replication of the virus. These enzymes are primarily the reverse transcriptase, integrase and protease. With this approach, the virus may likely remain in the body, but will be unable to replicate as one or more of the phases of its replication cycle are inhibited by the antiretroviral drugs. However, inappropriate dose and poor bioavailability of the therapeutic molecules will definitely impact on the antiretroviral drugs' effectiveness. With the right dose and bioavailability, the replication process is suppressed as long as the patient continues to take the drugs diligently. Excess dose results in side effects, which may include fatigue, diarrhoea, insomnia, rashes and numbness. However, subtherapeutic dose (which may be as a result of non-adherence to daily dosage recommendations) and poor bioavailability result in the cellular and anatomical regions across the body, often termed sanctuary sites, where the virus can continue to replicate in sub-therapeutic drug concentrations [39]. Moreover, the current therapy does not eliminate the viruses from the body; hence, it is employed to simply extend the lifespan of the patient. For patients whose immune systems are greatly weakened, the current approach may not offer the desired immune reconstitution. Therefore, there is a global quest for the development of effective permanent therapy as well as the possibility of vaccines.

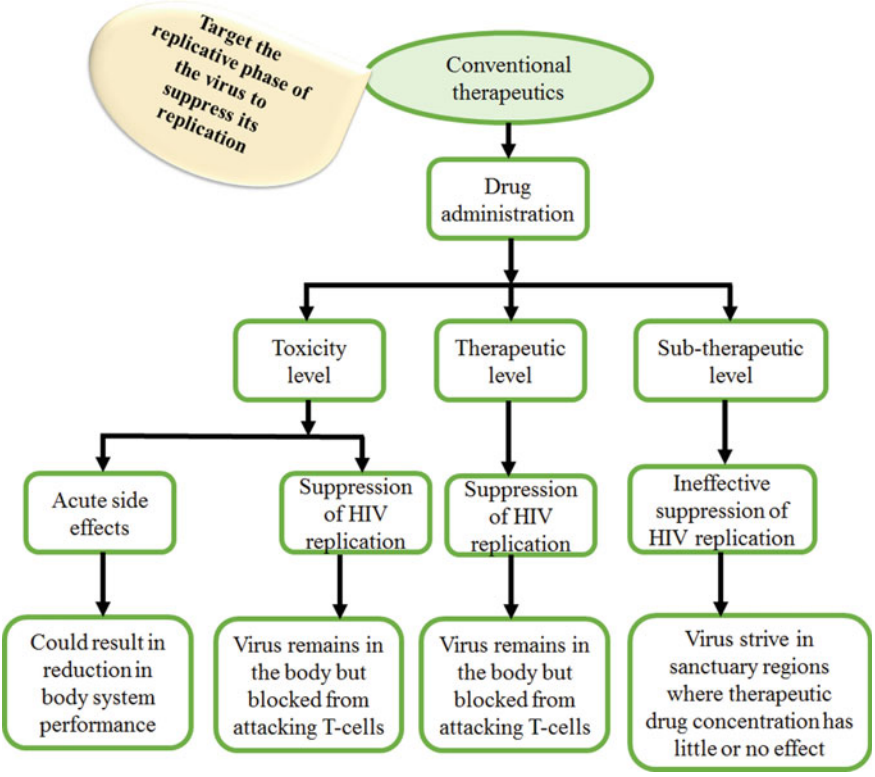

Fig. 7.7 Schematic illustration of the challenges associated with the contemporary therapeutic approach to HIV

It is also important to note that the characterisation of the many incurable diseases is centred on the uniqueness of detailed molecular profiling of the patient. This characterisation is distinctive for each HIV patient. For instance, it is expected that the ability of the virus to mutate over the course of administration may vary in different patients at different times [40]. Hence, the effectiveness of a set of antiretroviral drugs is dependent on finding the right treatment for the right patient at the right time. and it is based on detailed molecular profiling of the patient.

Again, nanomedicine, which sits on the ATN platform, promises to offer unique, interesting, novel and effective approaches to addressing the HIV challenge [41–43], as depicted in Fig. 7.8. For instance, molecular-level communication mapping, nanomedicine tools such as targeted drug delivery (to enhance bioavailability), high-precision and sensitive nanosystem and gene editing, networking capability among sets of nanosystems and robotics capabilities can provide more effective ways of tackling the HIV menace. A nanomedical approach has the potential to provide complete eradication of the virus, resulting in a cure. This can be achieved by molecular communications, nanoscale-level modelling and analysis of the disease with a view

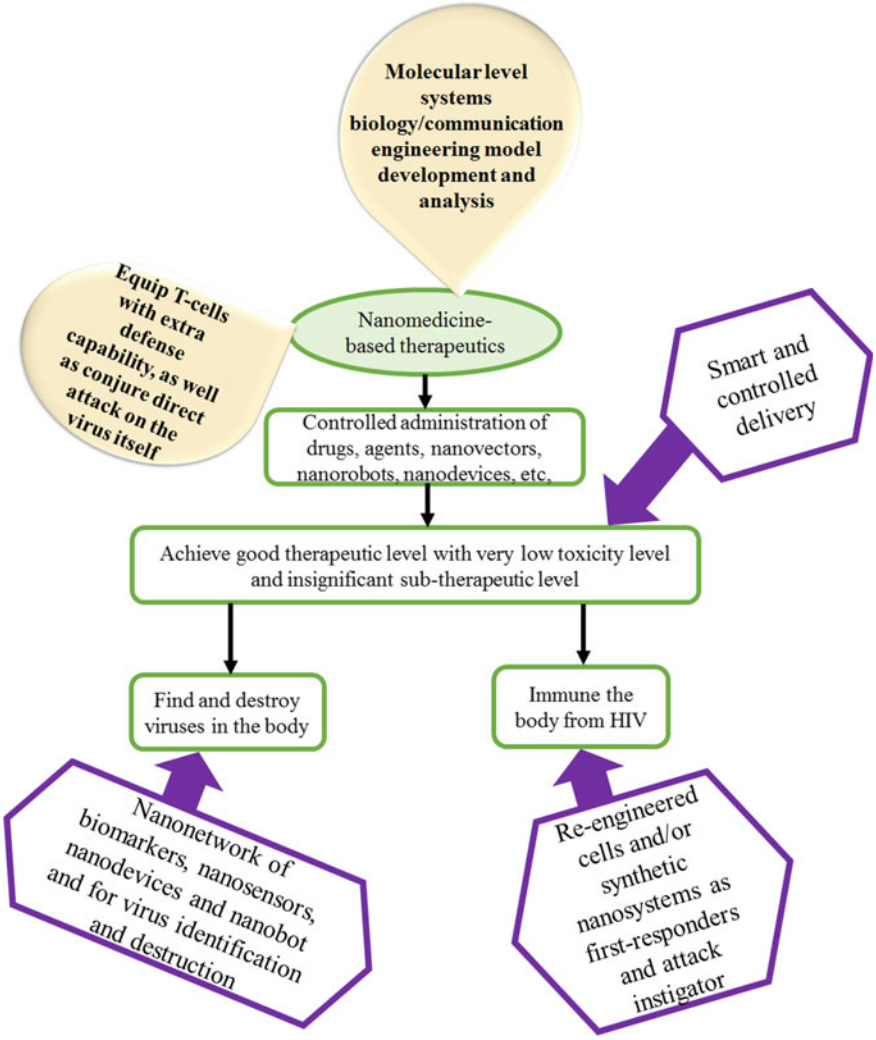

Fig. 7.8 Schematic illustration of the ATN approaches to HIV therapeutics

to obtaining a deeper understanding of the disease. Such exercises will facilitate the definition of accurate strategies for therapy and vaccination. For example, synthetic T cells or T cells extracted from HIV-positive patients with one or two of the receptors modified by gene editing or other related processes, can be used to fight the disease [44]. Moreover, by using ATN tools such as body area networks and IoBNT, real-time monitoring of therapeutic processes and remote control over the process can be achieved.

7.5 ATN Application to CVD Treatment

7.5.1 CVD Pathophysiology and Pathways

Cardiovascular diseases (CVD) such as heart failure, myocardial infarction, stroke and hypertension are among the most common causes of death in many countries of the world [45, 46]. As the name suggests, CVD encompasses all pathologies of the heart (cardiac) or circulatory system (vascular). The disease called atherosclerosis, which involves the building up of plaque resulting in the hardening and the narrowing of arteries, is generally implicated in CVD. The formation of plaque is driven by a low level of anti-oxidant enzymes such as glutathione peroxidase. A low level of this enzyme results in the oxidation of reactive oxygen species such as superoxide anion, hydrogen peroxide, lipid peroxides and peroxynitrite. Also, an increase in the production of *angiotensin II* (a hormone that regulates blood pressure and mediates tissue injury) and a reduction in glutathione peroxidase as results of cigarette smoking (which facilitates hypertension), result in high oxidation stress. The oxidation process eventually leads to enhanced inflammation and the eventual formation of plaque.

The plaque formed in the blood vessels may partially or completely occlude oxygen-rich blood from some cells. Partial occlusion results in poor blood circulation, which can have negative and consequential effects on the entire body. Depending on where the plaque is formed, symptoms of this condition may include fatigue, shortness of breath, feeling light-headed, loss of memory and unexplained headaches, cramps and numbness, loss of appetite, unexplained weight loss, colour swelling in the hands/feet/ankles and change in skin. Complete blocking of the blood vessel will reduce the oxygen and nutrient supply to the cells beyond the occlusion points, thereby triggering unintended apoptosis and inflammation in the cells. In the heart, *angina* will occur and possibly heart failure. In the brain, ischemic attack or stroke may result. When it is associated with the blood vessels leading to the arms and legs, peripheral artery diseases arise. If the occlusion is in the arteries leading to the kidneys, high blood pressure or kidney failure develop. In some scenarios, the plaque can burst, triggering a blood clot called an embolus, which can break off from the atherosclerotic plaque and travel in the bloodstream to lodge in a blood vessel [47]. The process can result in an embolic stroke [48].

7.5.2 Exemplary ATN Solution Perspective on CVD Treatment

The contemporary approaches to the treatment of CVD are basically either non-invasive or invasive [49, 50]. The non-invasive therapies include prescription medication and lifestyle alterations, while the invasive approach includes surgical therapy. These approaches act to inhibit enzymes and block receptors implicated in the disease [51, 52]. However, to maintain good health, many CVD patients are required

to be on medications for the rest of their lives, since no permanent cure is available. Consequently, the development of novel techniques for the early detection and treatment of CVD is crucial.

Nanomedicine in general, and ATN, in particular, may offer a novel approach and tools for monitoring, diagnosing, preventing, repairing damaged cells and ultimately treating the disease. ATN can offer the following advantages for CVD treatment.

i. Like most chronic diseases, the cause of CVD lies in altered biosignalling, which can be studied under the platform of molecular communication. Hence, ATN can offer deeper and more accurately personalised molecular-level modelling that is based on molecular communication concepts and tools. This may result in the discovery of novel therapeutic approach that may include gene therapies.
ii. Early diagnosis using nanoscale tools, devices and mechanisms is possible with ATN. Since autopsy studies show that atherosclerosis develops slowly over many years, nanoscopic tools such as high-precision and sensitive nanosystem can be used in the early detection of the onset of atherosclerosis.
iii. Targeted and smart delivery of CVD therapeutic molecules to any defective cell in the body where they are needed using nanosystem network is achievable.
iv. Synthesising new nanosystems by means of tissue engineering to replace defective valves, damaged heart muscle, clogged blood vessels, etc. can be realised. The ATN will also handle the transportation of the synthetically engineered biological systems to different locations in the body for therapeutic purposes. Nanoscale surgery may also replace contemporary surgical practice such as coronary artery bypass grafting and angioplasty.
v. Molecular imaging agents can be used to visualise and identify disease more specifically.
vi. By using ATN tools such as body area network and IoBNT, real-time monitoring of therapeutic processes and remote control over the process can be achieved. Devices such as biosignal sensors and implants can be used to monitor and correct some anomalies.

In the near future, it is considered that the nanomedicine approach will enable the establishment of accurate ‘personalised medicine’. It is also considered that gene therapies for cardiovascular applications will have potential usage in the field of cardiovascular applications in coming years.

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