Chapter 10

An Introduction to Nanomedicine

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Abstract*: In this paper we present the status of research in nanomedicine for the treatment of cancer as well as other biological diseases. We analyze the development of nanomedicine research based on – but not limited to – recent studies in the detection of diseased cells (including cancerous cells), drug delivery, and nanorobotics. The same approach may also be adopted in other respects, such as the targeting and removal of plaque and/or cholesterol in arteries as well as repairing damaged cells. Many of these approaches to nanomedicine can be simulated through the use of computer models. We will discuss one such model from the University of Southern California. Outstanding issues relating to the preliminary stage of nanomedical research will be covered as well, along with various approaches for cancer treatment using nanotechnology. Current challenges associated with these treatment approaches, as well as possible solutions for these challenges, will be discussed. We conclude with a discussion of biocompatibility, nanoscale power, and the current state of research in the field.*

1. Introduction

Nanotechnology promises a host of innovative solutions in medicine through precise, targeted operations on the cellular level. For more than a decade, researchers have been searching for ways to realize these solutions and overcome the difficulties encountered when attempting to use nanotechnology for the treatment of various ailments. Recently, researchers have begun to look into nanorobotics, a relatively new subset of nanotechnology that involves the control of multifunctional nanosystems. Nanorobots could integrate the diagnosis and treatment of cancer into a cohesive, potentially non-invasive unit. Although the field of nanorobotics remains largely theoretical, a number of advances have been made in the past few years that lead us to believe that a multifunctional medicinal nanorobot could be possible. In order to achieve this goal, we need to know what has already been achieved and what still remains to be done.

Nanotechnology as a whole is a relatively recent development in scientific research. First defined by Norio Taniguchi from the Tokyo Science University in 1974, nanotechnology "mainly consists of the process of separation, consolidation, and deformation of materials by one atom or molecule [1]." Prior to the year 2000, nanotechnology focused on passive nanostructures; now, active nanostructures and systems such as targeted drugs and nanorobots are being studied. Today, a widely accepted definition for nanotechnology is "engineering of functional systems at the molecular scale," according to the

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Center for Responsible Nanotechnology (CRN) [2]. The molecular scale or nanoscale refers to technology smaller than 100 nanometers.

Nanomedicine is a sub-discipline of nanotechnology first defined in late 1999 and early 2000. Robert A. Freitas first comprehensively addressed the topic in his book, *Nanomedicine*, which addresses the technical issues involved in the medical applications of molecular nanotechnology and medical nanodevices. Currently, there is no internationally agreed upon definition for nanomedicine. For the purposes of this paper, we apply the accepted definition of nanotechnology to medicine. We define nanomedicine as the use of nanoscale devices or materials for diagnosing and curing diseases by actively interacting at the molecular level within a cellular system. This definition is fairly broad, so we further restrict ourselves by including only those medicines whose active ingredients were specifically engineered with the intent of functioning on the nanoscale. This requirement rejects medications such as chap stick or sunscreen, which were not designed with a focus on the nano scale. We believe this definition adheres most closely to the original intent of the term. Nanomedicine is a broad field that encompasses multiple topics from detection, drug delivery, and nanodevices to nanoimaging and clinical issues, all of which we will address in detail.

Nanomedicine is exciting because many of its findings – though often based on preliminary or even theoretical experimentation – promise results that are impossible at the macro scale. For example, many devices and materials being studied experimentally may be used to detect faulty cells via antibody conjugation. Carbon nanotubes, for instance, are capable of detecting particular DNA mutation sequences that could give rise to cancer. Another viable application of nanoparticles in medicine is molecular imaging. Specific biomolecules can be tagged and quantitatively analyzed via nanoparticles that glow under infrared light. Both of these approaches have exciting and novel applications in medicine, but they only scratch the surface of how nanotechnology can potentially influence the future of medicine. In order to imagine the true scope, we must look at active nanostructures, or nanorobotics.

Nanorobotics is a multidisciplinary field that requires knowledge of physics, chemistry, biology, computer science, and electrical engineering. Nanorobots must possess the capability of actuation, control, communication, and interfacing between the organic, inorganic and biotic realms [3]. There are many directions from which to approach the problem of creating a viable nanorobot. Some researchers focuses on bionanorobotic systems made of biological components such as proteins and DNA, while others focus on inorganic materials like CMOS and carbon nanotubes at the cellular level. Still others choose to focus on hybrid nanosystems, combining the organic and inorganic domains together in order to the best of both domains into one nanorobot.

This paper will address the types of diseases investigated and the nanotechnology involved in medical treatment. Next, it will discuss the current detection and treatment methods used by researchers. The paper will then conclude with current nanotechnology used in cancer treatment, issues with biocompatibility, and current research. Specific examples of computer modeling will be discussed in depth.

2. Nanomedical Technology

In this section we will discuss nanotechnology as it applies to medicine, including different types of nanorobots and some of the challenges inherent to building robots on the nanoscale.

Nanorobotics is an emerging technological field that comprises the development of robots whose components are at or close to the nanometer scale [4]. Nanorobots designed to operate inside the human body should be less than 800 µm in diameter in order to traverse the bloodstream [5]. So far, no complex nanorobot has been fabricated - current medical robots are constrained to the millimeter level. Thus, inorganic nanorobot construction at the nanoscale is only a theoretical model. In this section we present a short overview of medical nanotechnology, including nanorobots, nanoparticles, and carbon nanotubes (CNTs) as nanodevices related to medicine. We also take a look at microscale devices that represent the current state-of-the-art in medical implantable and non-invasive technology.

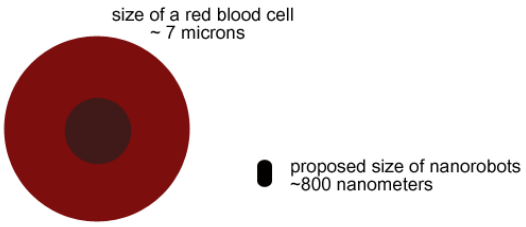

Figure 2.1: Size of nanorobots relative to red blood cells

Treatments based on nanorobots are expected to have two major advantages over traditional approaches: concentration and precision. These advantages enable therapies to become more efficient and cause fewer side effects because of their ability to concentrate drugs on a single tissue area or cell. Nanorobots can also work together in response to environmental stimuli and pre-programmed functionality in their control unit.

There are two main approaches to developing an assembled nanorobot system: organic and inorganic. Organic nanorobots are based on adenosine triphosphate (ATP) and DNA molecular assembly and function. Another subset of organic nanorobots is nanorobots based on bacteria, which have been proposed experimentally for drug delivery. Inorganic nanorobots are essentially nano-electromechanical systems (NEMS). As technology has developed, some approaches have begun to combine both organic and inorganic elements, creating a more advanced robot system known as a hybrid nanosystem. Although some nanorobots have already been tested, the majority of the current research is still in a theoretical simulation stage. Most of the subparts of nanorobots are being studied as individual entities, or 'modular-wise,' rather than as entire systems, since the elements of nanorobotics are still primarily in the research phase.

We believe that inorganic nanorobots are best suited as candidates for nanomedicine, and so we will concentrate our survey on inorganic nanorobots. There are several differences between inorganic and organic nanorobots, which determine how these two subsets will approach the many problems inherent

to medical nanorobots. For example, inorganic nanorobots could locate the exact position of a cell using the intensified magnetic property from the force of attraction inside the human body. In other words, they can isolate a target cell from a normal cell and at the same time allow for targeted drug delivery via a nanorobot at that destination. An organic nanorobot may be able to perform the same task using DNA biomarkers. However, the inherent programmability of inorganic nanorobots based on CMOS technology and the ability to leverage the existing control structures of macro-sized robots makes inorganic nanorobots the most likely to succeed in performing the complex, precise tasks required of medical nanorobots.

Still, there are many challenges to building a multi-functional inorganic nanorobot. In order to create a robot in the nanoscale, we must take into account sensing, actuation, control, data transmission, power, and interfacing across spatial scales as well as between the organic/inorganic and biotic/abiotic realms [6].

Although inorganic robots do not exist in the nanoscale today, we can look at microscale and larger medical robots that can be used as test cases for extending functionality into the nanoscale. Additionally, research on surgically implanted devices can provide information on how nanorobots may be able to solve the problems of biocompatibility, energy transfer, and data transfer.

One such area is diagnostic medicine in the digestive tract. Medical device companies have used capsule endoscopes for viewing and diagnosing diseases. These devices are considered microrobots – on the scale of a one-centimeter diameter by two centimeters length – and have onboard cameras and LEDs, and can send video wirelessly out of the body [7]. However, they are still limited in scope as they pass through the body without self-propulsion, drawn solely through peristaltic pressure, and therefore cannot complete tasks such as truly targeted medication or a thorough search for cancerous regions. There are groups searching for ways to overcome these challenges, however, by developing motors [7], controlling several microrobots in a system [8], and looking at the potential for microrobots that could dispense medicine into the stomach for months at a time [9].

Although microscale and nanoscale robots face very different problems in terms of motion and energy supply [10], microscale medical devices are important to the emerging field of nanorobotics both as a technological precursor and as a testing ground for the human side of medical nanorobotics. Microrobots open the discussion of the legal issues of data security and how the medical and device-making community will deal with implantable devices that are constantly streaming important personal data.

Today, nanorobotics is rapidly becoming a reality. Penn State published an article in February 2014 showing nanomotors individually controlled inside living cells [11]. This is an important step, as it addresses both control methods and biocompatibility. However, there are still many steps to be taken before nanorobots are viable inside the human body.

Current nanorobot components, control methods, and developing manufacturing methods provide platforms and possibilities for building multifunctional nanorobots that may be able to swim through

vessels, detect and destroy cancer cells, or send pictures back to its controlling device with accuracy, controllability, and precision. As previously stated, we wish to develop nanorobots in order to perform precise drug delivery.

3. Detection

In the last section we looked at nanotechnology as it applies to medicine, different types of nanorobots, and why we chose to focus this chapter on inorganic nanorobots. In the following section, we will discuss a number of different nanostructures we can use to detect the presence of cancer or other diseases in the body.

Nanomedicine can assist in the treatment of a wide range of diseases. Our research focuses on those that can be treated by nanorobots in the bloodstream, including diabetes, cardiovascular disease, neurodegenerative disease, and cancer, among others. While a major part of nanomedical research is still in its infant stages, significant research and experiments have been performed on these and other diseases. While all of these diseases are a threat to public health and could potentially be treated or cured by nanomedicine, our research focuses specifically on cancer.

Cancer is a group of diseases characterized by uncontrolled cell growth. The body does not regulate cancer cells as it does healthy cells, thereby allowing them to replicate at a rapid rate without being killed off as they normally would. Cancer cells replicate so uncontrollably due to damaged deoxyribonucleic acid (DNA), which prevents the cell's natural death and causes changes in material (physical, electrical, or chemical) properties within the cell.

Early detection and prevention are the best cures for any disease, including cancer. Currently, early detection is accomplished by identifying biomarkers, an indicator of a biological state of disease. Biomarkers can be DNA, RNA, or a protein and its fragments. In the future, even earlier detection may be possible thanks to ubiquitous computing and constant monitoring of at-risk patients. Today's detection tools, however, function in response to changes in material properties, such as those caused by the damaged DNA in cancer cells. Detection tools under discussion in this paper are nanowires, carbon nanotubes, nanoscale cantilevers, various nanoparticles (gold and magnetic, among others), quantum dots, and nanorobots. In this section, detection tools for biomarkers are discussed.

3.1 Nanowires

Nanowires inherently have excellent selectivity and specificity properties. For example, nanowires can be laid down across a microfluidic channel, not unlike a filter or a spider's web. As cells or particles flow through it, nanowires can sense and pick up tumor cells. Nanowires can be coated with a probe such as an antibody or oligonucleotide – a short stretch of DNA that can be used to recognize specific DNA/RNA sequences – that binds to a target protein on the enemy cell. Proteins that bind to the antibody will change the nanowire's electrical conductance, which can be measured by a detector [12].

3.2 Carbon Nanotubes

Carbon nanotubes are also being used as DNA biosensors. They scan down DNA and look for single polymorphic nucleotides that can lead to a possible detection of an individual who may develop diseases in the future. This application uses self-assembled carbon nanotubes and searches for covalently bonded DNA oligonucleotides. When hybridization between the probe and the target DNA sequence occurs, the voltammetric peak picks up the change [13]. DNA biosensors being developed for future use are more efficient and more selective than current detection methods.

3.3 Nanoscale Cantilevers

Another potential tool is the nanoscale cantilever. Similar in structure to rows of diving boards, these cantilevers are constructed using semiconductor lithographic techniques [14] and coated with antibodies that specifically target molecules produced by cancer cells. These target molecules bind to the antibodies on the cantilever, causing a change in its physical properties. For quantitative analysis, researchers can study the binding in real time. These cantilevers are exceptionally sensitive and can detect single molecules of DNA or protein, hence providing precise detection methods for cancer related molecules. Figure 3.1 below shows how nanoscale cantilevers detect proteins produced by cancer cells.

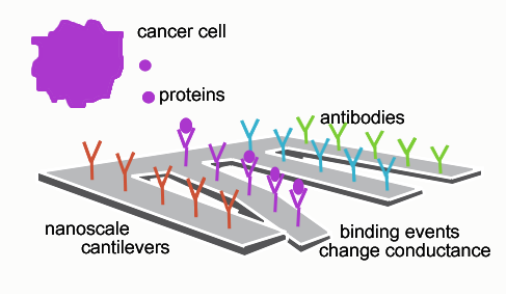

Figure 3.1: Detection of cancer cells by nanoscale cantilevers

3.4 Gold Nanoparticles

Gold nanoparticles (GNPs) have been emerging as powerful imaging labels and contrast agents – hence effective detectives. GNPs readily get conjugated to antibodies and other proteins due to the affinity of the functional group (-SH) for their gold surface. They are especially effective when targeting cancer cells [15]. GNPs are used for photothermal therapy, where tunable optical properties cause them to convert laser light into heat and destroy cancer cells [16, 17]. In addition to spherical GNPs, gold nanoshells and gold nanorods have been applied to biomarker detection [18-20]. They can absorb and emit light at near infrared region, providing deep tissue penetration.

3.5 Magnetic Nanoparticles and Magneto-Electric Nanoparticles

Magnetic nanoparticles have been widely used as an imaging tool. Since transverse relaxation time decreases due to aggregation of magnetic nanoparticles when target molecules are present, the concentration of cancer biomarkers can be measured. This allows for in vivo, local monitoring for cancer biomarkers and possible continuous monitoring. Magneto-electric nanoparticles have also proven to be a promising new technology. In one specific study, researchers have been able to isolate a

cancerous cell based on differences in the electric properties of its membrane [21]. This method of detection has been proven effective as applied to ovarian cancer cells, but may potentially be applied to other types of cancer as well. More on this topic can be found in chapter 11 of this book.

3.6 Quantum Dots

Quantum dots can be linked to antibodies and combined to create arrays that are capable of detecting multiple substances simultaneously. They can be used to measure levels of cancer markers such as breast cancer marker Her-2, actin, microfibril proteins, and nuclear antigens [14]. Quantum dots are robust and very stable light emitters. The photochemical stability and the ability to tune broad wavelengths make quantum dots extremely useful for biolabelling [22].

3.7 The Medical Nanorobot

The ultimate tool of nanomedicine is the medical nanorobot – a robot the size of a bacterium composed of multiple mechanical parts [23]. Although still a hypothetical concept, the medical nanorobot is a promising tool for the future of the field of medicine – a future in which artificially intelligent nanorobots can be fabricated to repair tissues, clean blood vessels and airways, and transform physiological capabilities. A more in-depth discussion of the technology behind nanorobots can be found in the previous nanomedical technology section of this chapter, as well as chapter 2 of this book. The next section will deal with actually treating the disease cells once they are detected.

4. Treatment

In the previous section, we identified six methods of cancer detection. In the following section we discuss the problems with current cancer treatments, as well as methods that can be used to treat disease at the cellular level within the body.

Modern cancer treatment is anything but ideal. Conventional treatments such as chemotherapy, radiation, surgery, and immunotherapy destroy malignant tissue, but also damage benign tissue. These methods are found to be useful in remission, but depend on the concentration and delivery of the drug. Highly toxic drug concentrations that destroy the tumor cells can potentially kill the patient. Thus, the aggressiveness of chemotherapy treatment is usually determined by the dosage that the patient can withstand, rather than the dosage needed to eliminate all cancerous cells.

A more efficient approach to cancer treatment would be the destruction of cancer cells with little to no side effects on healthy cells. With the current trend of rapid developments in nanomedicine, it seems that this technology can be used for detection, analysis, and destruction of cancer cells more effectively and with more precision than is possible with current treatments.

As stated, the key problems of conventional technology are the method of drug delivery and the concentration of the drug cocktail required to destroy the cancerous cells – problems that can be easily overcome by nanotechnology, as the particle size has an effect on serum lifetime and pattern of deposition. This allows drugs on the nanoscale to be used in lower concentrations, which results in an

earlier outset of action. Nanotechnology also allows drugs to be directed to the exact location where cancerous cells have been observed, thus killing malignant tissue while leaving healthy tissue relatively unaffected. There have been several studies done into the individual treatment of cancer cells. This section will explore some of these treatments in more detail.

4.1 Nanoparticle Heating Method

The nanoparticle heating method for cancer therapy has great potential for treating selective cancer tissue. The concept is very efficient. In this method, the nanoparticles conjugated with antibodies are injected into the human body and are allowed to position themselves around the cancer tissue. These particles are then heated by an external non-invasive heating source, destroying the targeted cancer tissues via thermal necrosis [24]. Capacitively coupled RF field sources [25] and Near-Infrared Light sources (NIR) [26] are two of the heating sources that could be used to heat up these nanoparticles. A major advantage of this technique is its lack of dependence on traditional drugs. As invading bacteria become less and less sensitive to antibiotics and other drugs, a new solution may soon be required to treat these bacterial infections. Nanoparticle heating may well be one solution. Two treatments that employ the nanoparticle heating method by way of infrared and laser light are discussed below.

4.1.1 Gold Nanoparticles

As discussed in section 3.1.4, one of the most researched nanomedicical applications is gold nanoparticles (GNPs). These nanoparticles bind to certain proteins that only cancer cells produce. Gold nanoparticles can also be seen as “the drugs that deliver themselves” for their special heating ability, which, when exposed to laser light, kills cells with which the nanoparticle interacts. The downside of this method is that unless properly coated, the immune system would attack such particles because the body would treat them as unwanted foreign agents. See section 5.1 on biocompatibility for more information on immune reactions and immunosuppression.

4.1.2 Metal Nanoshells

Another novel approach uses metal nanoshells. These shells have the ability to capture and absorb light, and are coated with a bioactive substance that binds them to cancer cells [27-29]. Near-infrared light is used to heat up these shells, leading to the destruction of the cancer cells with minimal damage to adjacent healthy cells. The advantages of high sensitivity, specificity, and cost-effectiveness have made metallic nanoshells a particularly attractive choice for modern-day cancer treatment. Alam and Massoud have developed an accurate analytical closed-form model for the frequency resonance and scattering characteristics of a single nanoshell [16].

4.2 Supermagnetic Beads

Apart from gold nanoparticles and metal nanoshells, another method that emphasizes the destruction of targeted cancer cells uses mono-sized supermagnetic beads. The beads are macroporous particles having narrow pores that contain magnetic materials (Fe_20_3 and Fe_3O_4) distributed throughout their entire volume. In studies, two different types of beads having different magnetic mass susceptibility

and different diameters were used: Dynabeads Pan Mouse IgG (diameter 4.5±.2um, magnetic susceptibility (16±3)x$10^{-5}m^3$/kg) and Dynabeads Protein G (diameter 2.8±.2um, magnetic mass susceptibility (10±2.5)x$10^{-5}m^3$/kg). These magnetizable beads aggregate under instantaneous pulsed magnetic forces and penetrate forcefully to effectively destroy the cancerous cells [21].

4.3 Magnetic Manipulation

Magnetic manipulation is another viable method to efficiently deliver medication. Recently, scientists have successfully used a direct current magnetic field to manipulate the membranes of magneto-electric particles. They then used this ability to load the same magneto-electric particles with paclitaxel, a common cancer drug, and deliver it to a mix of healthy and cancerous cells in-vitro. The drugs, when released by the particles, passed through the membranes of the cancer cells and killed only the targeted cells. The healthy cells were left alive [30]. In the same study as previously mentioned in section 3.5 of this chapter, magneto-electric nanoparticles were used to manipulate the magnetic field of the membrane of the tumor cell to allow large quantities of medication to pass through into the cell. The diseased cell was killed with no harm at all to surrounding healthy cells [21], as can be seen in more detail in the following chapter. These results show early promise in specific targeting of cancer cells within the human body, and certainly deserve further research.

4.4 E-cadherin

Nanorobots can also be used to analyze levels of E-cadherin in the body and target cancer cells based on the varying E-cadherin levels from one cell to the next [31, 32]. E-cadherin is a calcium-regulated adhesion expressed in most normal epithelial tissues. E-cadherin is associated with gland formation, stratification, and epithelial polarization. Perturbation or selective loss of this E-cadherin function results in the loss of intercellular adhesion, with possible consequent cellular transformation and tumor generation. The efficient use of nanorobots by proper control methodologies is one of the methods under study for the treatment of cancer cells, as it is quite capable of differentiating normal cells from malignant cells by checking surface antigens. This in turn greatly reduces the probability of destroying normal cells.

4.5 Treatments for Other Diseases

While this paper does focus primarily on cancer treatment, there are also many other nanoscale techniques for treating diseases other than cancer. The following subsections will describe three of them briefly.

4.5.1 Transfection

As opposed to the methods of drug delivery discussed throughout the rest of this section, transfection is a method of gene delivery. Transfection can be accomplished by both chemical and non-chemical processes. Chemical-based transfection can be divided into several categories, including cyclodextrin, polymers, liposomes, and nanoparticles. There are various non-chemical processes as well, including electroporation, sonoporation, and impalefection. Impalefection is different from these other non-

chemical methods in that DNA is introduced into the cell through the use of nanomaterials. In this process, nanowires and similar nanoparticles are used as transport systems. Vertical arrays of nanowires are prepared by photolithography and plasma enhanced chemical vapor deposition before they are coated in DNA containing the sequence meant for delivery. Target cells are cultured on these nanowire arrays, which proceed to impale the target cells as they settle on the surface of the nanowires. This method is able to deliver DNA directly to the cell cytoplasm of the nucleus of the cell, which then begins to act in accordance with the newly introduced sequence of DNA. Appropriately, the term "transfection" is a combination of both 'impalement' and 'infection [33-36].'

4.5.2 Tissue Engineering

Nanomedical technology is being investigated as a possible method to further the field of tissue engineering. Nanotechnology could potentially be used to help repair damaged tissue through the use of suitable nanomaterial-based scaffolds and growth factors. If successful, tissue engineering may be able to replace conventional treatments such as organ transplants and artificial implants. Nanoparticles such as graphene, CNTs, molybdenum disulfide, and tungsten disulfide are being investigated as potential reinforcing agents to make strong, biodegradable polymeric nanocomposites for bone tissue engineering applications. As a result of the addition of these nanoparticles into the polymer matrix at low concentrations of about 0.2% by weight, the compressive and flexural mechanical properties of polymeric nanocomposites are significantly increased. These nanocomposites could potentially be used to further nanonephrology (defined as nanomedicine of the kidney), create strong, lightweight composite bone implants, or even weld arteries during surgery [37, 38].

4.5.3 Monitoring

Medical monitoring is the practice of observing a patient to either make sure they remain healthy or gathering data to assist in diagnosis or treatment. Traditionally, this has been done primarily in controlled environments where a doctor ac physically observe the patient. Using current technology, however, doctors can observe patients from anywhere by way of a small chip either implanted under the patent's skin, swallowed in pill form, or introduced to the body by other means. This is a major improvement over in-person monitoring, due to the fact that it enables constant monitoring. Constant monitoring of the patient allows doctors to gather more data from the patient, all while the patient goes about their normal daily routine. Both of these benefits can result in faster, more accurate diagnosis and treatment of disease. Unfortunately, due to the relatively large size of these modern implants as compared to objects on the nanoscale, they can only be implemented in limited locations throughout the body. This restricts their access to certain data that can only be obtained in locations in which they cannot be utilized. Nanomedical technology has the potential to overcome this obstacle by producing nanoscale implants that can be utilized virtually anywhere within the body. Using the concept of a nanoscale lab-on-chip implant, scientists can potentially gather data from tests ranging from continuous evaluation of blood sugar levels and neuroimaging to predicting both hypo and hyperglycemic states as well as seizures. In Vivo Bio MEMS based biosensors and serotonin biosensors may also be used in preventing an early detection of mental health disorders, such as depression [39, 40].

This section discussed just some of the multitude of treatment options currently under investigation. In the next section, we will explore challenges introduced when introducing any of these foreign agents into the human body – a topic known as biocompatibility.

5. Biocompatibility

In past sections, we have covered methods to detect and cure cancer on the nanoscale. Achieving a treatment, however, is more difficult than that. The nanorobots need to be able to survive within the body for long enough to arrive at the cancerous cells and deliver their medication. In the following section we discuss the challenges presented by this requirement, commonly known as biocompatibility.

Biocompatibility, or "the ability of a material to perform with an appropriate host response in a specific situation," [41] is an important factor in the development of nanomedical robots. Any nanorobot designed to enter the human body must be biocompatible in order to function correctly, or its introduction will trigger unwanted immune responses in the body. Biocompatibility has traditionally been an important consideration in prosthetics and organ transplants, as a rejected transplant can have serious complications. Biocompatibility in nanomedicine, however, in part due to its large surface area to volume ratio, introduces challenges unique to its scale [42]. This section will address both possible effects of nanorobots on the body and factors that determine biocompatibility on the nanoscale.

5.1 Immunostimulation

If medical nanorobots are not appropriately biocompatible, there is a risk of a number of complications within the host. The two very broad categories of immune responses to nanoparticles are immunostimulation and immunosuppression. If the nanorobots trigger an immune response within the host, the reaction can be considered one of immunostimulation [43]. It is important to note here that biocompatibility requires an immune reaction appropriate to the desired function, not simply a non-reaction. Immunostimulation is not necessarily a negative reaction; it can, in fact, be the desired effect. For example, nanoparticles can be injected into the blood stream to aid the immune system in fighting off a disease [42, 43]. In fact, this method has been used since the advent of vaccines with non-nanoscale materials known as immunologic adjuvants [44, 45]. Immunostimulation can, however, be harmful to both host and nanorobots. Immunostimulation produces side effects including hypersensitivity to allergens, inflammation, fever, and other flu-like symptoms [43]. It can also aggravate other conditions, such as autoimmunity. Immunostimulation also results in the increased production of macrophages, which can attack and destroy nanorobots before they are able to accomplish their task within the body.

5.2 Immunosuppression

Introducing nanoparticles into the body does not always cause immunostimulation – it can also trigger immunosuppression. As its name suggests, immunosuppression is the opposite of immunostimulation: it is defined as "suppression of the body's immune system and its ability to fight infections and other diseases [46]." Immunosuppression is vital to successful organ transplants and skin grafts, as well as

autoimmunity treatments. Immunosuppression can make it easier for drug-delivery nanorobots to accomplish their jobs in the body, but also has the potential to harm or even kill the host [43]. Immunosuppression leaves the body open to attack, and is the symptom of diseases like HIV and AIDS that eventually leads to death. When nanorobots are used as drug delivery devices, as is the focus of this paper, they will likely be most effective if they are seen as native entities with no immunostimulation or immunosuppression [44]. This is the goal of nanoscale biocompatibility.

5.3 Factors of Nanobiocompatibility

In the previous subsections, we discussed two major effects that the introduction of foreign nanorobots can have on the immune system – the immunostimulation and immunosuppression reactions. In this subsection, we present many of the factors that can influence these reactions. Biocompatibility on the nanoscale presents challenges not faced in traditional prosthetics or transplants. On the nanoscale, biocompatibility is determined by a number of factors: size, amount, density, location, duration, geometric surface planes, and material, among others [34-36]. Material may be the largest factor in determining biocompatibility. Some materials, such as metal traces in certain carbon nanotubes [42], are known to cause undesired immune reactions, while others, such as diamond [47, 48] and possibly graphene [43], have been shown to have minimal biocompatibility issues in animals. Size is a key factor as well – even if a material is considered biocompatible on a larger scale, nanoparticles of the same material can potentially prove to be carcinogenic [48]. Also, the smaller the particle, the longer they tend to survive in the blood stream. According to Bastús et al, this is an observable, universal trend [44]. Surface orientation plays a large role in determining biocompatibility as well, as each geometric plane presents a different physical structure to the surrounding environment. Immune responses differ between planes, causing biocompatibility to vary even within nanoparticles of the same material [47]. Biocompatibility also differs based on location. For example, nanorobots will encounter very different biological conditions if injected directly into the bloodstream, as opposed to being ingested orally or inhaled. Each set of conditions will affect the nanorobot differently, so the same nanorobot may be biocompatible in the bloodstream, but not in the stomach. Duration is also a major – if often overlooked – factor in biocompatibility. Nanorobots must have a pre-planned way to leave the body once they accomplish their task. They may be excreted normally, mimic pathogens so as to be removed by the immune system, or make use of other exit techniques [43]. If there is no exit strategy nanorobots can build up in vital internal organs, such as the liver or spleen, causing side effects including liver failure and cancer [42-44].

Nanomedicine does have the potential to revolutionize the way medicine is practiced around the world, but it is clear that biocompatibility on the nanoscale is one of many major challenges that must be overcome before nanomedicine can be safely implemented on a large scale.

6. Power

In the previous section, we discussed biocompatibility and the difficulties presented by this concept. But even if a nanorobot can detect cancer, treat cancer, and be fully biocompatible, it still needs a way to power itself. In this section, we will discuss recent progress in wireless power and how this idea can be

directly applied to nanomedicine.

Unless the nanorobots of the future are designed to be totally passive – relying only on outside sources for all movement and actions – they will need a source of power. Powering a nanorobot with wires as it circulates through the human bloodstream is obviously impractical, and nanoscale batteries would likely hold only a very limited charge and do not currently exist in forms useful in nanomedicical applications. Ignoring external wires and internal batteries leaves us with a very likely solution to nanorobot power: wireless inductive power.

When powering a device like a nanorobot remotely, a four-part system consisting of a transmitter, rectifier, bandgap reference circuit, and matching network is required. The transmitter transmits AC power, which is converted to DC power by the rectifier. The bandgap reference circuit and a regulator use analog circuitry techniques to transform this DC voltage into a stable, non-temperature dependent voltage source usable by the device. The network must be impedance matched for the particular operating to minimize power loss, thereby providing more power to the chip [41]. There are many known designs for wireless inductive power systems that could potentially be adapted for implantable devices, some of which have been shown to operate with up to 72% power efficiency [42]. The Caltech Nanofabrication lab developed one such device, a 1.4mm by 1.4mm glucose monitoring implant that is powered by an external RF signal at 900Mhz and uses 5 μW of power [43].

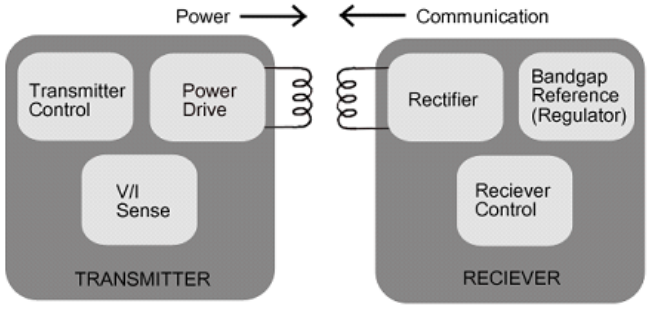

Figure 6.1: Basic block diagram of a four-part wireless power system

Inductive power is not perfect. The coils must be both matched perfectly and in perfect alignment with each other to realize maximum range, which is still normally only a matter of centimeters. Researchers at MIT, however, have developed a solution to these problems known as highly resonant wireless power transfer. Using this technology, they developed a system to efficiently transmit 60 watts over two meters [44]. This technology could be hugely beneficial in longer-term implants, such as cochlear implants or pacemakers, which are currently battery powered and require invasive surgery to replace the battery when it begins to fail. Highly resonant wireless power could also be used to more easily power nanomedical devices. Assuming a short lifespan for nanorobots in the body, the patient may be able to stay easily within range of a hospital transmitter implanted in their bed or wall for the entire procedure – potentially eliminating the complications introduced by the range and alignment requirements of more traditional inductive power.

Other recent examples of studies using wireless power include the design of a telemetry system based

on wireless power transmission for physiological parameter monitoring [41] and a method of tracking optimal efficiency of magnetic resonance wireless power transfer system for biomedical capsule endoscopy [42]. In the former, an implanted telemetry system for experimental animals can be used to continuously monitor physiological parameters. This system is significant not only in the study of organisms but also in the evaluation of drug efficacy, artificial organs, and auxiliary devices. The system is composed of a miniature electronic capsule, a wireless power transmission module, a data-recording device, and a processing module. An electrocardiograph, a temperature sensor, and a pressure sensor are integrated in the miniature electronic capsule, in which the signals are transmitted in vitro by wireless communication after filtering, amplification, and A/D sampling. To overcome the power shortage of batteries, a wireless power transmission module based on electromagnetic induction was designed. In the latter, researchers were looking for a solution to the problem of limited battery capacity in commercialized capsule endoscopy. Their paper presents a theory for tracking the optimal efficiency of an MR-WPT (Resonant Wireless Power Transfer) system, along with its experimental verification. A system with a 9-mm-diameter receiver is implemented, which is small enough to fit in the current capsule endoscope.

The current advances in wireless power technology are essential for the future development of nanomedical robots. However, power is only one piece of the puzzle. Until we can assemble a complete nanorobot for testing purposes, we must rely on other methods to determine how different designs interact with the human body. In the following section, we will discuss one such method: computer modeling.

7. Computer Modeling

In previous sections, we have discussed many of the basic requirements for cancer-treating nanorobots. In the following section, we walk through one attempt to model all of these systems together within the human body through the use of computers.

In order to create viable nanorobots for medical purposes, all of these systems must come together in one unit. Because we are not yet able to physically produce robots on the required scale, we can use computer modeling to attempt to determine how specific combinations of all of the above systems will function once introduced into the body. In one recent example of computer modeling for nanomedicine, a research team at the University of Southern California has developed a system that models nanoscale drug delivery through the bloodstream. It has the ability to represent both active and passive targeting nanorobots. It simulates the flow of nanorobots through the bloodstream until they detect cancer cells, at which point they maneuver to the tumor and begin the process of drug delivery. This model accounts for various possible drug delivery failures, such as early release, delayed release, non-release, power failure, and immunostimulation. Upon failure, the representation of the nanorobot exits the model. Each failed delivery can be viewed in a bar graph by type of failure. When a nanorobot successfully attaches to a cancer cell, the representative nanorobot in the model incurs latency, which accounts for attaching to the cancer cell and the actual act of drug deployment. The number of successful deliveries as compared to the number of failed deliveries can be seen in another bar graph.

Figure 7.1 shows an example of the included Position Tracking Scatter Plot, which displays the location of each nanoparticle or nanorobot currently in the body. The figure shows this plot immediately before nanorobots are first introduced to the body.

The model also takes into account drug toxicity and biocompatibility issues, topics discussed in the biocompatibility section of this chapter. These topics can be impractical to test for in the lab, due to the difficulty of introducing different planes of different materials to a realistic human immune system without endangering anyone in the process. While model outputs are not as definitive as lab results, computer models can cheaply simulate the introduction of different materials into the human bloodstream to within an acceptable degree of accuracy. In this specific model the body has an assumed toxicity capacity, which is the density of toxins it can contain and still be healthy. Each drug has its own toxicity level, which can be thought of as generally anti-proportional to its biocompatibility. The nanorobots release their toxins into the bloodstream every time they fail drug delivery in specific ways. This gradually increases the current concentration of toxins in the body based on the amount released, the time between subsequent releases, the distance between subsequent releases, and the toxicity value assigned to the medicine in question. Once the toxicity level is too great, the simulation ends in failure.

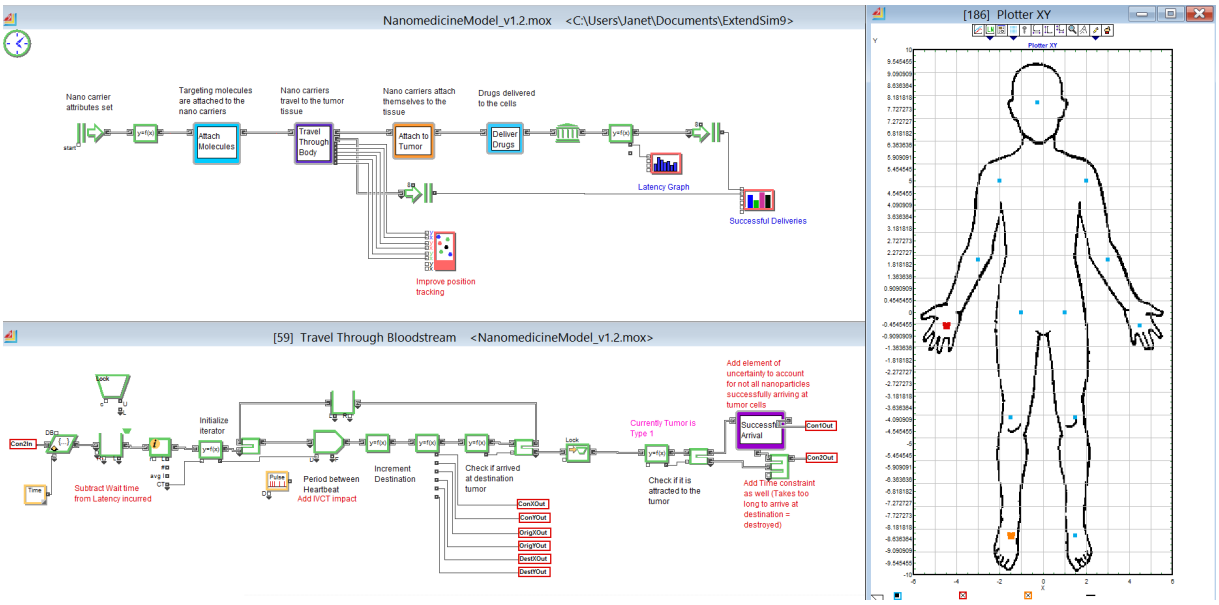

Figure 7.1: Position Tracking Scatter Plot before introduction of nanorobots

This model was created in ExtendSim 9, a program designed specifically for creating dynamic system models. The software was run under an educational grant provided by Imagine That!, the creators of ExtendSim. Figure 7.2 shows a flow chart of the model design within ExtendSim 9.

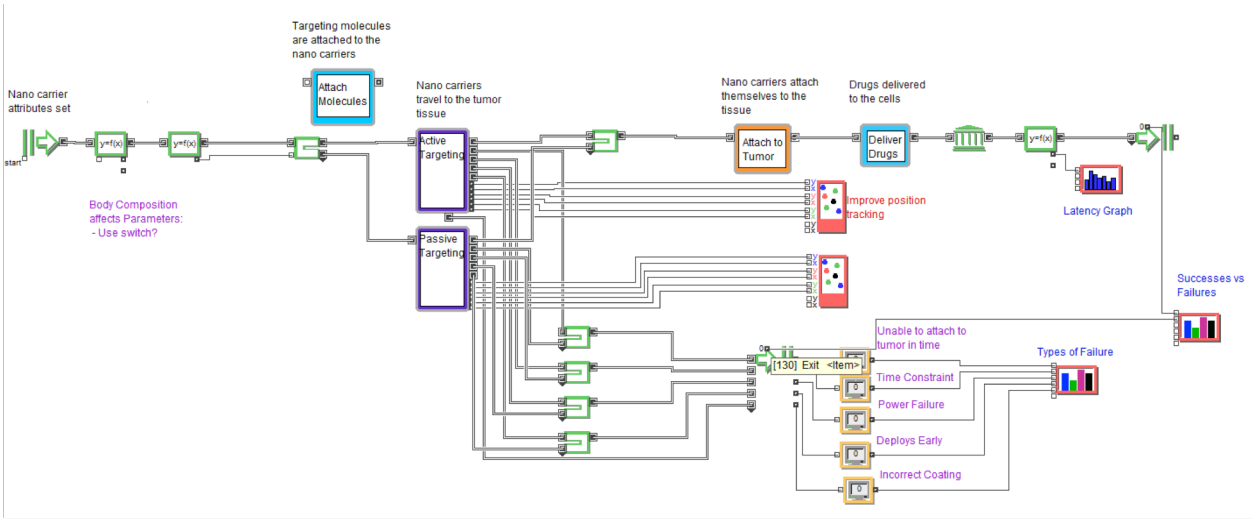

Figure 7.2: Flow chart of model as seen within ExtendSim 9

Data from this model can point scientists toward materials and molecular planes that are viable candidates for successful introduction to the human body, which can then be tested in the lab. This model can also predict both the overall amount and density of a specific medication can be safely released into the bloodstream before the concentration due to nanorobot failures is high enough to be dangerous to the patient.

This model has been purposely designed to grow with the increase of knowledge within the still relatively new field of nanomedicine. As more research is done and new results become available, this data can be added to the model. This will further refine the results, making this model – in theory – incredibly accurate over time. As we learn more about nanomedicine, Data from this model can point scientists toward materials and molecular planes that are viable candidates for successful introduction to the human body, which can then be tested in the lab. The information collected can also help scientists develop appropriate dosages for treatment or design more efficient nanorobots with a higher delivery success rate.

8. Research Institutions

In previous sections, we have explored some of the specifics of nanomedical research for cancer. In the following section, we will discuss the organizations, centers, universities, and scientists actually doing the research as of the fall of 2014.

Funding for nanomedical research has been growing steadily. Research institutions are receiving funding to study nanomedicine and nanotechnology around the world. The National Institute of Health (NIH) has formed a national network of nanomedicine centers in the United States. This network is comprised of eight Nanomedicine Development Centers. These centers, or NDCs, were created to both advance the field of nanomedicine through research and "begin training the next generation of students in [the] emerging field [of nanomedicine] [55]."

The NIH focuses their efforts on understanding the inner workings of cells on the nanoscale and using

that knowledge to "develop new technologies that could be applied to treating diseases, and/or leverage the new knowledge to focus work directly on translational studies to treat a disease or repair damaged tissue [56]." The program runs for ten years, from 2005 to 2015. The NIH counts New York University, the University of California San Francisco, and the University of California Berkeley among its eight NDC locations. As of 2014, current research at New York University includes "developing culture systems to improve adoptive immunotherapy [57]," through growing cultures of memory T cells in cultures before injecting them into the body to stimulate immune response to specific pathogens. Meanwhile, the Nanomedicine Center for Nucleoprotein Machines at Georgia Tech is researching protein creation and DNA modification with the hopes of using that knowledge to either more effectively treat or even cure sickle cell disease [58], and the University of California, San Francisco is trying to create entirely new nanotechnological systems to diagnose and treat diseases like cancer [59].

In Europe, the European Commission created the European Technology Platform on Nanomedicine (ETPN) in 2005 with the goals of focusing research and raising money for funding. Their three priority focus areas are nanotechnology-based diagnostics including imaging, targeted drug delivery and release, and regenerative medicine [60]. Current (2014) research under the ETPN includes NANOCI, or Nanotechnology Based Cochlear Implants, who are working on just that – creating cochlear implants that connect directly to auditory nerve fibers, solving multiple problems with current assistive audio technology at once [61, 62]. Another group, NANOFOL, is working to design nanorobots to cure inflammatory diseases such as rheumatoid arthritis [61, 63].

Both the NIH and the ETPN, along with other institutions worldwide, have seen the potential for nanomedicine to forever change the landscape of modern medicine. Only with continued funding and research, however, will we develop the technology to realize the incredible potential of nanomedicine.

9. Conclusion

Although nanomedicine has the theoretical potential to repair organs, restore lost spinal function, and even reverse the aging process, for this paper we have focused specifically on the role of nanorobots, nanoparticles, carbon nanotubes, and other nanoscale devices in the treatment of disease. Though many of the above scenarios are currently only hypothetical, modern nanomedical research provides a solid foundation for future advances in nanoscale healthcare technology.

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