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

U. Chude-Okonkwo et al., *Advanced Targeted Nanomedicine*, Nanomedicine and Nanotoxicology, https://doi.org/10.1007/978-3-030-11003-1_3

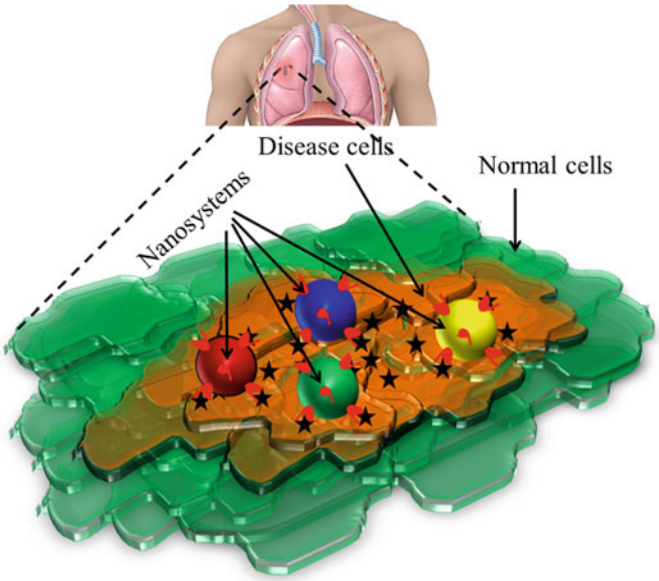

Fig. 3.1 Schematic of ATN in-body nanonetwork of nanosystems

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

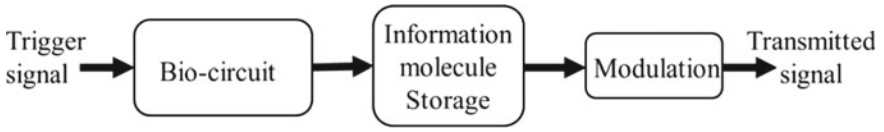

Fig. 3.2 Generalised block diagram of an ATN pre-encoded nanotransmitter

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

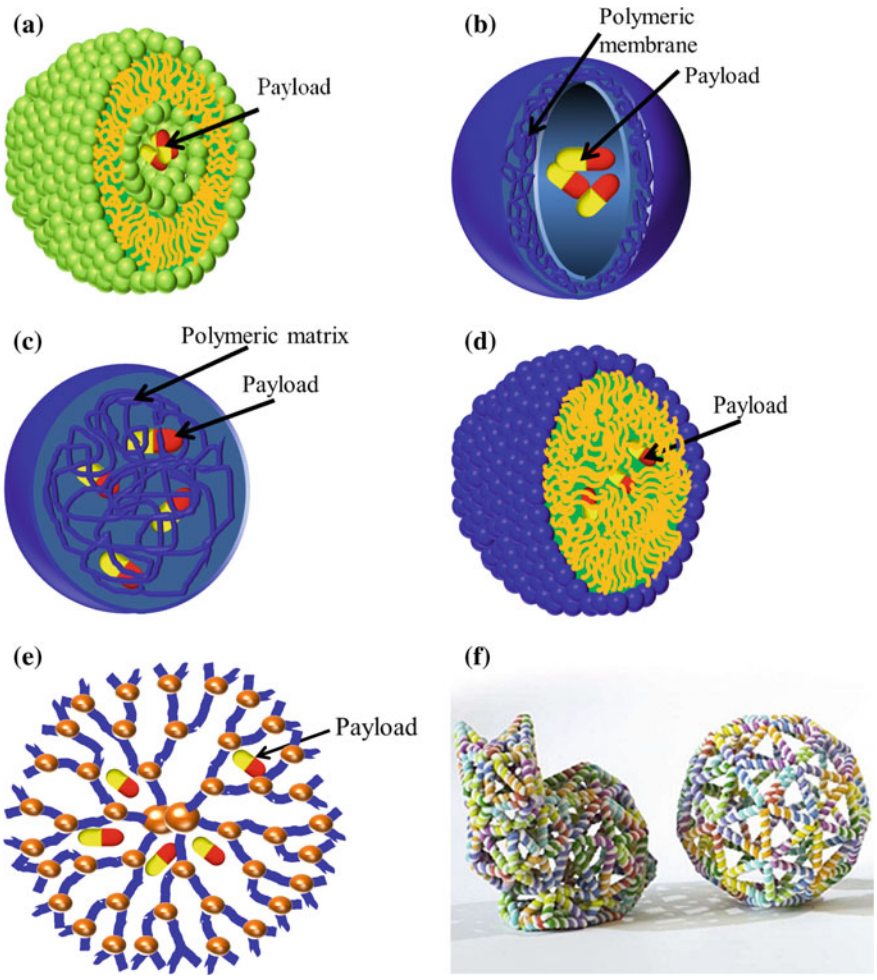

Fig. 3.3 Examples of ATN nanotransmitter structures: **a** liposome, **b** nanocapsule, **c** nanosphere, **d** micelle, **e** dendrimer, **f** DNA capsules Reprint from [12]. Copyright (c) 2017, with permission from IEEE

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

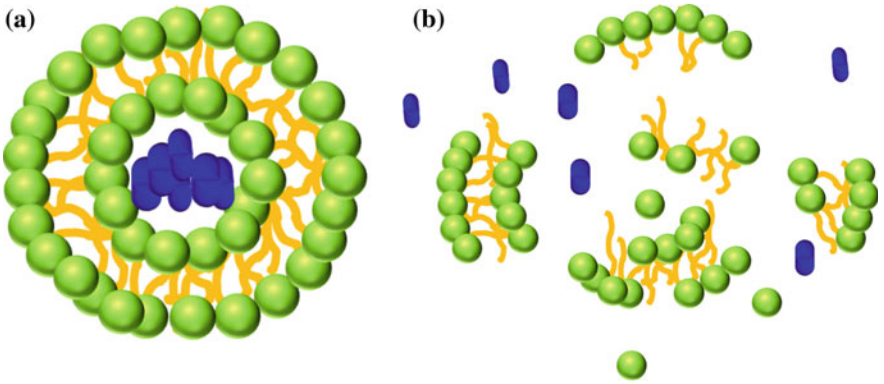

Fig. 3.4 Illustration of liposome information molecule release mechanism indicating, **a** liposome encapsulating information molecules, and **b** liposome rupture and release of information molecules

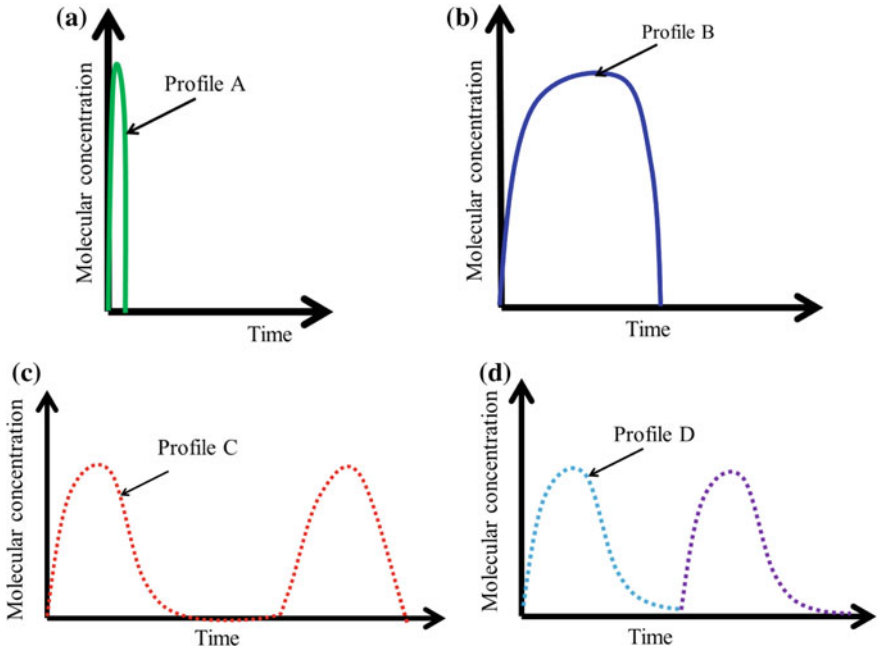

Fig. 3.5 Typical examples of the release profiles depicted as **a** instantaneous release, **b** gradual release, **c** multiple releases of one molecular species, and **d** multiple release of two molecular species

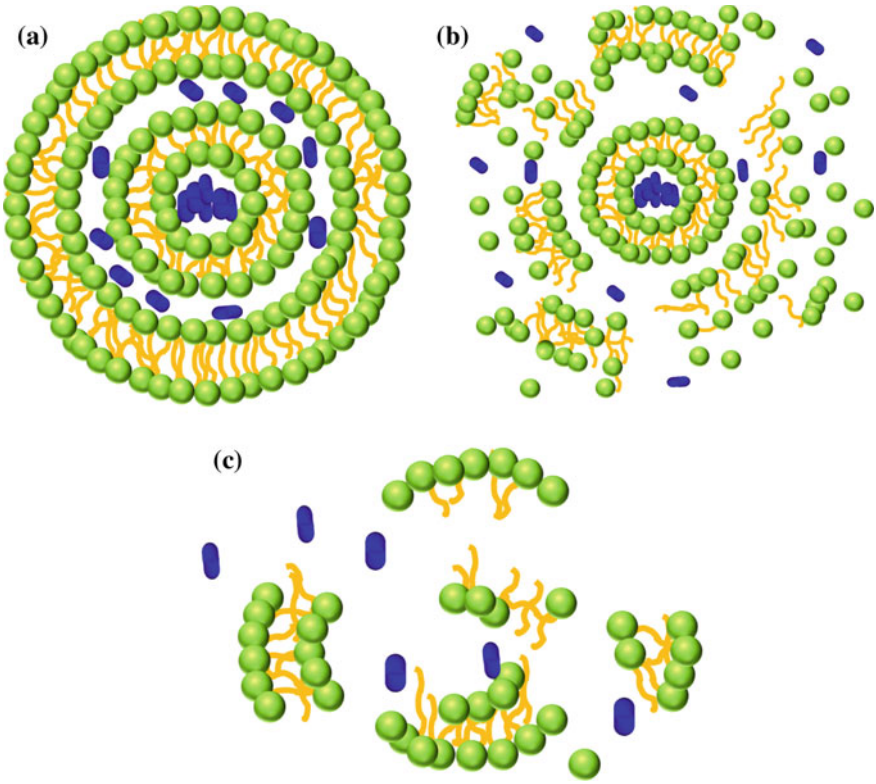

Fig. 3.6 Illustration of multilayer liposome release mechanism indicating, **a** liposome encapsulating information molecules in two layers, **b** rupture and release of information molecules at first layer, and **c** rupture and release of information molecules at the second layer

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.

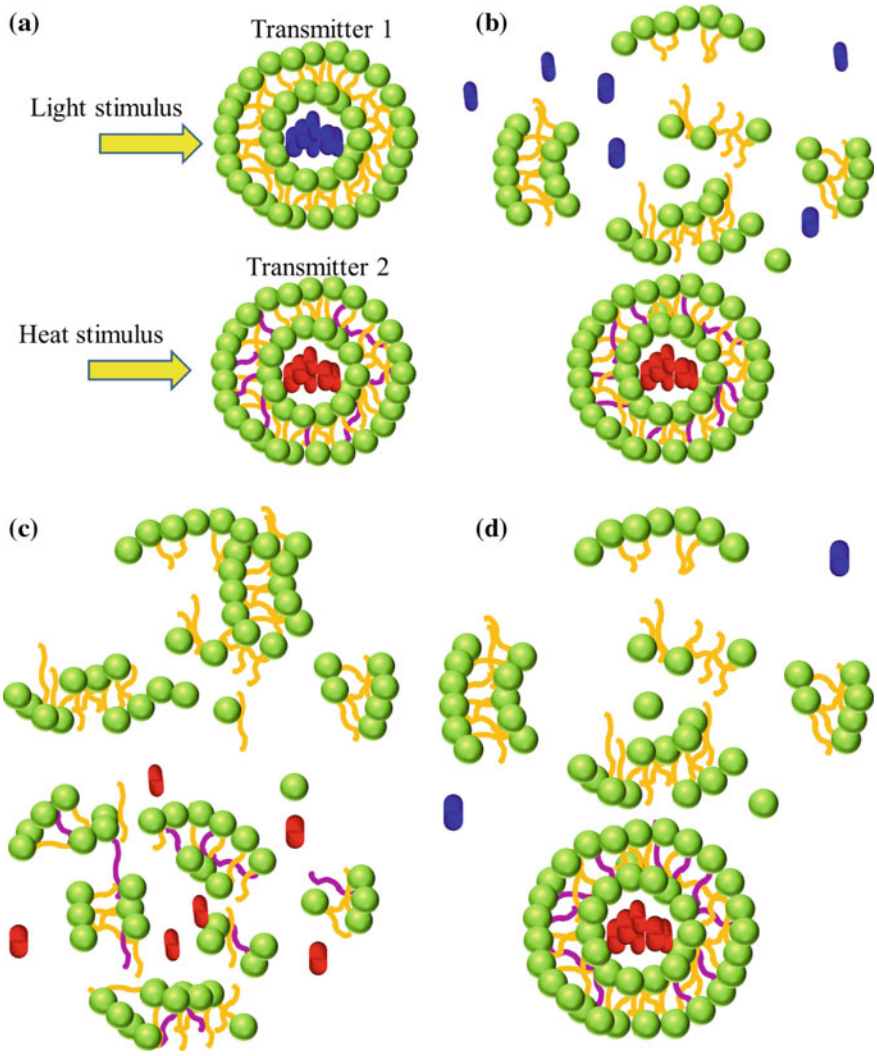

Fig. 3.7 Illustration of two single-layer liposome release mechanisms indicating, **a** the two single-layer liposome encapsulating different information molecules, **b** rupture and release of information molecules by one liposome, **c** release molecules diffuse away over a certain period, and **d**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

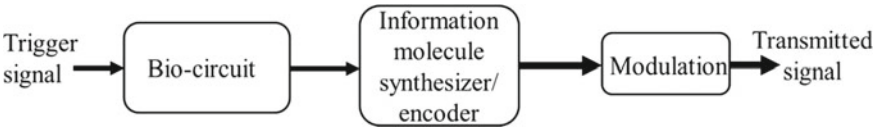

Fig. 3.8 Generalised block diagram of an ATN generic nanotransmitter

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

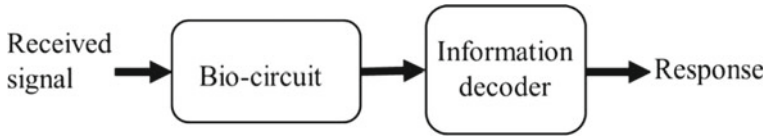

Fig. 3.9 Generalised block diagram of an ATN generic nanoreceiver

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].

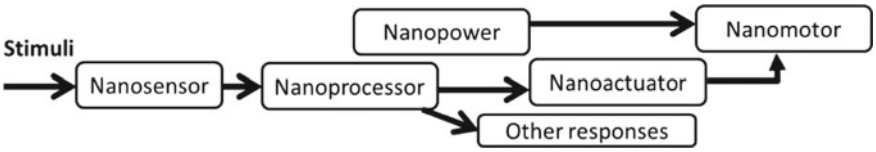

Fig. 3.10 Generalised block diagram of an ATN nanorobot

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).

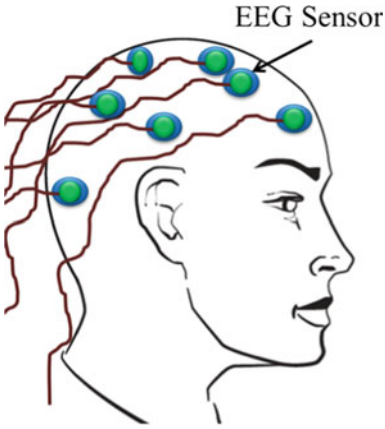

Fig. 3.11 Schematic diagram of EEG sensors on a human body

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.

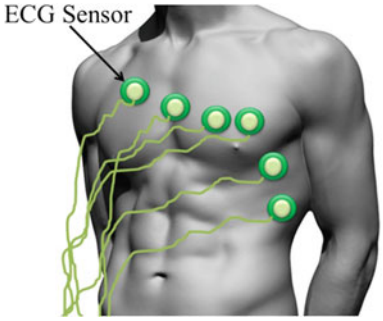

Fig. 3.12 Schematic diagram of ECG sensors on a human body

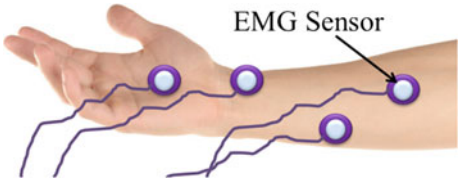

Fig. 3.13 Schematic diagram of EMG sensors on a human body

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

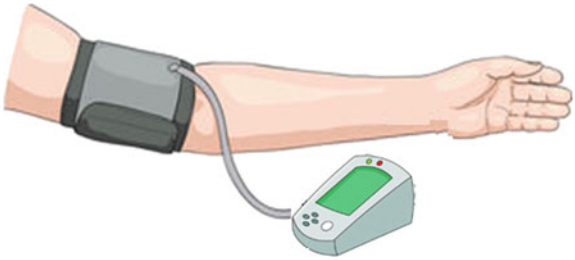

Fig. 3.14 Schematic diagram of blood pressure sensor on a human body

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.

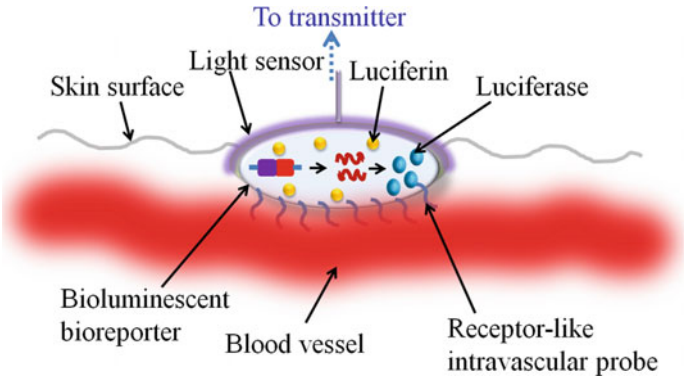

Fig. 3.15 Schematic of a typical bio-cyber interface unit Reprint from [75]. Copyright (c) 2016, with permission from IEEE

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.

References

1. Wiederrecht G (2010) Handbook of nanofabrication. Academic Press
2. Nishimura Y, Ishii J, Ogino C, Kondo A (2014) Genetic engineering of bio-nanoparticles for drug delivery: a review. J Biomed Nanotechnol 10:2063–2085
3. Yoo JW, Irvine DJ, Discher DE, Mitragotri S (2011) Bio-inspired, bioengineered and biomimetic drug delivery carriers. Nat Rev Drug Discov 10:521–535
4. Tan S, Wu T, Zhang D, Zhang Z (2015) Cell or cell membrane-based drug delivery systems. Theranostics 5:863
5. Lockney D, Franzen S, Lommel S (2011) Viruses as nanomaterials for drug delivery. Biomed Nanotechnol Methods Protocols, 207–221
6. Esfandiari N, Arzanani MK, Soleimani M, Kohi-Habibi M, Svendsen WE (2016) A new application of plant virus nanoparticles as drug delivery in breast cancer. Tumor Biol 37:1229–1236
7. Steidler L (2004) Live genetically modified bacteria as drug delivery tools: at the doorstep of a new pharmacology? Exp Opin Biol Ther 4:439–441
8. Yacoby I, Bar H, Benhar I (2007) Targeted drug-carrying bacteriophages as antibacterial nanomedicines. Antimicrob Agent Chemother 51:2156–2163
9. Su Y, Xie Z, Kim GB, Dong C, Yang J (2015) Design strategies and applications of circulating cell-mediated drug delivery systems. ACS Biomater Sci Eng 1:201–217
10. Batrakova EV, Gendelman HE, Kabanov AV (2011) Cell-mediated drug delivery. Exp Opin Drug Deliv 8:415–433
11. Boehm F (2016) Nanomedical device and systems design: challenges, possibilities, visions. CRC Press
12. Chude-Okonkwo UA, Malekian R, Maharaj BT, Vasilakos AV (2017) Molecular communication and nanonetwork for targeted drug delivery: a survey. IEEE Commun Surv Tutor 19:3046–3096
13. Rogers K (2012) The kidneys and the renal system. Britannica Educ Publ, New York
14. Milici AJ, L'Hernault N, Palade GE (1985) Surface densities of diaphragmed fenestrae and transendothelial channels in different murine capillary beds. Circ Res 56:709–717
15. Alexis F, Pridgen E, Molnar LK, Farokhzad OC (2008) Factors affecting the clearance and biodistribution of polymeric nanoparticles. Mol Pharm 5:505–515
16. Blanco E, Shen H, Ferrari M (2015) Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nat Biotechnol 33:941–951
17. Desai N (2012) Challenges in development of nanoparticle-based therapeutics. AAPS J 14:282–295
18. Longmire M, Choyke PL, Kobayashi H (2008) Clearance properties of nano-sized particles and molecules as imaging agents: considerations and caveats. Nanomedicine 3(5):703–717
19. Wiig H, Swartz MA (2012) Interstitial fluid and lymph formation and transport: physiological regulation and roles in inflammation and cancer. Physiol Rev 92:1005–1060
20. Elsaesser A, Howard CV (2012) Toxicology of nanoparticles. Adv Drug Deliv Rev 64:129–137
21. Kagan VE, Bayir H, Shvedova AA (2005) Nanomedicine and nanotoxicology: two sides of the same coin. Nanomed Nanotechnol Biol Med 1:313–316
22. Szoka F Jr, Papahadjopoulos D (1980) Comparative properties and methods of preparation of lipid vesicles (liposomes). Ann Rev Biophys Bioeng 9:467–508
23. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, et al (2013) Liposome: classification, preparation, and applications. Nanoscale Res Lett 8:102

24. Patil YP, Jadhav S (2014) Novel methods for liposome preparation. Chem Phys Lipids 177:8–18
25. Lasic DD (1998) Novel applications of liposomes. Tr Biotechnol 16:307–321
26. Shi J, He J, Deng R, Wei Y, Long F, Cheng Y et al (2017) Multilevel modulation scheme using the overlapping of two light sources for visible light communication with mobile phone camera. Opt Express 25:15905–15912
27. Kiel C, Yus E, Serrano L (2010) Engineering signal transduction pathways. Cell 140:33–47
28. Fakhrullin RF, Zamaleeva AI, Minullina RT, Konnova SA, Paunov VN (2012) Cyborg cells: functionalisation of living cells with polymers and nanomaterials. Chem Soc Rev 41:4189–4206
29. Basu S, Gerchman Y, Collins CH, Arnold FH, Weiss R (2005) A synthetic multicellular system for programmed pattern formation. Nature 434:1130–1134
30. Anderson JC, Clarke EJ, Arkin AP, Voigt CA (2006) Environmentally controlled invasion of cancer cells by engineered bacteria. J Mol Biol 355:619–627
31. Wegmann U, Carvalho AL, Stocks M, Carding SR (2017) Use of genetically modified bacteria for drug delivery in humans: Revisiting the safety aspect. Sci Reports 7:2294
32. Hess B (2000) Periodic patterns in biology. Naturwissenschaften 87:199–211
33. Polikanov YS, Blaha GM, Steitz TA (2012) How hibernation factors RMF, HPF, and YfiA turn off protein synthesis. Science 336:915–918
34. Kuran MS, Yilmaz HB, Tugcu T, Özerman B (2010) Energy model for communication via diffusion in nanonetworks. Nano Commun Netw 1:86–95
35. Chude-Okonkwo UA (2014) Diffusion-controlled enzyme-catalyzed molecular communication system for targeted drug delivery. In: 2014 IEEE Global Communications Conference, pp 2826–2831
36. Okonkwo UA, Malekian R, Maharaj BT (2016) Molecular communication model for targeted drug delivery in multiple disease sites with diversely expressed enzymes. IEEE Trans Nanobiosci 15(3):230–245
37. Oberholzer T, Meyer E, Amato I, Lustig A, Monnard PA (1999) Enzymatic reactions in liposomes using the detergent-induced liposome loading method. Biochimica et Biophysica Acta (BBA)—Biomembr 1416:57–68
38. Matsumoto R, Kakuta M, Sugiyama T, Goto Y, Sakai H, Tokita Y et al (2010) A liposome-based energy conversion system for accelerating the multi-enzyme reactions. Phys Chem Chem Phys 12:13904–13906
39. Douglas SM, Bachelet I, Church GM (2012) A logic-gated nanorobot for targeted transport of molecular payloads. Science 335:831–834
40. Li S, Jiang Q, Liu S, Zhang Y, Tian Y, Song C, et al (2018) A DNA nanorobot functions as a cancer therapeutic in response to a molecular trigger in vivo. Nat Biotechnol 36:258
41. Cavalcanti A, Shirinzadeh B, Fukuda T, Ikeda S (2009) Nanorobot for brain aneurysm. Int J Robot Res 28:558–570
42. Dollard MA, Billard P (2003) Whole-cell bacterial sensors for the monitoring of phosphate bioavailability. J Microbiol Methods 55:221–229
43. Yeo D, Wiraja C, Chuah YJ, Gao Y, Xu C (2015) A nanoparticle-based sensor platform for cell tracking and status/function assessment. Sci Reports 5:14768
44. Eckert MA, Vu PQ, Zhang K, Kang D, Ali MM, Xu C et al (2013) Novel molecular and nanosensors for in vivo sensing. Theranostics 3(8):583–594
45. Monson E, Brasuel M, Philbert M, Kopelman R (2003) PEBBLE nanosensors for in vitro bioanalysis. Biomed Photonics Handb 9
46. Gu MB, Kim HS (2014) Biosensors based on aptamers and enzymes, vol 140. Springer
47. Roberts JR, Park J, Helton K, Wisniewski N, McShane MJ (2012) Biofouling of polymer hydrogel materials and its effect on diffusion and enzyme-based luminescent glucose sensor functional characteristics. J Diabetes Sci Technol 6:1267–1275
48. Kuscu M, Akan OB (2016) On the physical design of molecular communication receiver based on nanoscale biosensors. IEEE Sens J 16:2228–2243
49. Feringa BL, Browne WR (2011) Molecular switches. Wiley
50. Li H, Qu DH (2015) Recent advances in new-type molecular switches. Sci China Chem 58:916–921

51. Sivan S, Tuchman S, Lotan N (2003) A biochemical logic gate using an enzyme and its inhibitor. Part II: the logic gate. Biosystems 70:21–33
52. Katz E, Privman V, Wang J (2010) Towards biosensing strategies based on biochemical logic systems. In: Fourth international conference on quantum, nano and micro technologies, ICQNM'10, pp 1–9
53. Privman V, Katz E (2015) Can bio-inspired information processing steps be realized as synthetic biochemical processes? Physica Status Solidi (a) 212:219–228
54. Stein V, Alexandrov K (2015) Synthetic protein switches: design principles and applications. Trends Biotechnol 33:101–110
55. Hansen CH, Yang D, Koussa MA, Wong WP (2017) Nanoswitch-linked immunosorbent assay (NLISA) for fast, sensitive, and specific protein detection. Proc Nat Acad Sci 114:10367–10372
56. Dasgupta T, Croll DH, Owen JA, Vander Heiden MG, Locasale JW, Alon U et al (2014) A fundamental trade-off in covalent switching and its circumvention by enzyme bifunctionality in glucose homeostasis. J Biol Chem 289:13010–13025
57. Ostermeier M (2005) Engineering allosteric protein switches by domain insertion. Protein Eng Design Sel 18:359–364
58. Pohanka M, Skládal P (2008) Electrochemical biosensors: principles and applications. J Appl Biomed 6(2):57–64
59. Ullah S, Mohaisen M, Alnuem MA (2013) A review of IEEE 802.15. 6 MAC, PHY, and security specifications. Int J Distrib Sens Netw 9:950704
60. Darwish A, Hassanien AE (2011) Wearable and implantable wireless sensor network solutions for healthcare monitoring. Sensors 11:5561–5595
61. Zhen B, Li HB, Kohno R (2007) IEEE body area networks for medical applications. In: 4th international symposium on wireless communication systems ISWCS, pp 327-331
62. Negra R, Jemili I, Belghith A (2016) Wireless body area networks: applications and technologies. Procedia Comput Sci 83:1274–1281
63. Smith DB, Hanlen LW (2015) Channel modeling for wireless body area networks. In: Ultra-low-power short-range radios. Springer, pp 25–55
64. Balouchestani M, Raahemifar K, Krishnan S (2013) New channel model for wireless body area network with compressed sensing theory. IET Wireless Sensor Syst 3:85–92
65. Tsolaki A, Kazis D, Kompatsiaris I, Kosmidou V, Tsolaki M (2014) Electroencephalogram and Alzheimer's disease: clinical and research approaches. Int J Alzheimer's Disease 2014:349249
66. Natarajan A, Parate A, Gaiser E, Angarita G, Malison R, Marlin B, et al (2013) Detecting cocaine use with wearable electrocardiogram sensors. In: Proceedings of the 2013 ACM international joint conference on Pervasive and Ubiquitous computing, pp 123–132
67. Giggins OM, Persson UM, Caulfield B (2013) Biofeedback in rehabilitation. J Neuroeng Rehabil 10:60
68. De Freitas GS, Mituuti CT, Furkim AM, Busanello-Stella AR, Stefani FM, Arone MMAD et al (2016) Electromyography biofeedback in the treatment of neurogenic orofacial disorders: systematic review of the literature. Audiol Commun Res 21
69. Iversen NK, Frische S, Thomsen K, Laustsen C, Pedersen M, Hansen PB et al (2013) Superparamagnetic iron oxide polyacrylic acid coated γ-Fe2O3 nanoparticles do not affect kidney function but cause acute effect on the cardiovascular function in healthy mice. Toxicol Appl Pharmacol 266:276–288
70. Heikal L, Starr A, Martin GP, Nandi M, Dailey LA (2016) In vivo pharmacological activity and biodistribution of S-nitrosophytochelatins after intravenous and intranasal administration in mice. Nitric Oxide 59:1–9
71. Lee H, Song C, Hong YS, Kim MS, Cho HR, Kang T, et al (2017) Wearable/disposable sweat-based glucose monitoring device with multistage transdermal drug delivery module. Sci Adv 3:e1601314
72. Wu JZ, Williams GR, Li HY, Wang D, Wu H, Li SD, et al (2017) Glucose-and temperature-sensitive nanoparticles for insulin delivery. Int J Nanomed 12:4037

73. Rehman A, Setter SM, Vue MH (2011) Drug-induced glucose alterations part 2: drug-induced hyperglycemia. Diabetes Spectrum 24:234–238
74. Blackburn DF, Wilson TW (2006) Antihypertensive medications and blood sugar: theories and implications. Can J Cardiol 22:229–233
75. Chude-Okonkwo UA, Malekian R, Maharaj BT (2016) Biologically inspired bio-cyber interface architecture and model for Internet of Bio-NanoThings applications. IEEE Trans Commun 64:3444–3455