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.

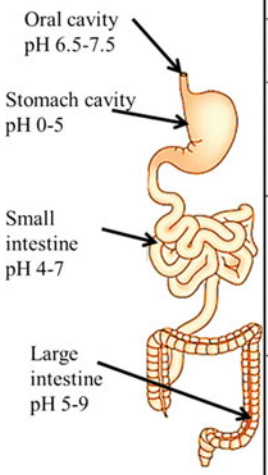
In this chapter, the different modalities for administering nanosystems into the body are explored. And based on these modalities, the different routes the nanosystems take to reach the targeted locations inside the body are discussed. Finally, the possible approaches to the representation, modelling, 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

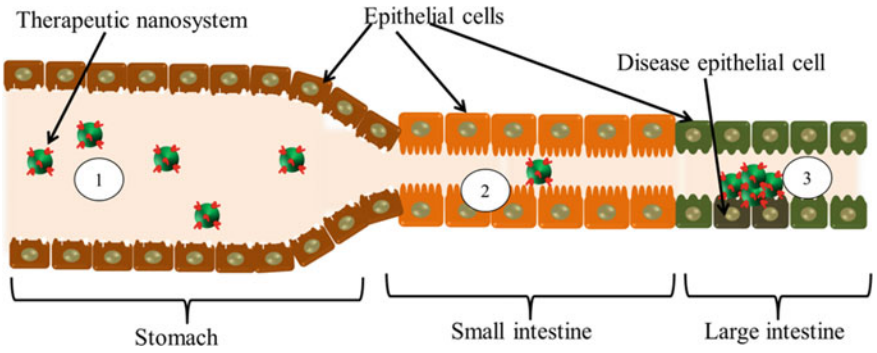


Fig. 4.2 Illustration of nanosystem journey through the GI environment

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

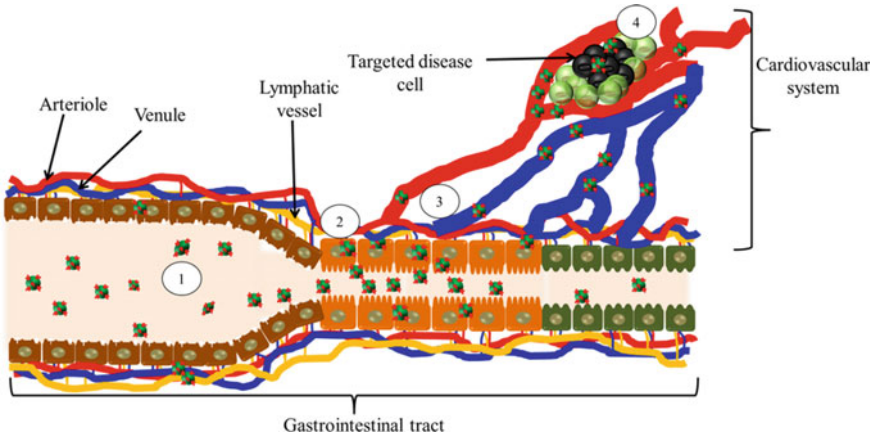


Fig. 4.3 Illustration of nanosystem journey through the non-GI environment

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].

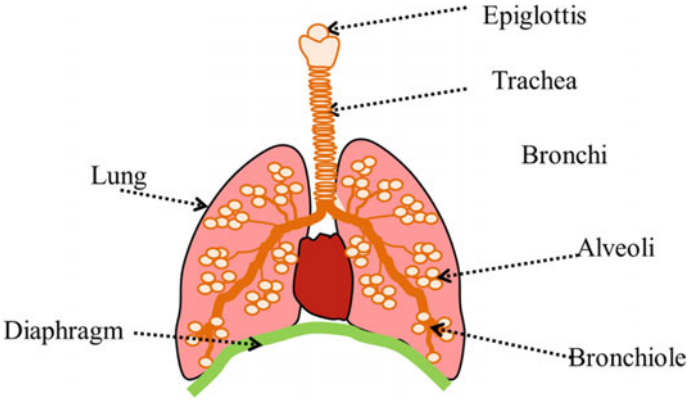


Fig. 4.4 A schematic diagram of the respiratory tract

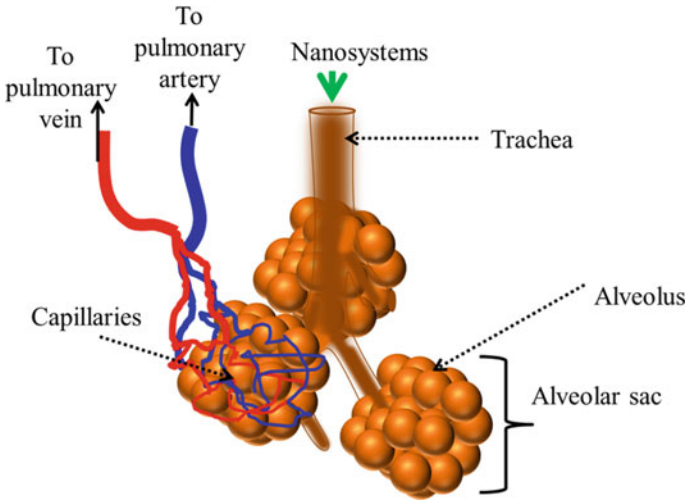


Fig. 4.5 Illustration of alveolar sacs with dense number of capillaries surrounding them

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.

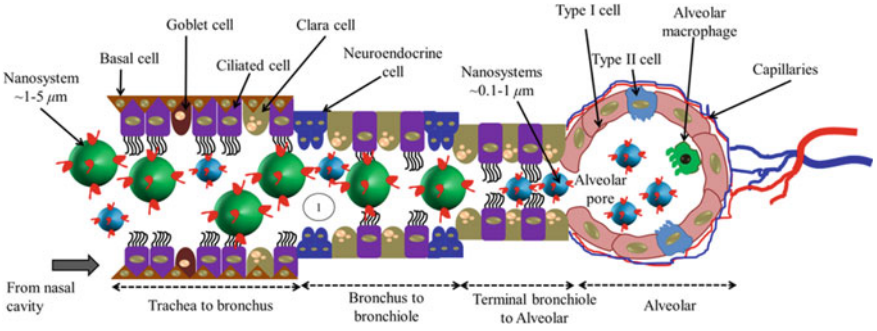


Fig. 4.6 Illustration of size differentiation of nanoparticles/systems along the pulmonary route

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.

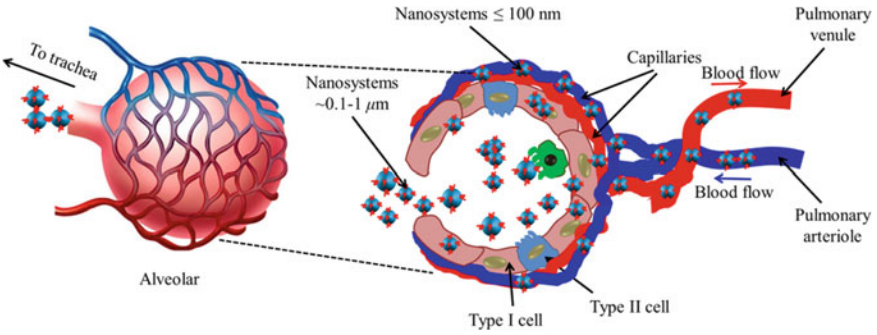


Fig. 4.7 Generalised block diagram of an ATN pre-encoded nanotransmitter

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

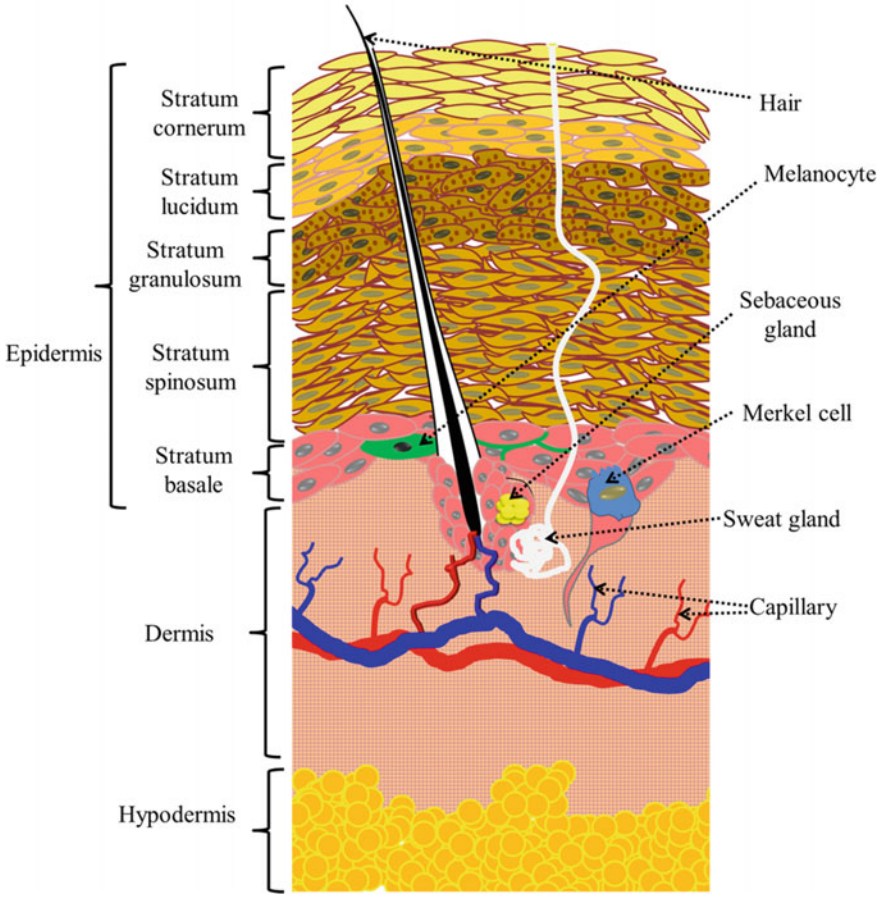


Fig. 4.8 Schematic diagram of the skin barrier

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

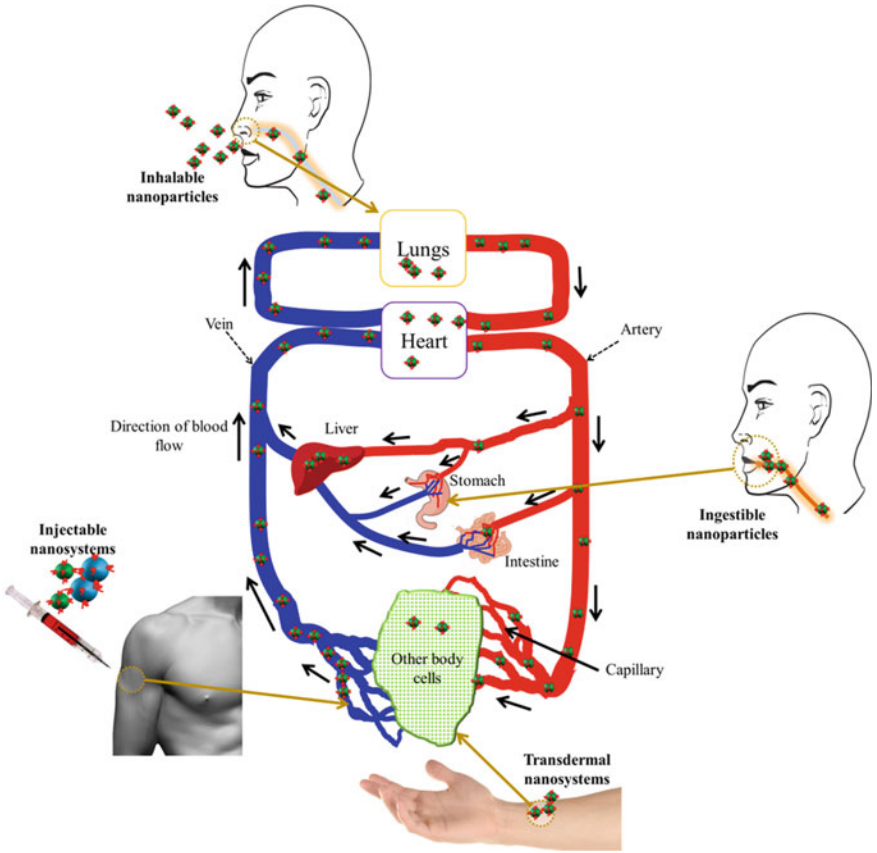


Fig. 4.9 Schematic diagram of nanoparticle routes into the intravascular route

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

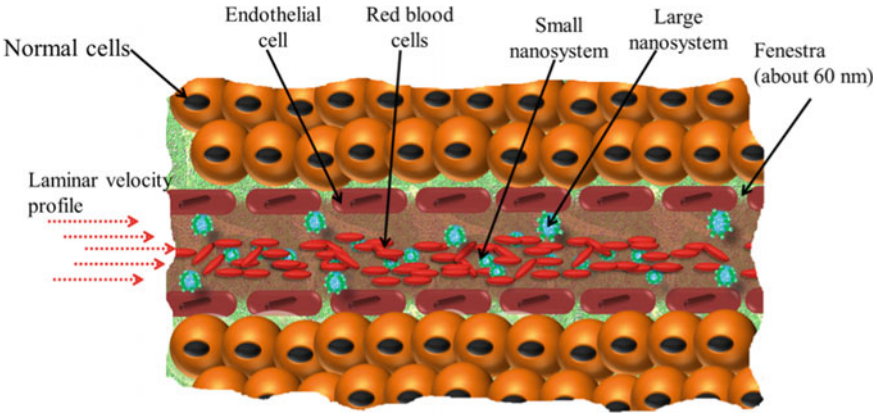


Fig. 4.10 Schematic of nanoparticle targeting of the vascular environment

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-

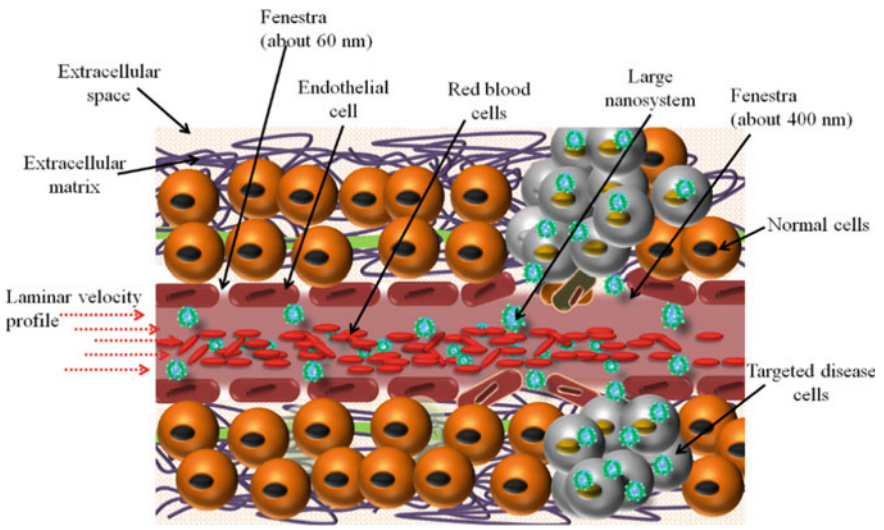


Fig. 4.11 Schematic representation of nanoparticle targeting of tissues in extracellular space

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

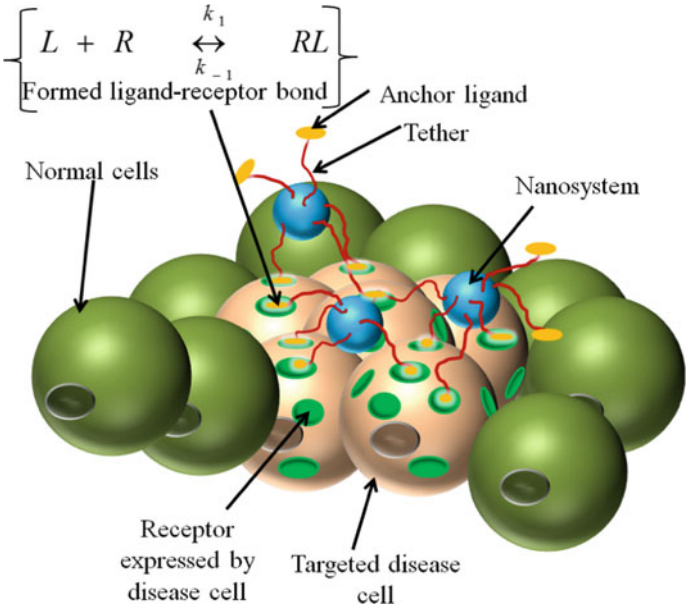


Fig. 4.12 Schematic of nanosystems binding to the targeted cells' surface receptors by mean of high-affinity ligand-receptor binding activities

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.

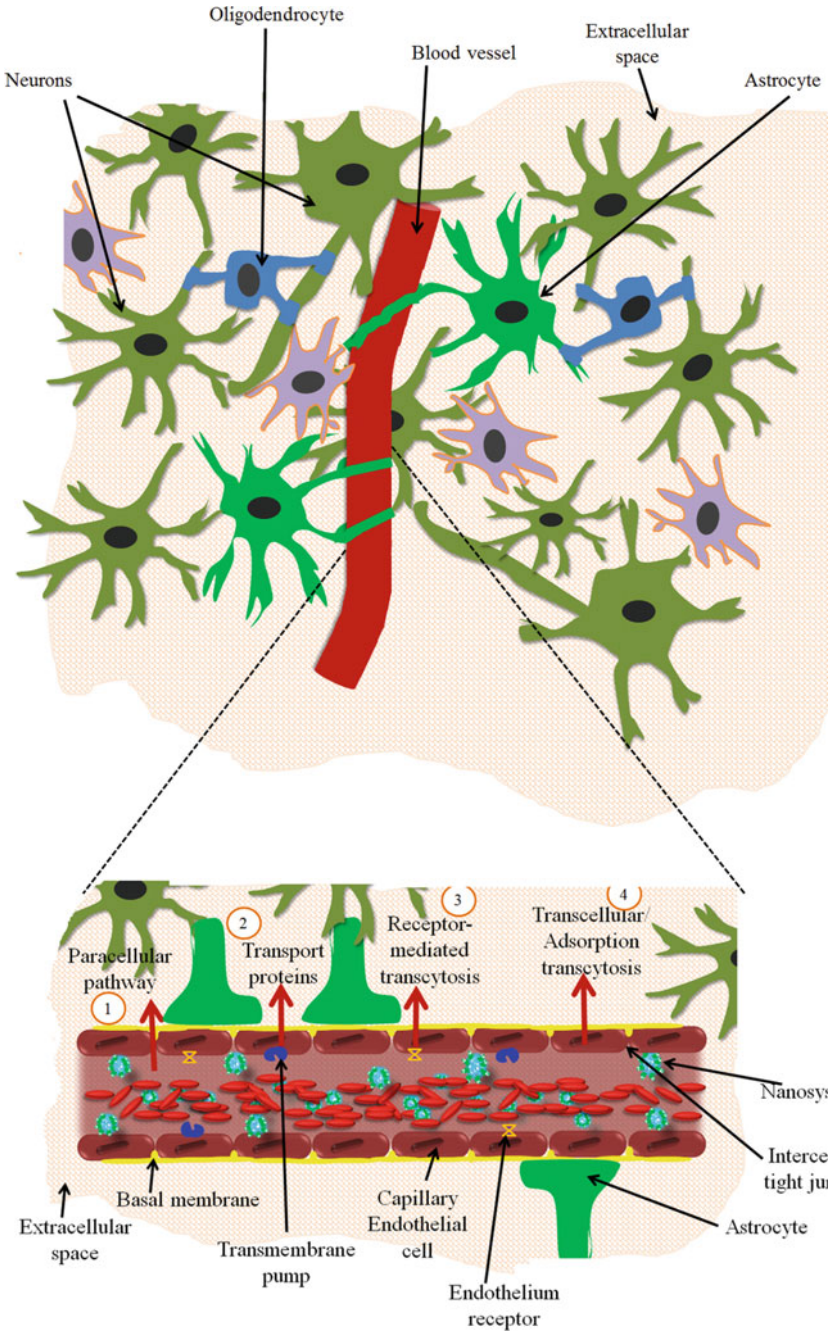


Fig. 4.13 Illustration of nervous system targeting

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

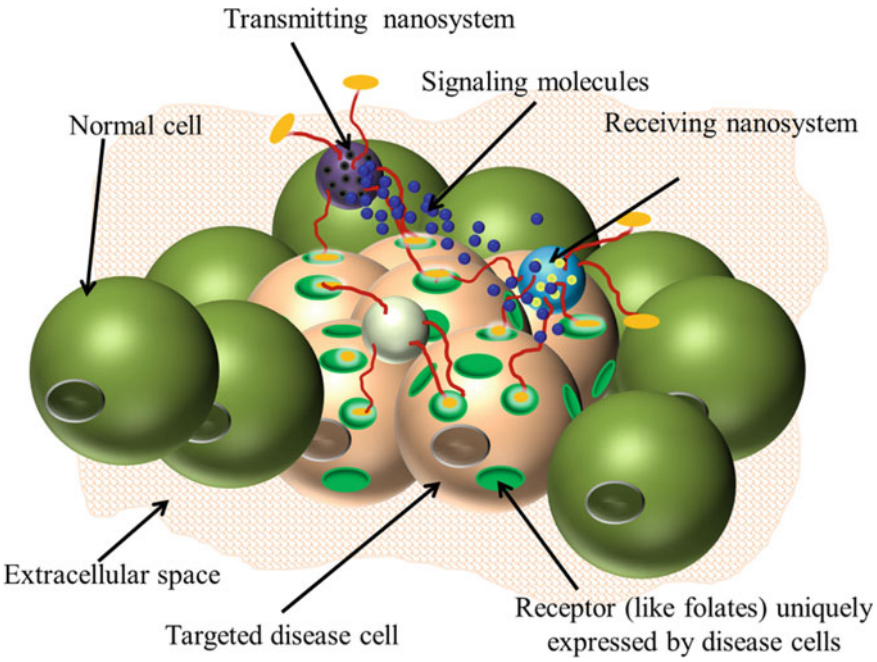


Fig. 4.14 Schematic of the basic operating environment of the nanosystems

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.

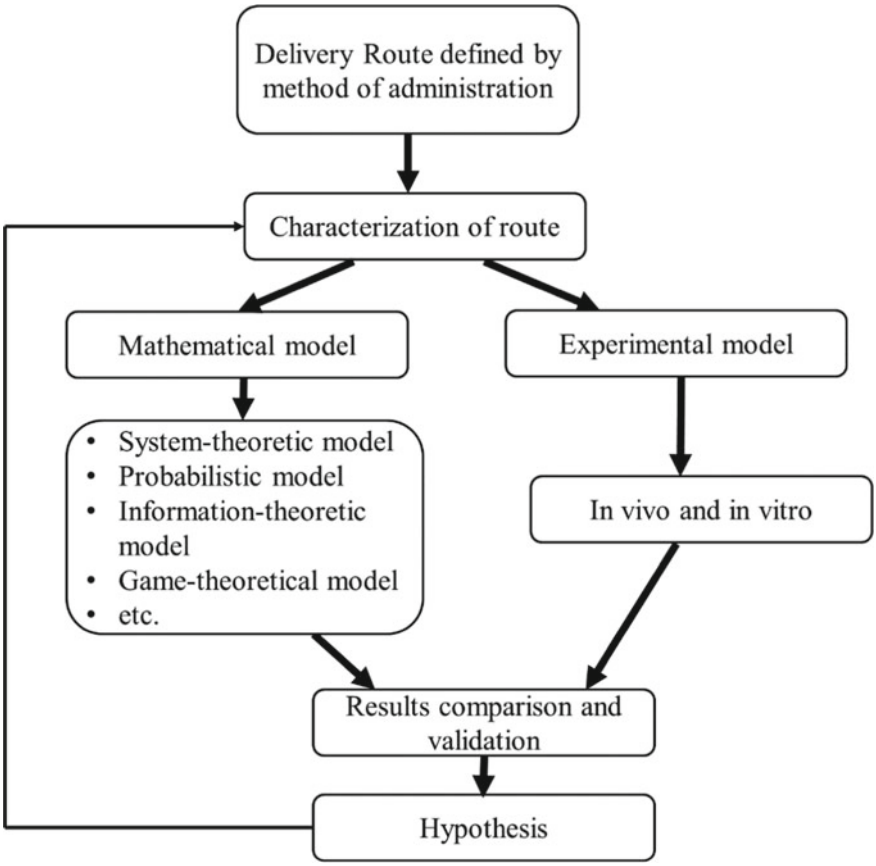


Fig. 4.15 Schematic diagram of delivery route modelling and analysis

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

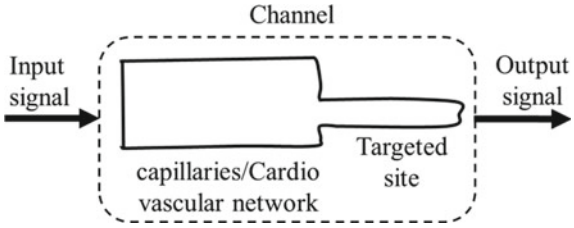


Fig. 4.16 Abstracted block diagram of the intravascular delivery channel

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

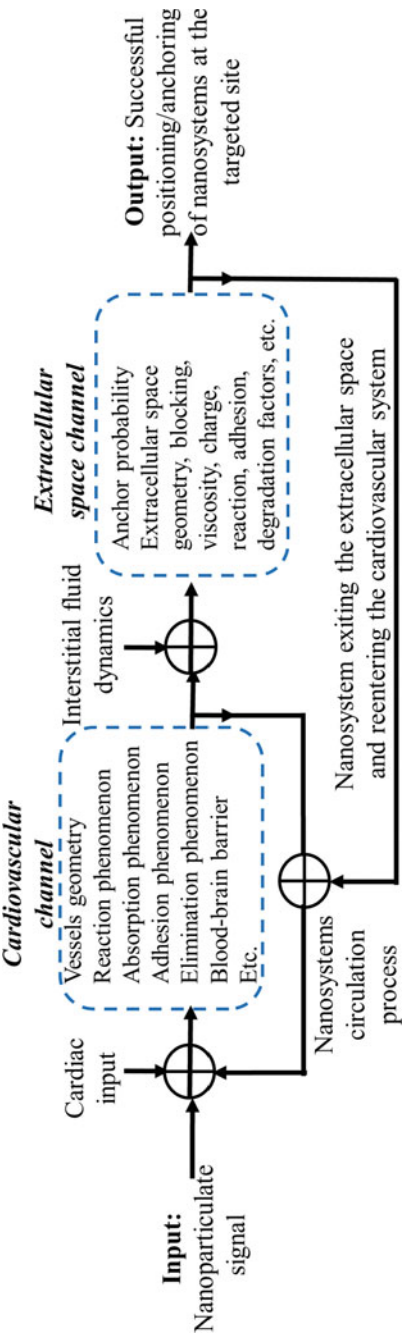


Fig. 4.17 Block diagram of the intravascular delivery channel characteristics

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.

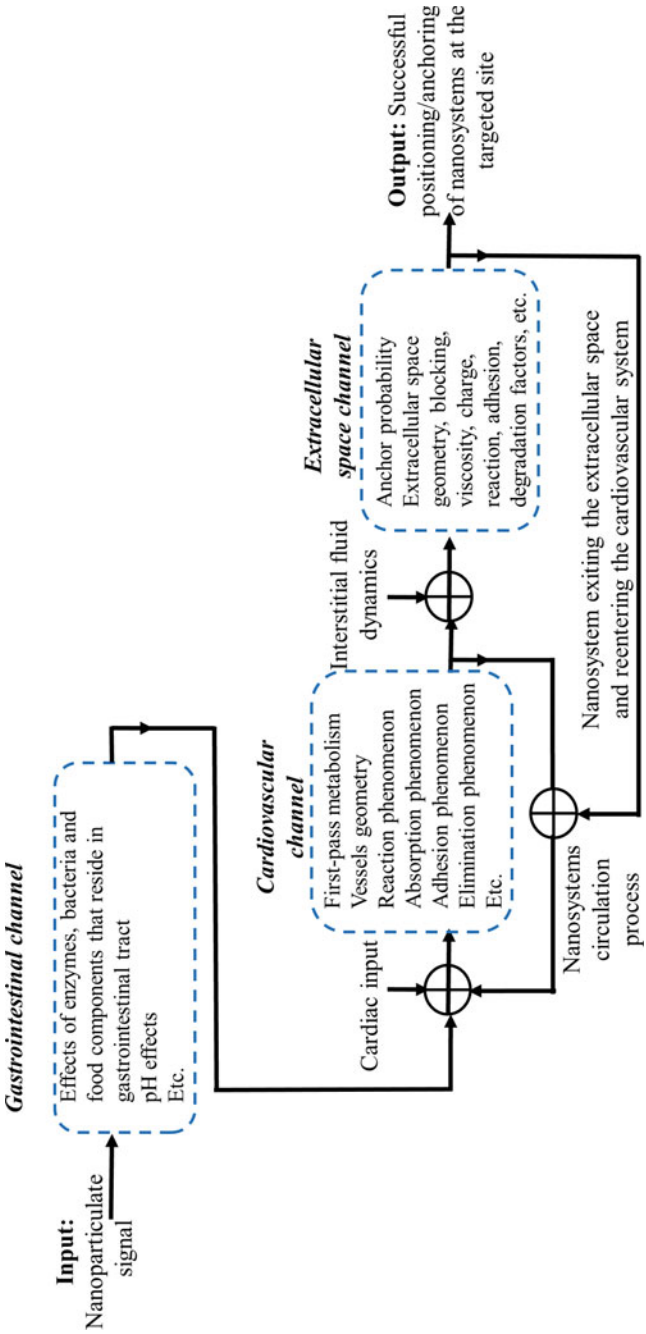


Fig. 4.18 Block diagram of the oral delivery channel characteristics

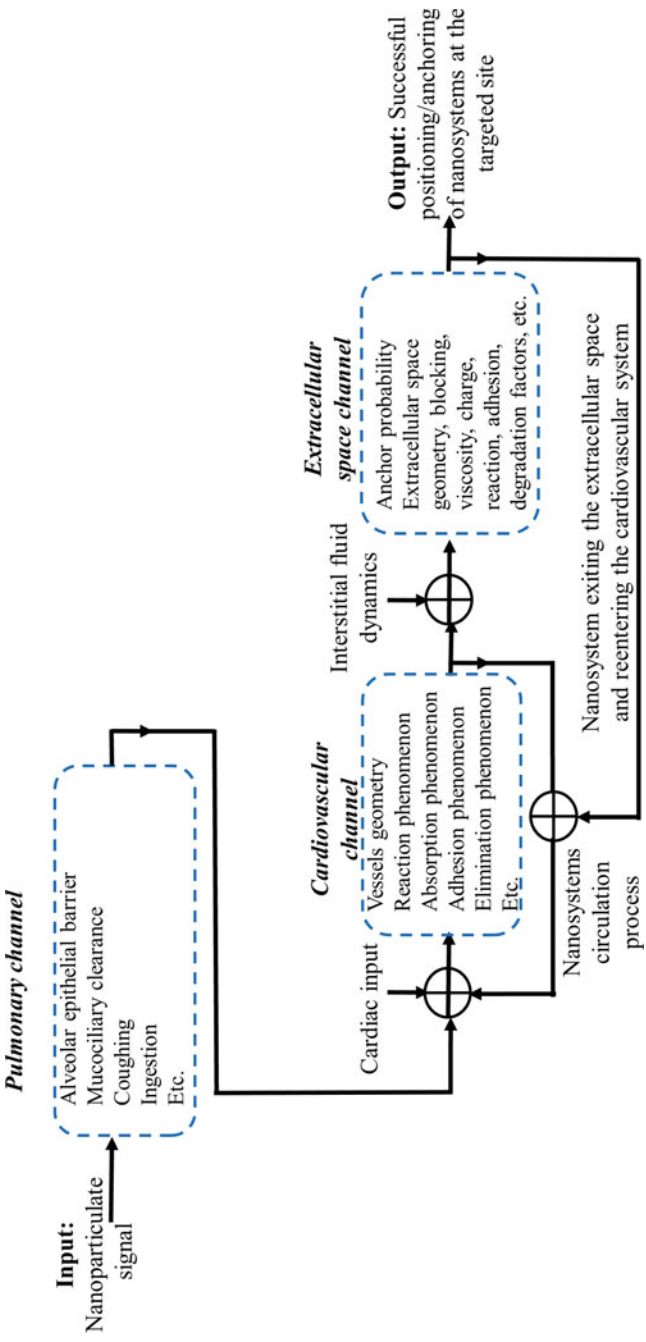


Fig. 4.19 Block diagram of the pulmonary delivery channel characteristics

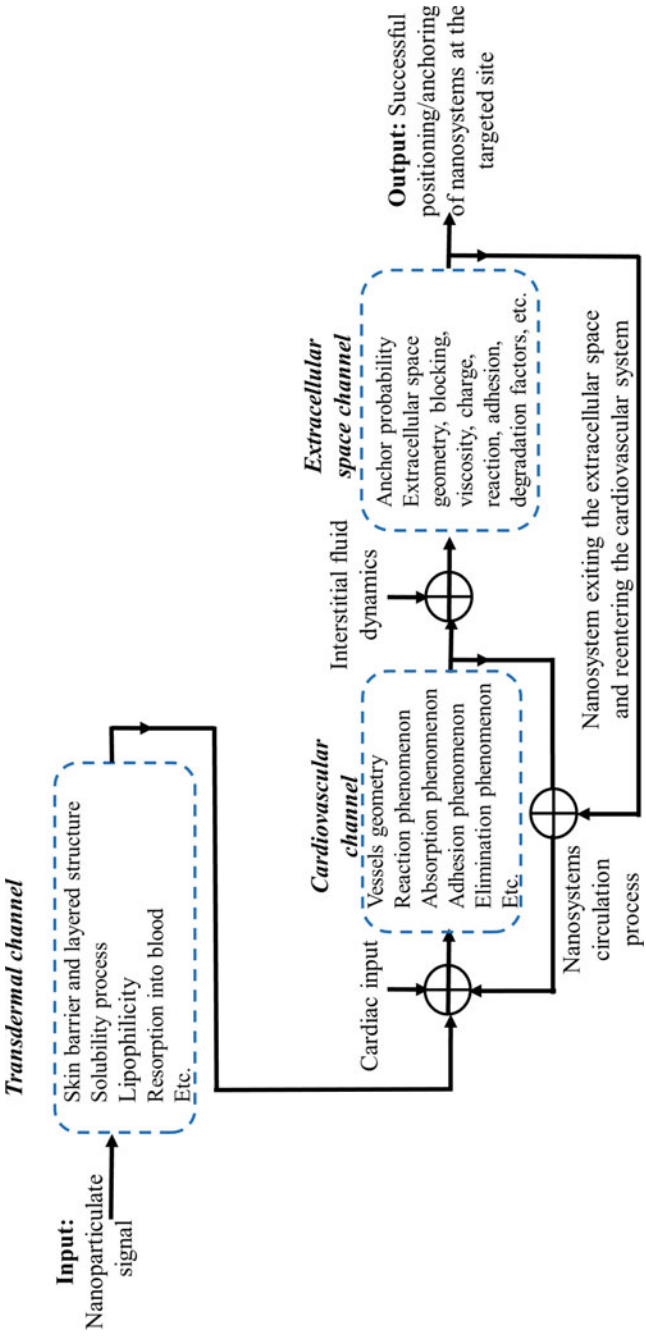


Fig. 4.20 Block diagram of the transdermal delivery channel characteristics

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