Chapter 2
Monitoring Tissue Healing Through Nanosensors

Lei Yang and Thomas J. Webster

Abstract Nanotechnology is the use of materials with at least one dimension less than 100 nm. Nanotechnology has already revolutionized numerous fields, from construction to computers. Recently, nanotechnology has also been used to improve disease detection and treatment by developing wireless in situ sensors. Importantly, the use of wireless technologies in medicine, such as wireless body area networks and wireless personal area networks, is not new as they provide many promising applications in medical monitoring systems to measure physiological data from specific anatomical areas. Nanotechnology can aid in the functioning of wireless medical devices since it can provide for materials smaller in size (thus, minimally interacting with tissues to invoke an immune response), better in properties (such as electronic), and more similar to those of natural tissues since natural tissues are composed of nanoscale entities. In fact, studies have demonstrated increased tissue growth, decreased inflammation, and decreased infection of numerous nanoscale compared to currently used micron-scale materials. Due to the above, an ever-expanding range of therapeutic and diagnostic applications are being pursued by academic and industrial researchers. This chapter aims to provide a comprehensive review of recent developments in wireless sensor nanotechnology for monitoring and controlling cell responses.

Keywords Wireless • Nanotechnology • Sensors • Diagnosis • Treatment • Diseases

1 Introduction

It is widely recognized that the growing global population is aging and this trend will place an increasing demand on medical and healthcare resources. Specifically, in 2008, there were more than 650 million people over the age of 65 and this number will double over the next 10 years. In the United States, about 20% of the population...
will be over 65 by 2030, compared to only 12% today. As a consequence of this aging, a number of chronic age-related diseases (specifically, Type 2 diabetes, cancer, congestive heart failure, chronic obstructive pulmonary disease, arthritis, osteoporosis, and dementia) have significantly increased (Fass 2007). In addition, there are more than one billion adults worldwide today who are overweight. Clearly, there is an ever-increasing shortage of doctors and nurses, and an increasing demand for healthcare services (Feied et al. 2006). Such an unbalance between “supply and demand” in medicine will place an enormous strain on our medical communities unless we develop new, novel, medical care technologies.

Some believe the future of medicine resides in wireless sensor technologies. Such wireless medical technologies may be more efficient and effective than today’s medical practices. As an example of the importance of wireless medical technologies, today, over 50% of hospitals in the United States have wireless local area networks (WLANs) and widely accessible Wi-Fi and WiMax devices, enabling practitioners to access patient medical information, both at the point of care and anywhere else it is needed (Hao and Foster 2008). Similarly, tablet PCs, PDAs and laptops connected to the WLAN allow clinicians to immediately record medical information in an electronic format, as well as order tests and prescribe medication at the patient’s bedside, all from their chosen device (Hao and Foster 2008). It is now commonplace to find doctors with computers (rather than old-fashion paper folders) when meeting with patients.

Inside the body, the use of wireless medical devices is also undergoing a revolution. Proponents of wireless medical devices highlight the possibility to now develop small, low-power, lightweight, and intelligent physiological monitoring devices. Wireless body sensor networks (WBSN) have been developed to provide real time information concerning patient health (Hao and Foster 2008). This chapter will cover some of the more exciting advances in this electronic age where wireless medical devices are revolutionizing medicine. Nanotechnology, or the use of materials with one dimension less than 100 nm, is playing a large part in this revolution by allowing for the design of materials with unique properties to interface with tissues and cells.

2 Wireless Medical Monitor Advantages and Disadvantages: The Concept

There are two essential categories of wireless medical devices: (1) wireless medical monitors and (2) wireless medical devices. Differences between these categories involve whether the devices only monitor health or also treat a medical problem. Wireless physiological measurements have a number of advantages over wired measurements, including ease of use, reduced risk of infection, reduced risk of failure, reduced user discomfort, enhanced mobility, and lower cost of care delivery.
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(Townsend et al. 2005) (Fig. 1). Many of these advantages come from the fact that no invasive procedure is needed to obtain a diagnosis using wireless medical monitors.

The paramount advantage of wireless measurements and, thus, wireless medical devices, is their potential to treat a medical problem at the location it was measured (Hao and Foster 2008). Moreover, the use of wireless physiological measurement systems outside the hospital could also help to reduce overall healthcare costs, especially among patients with chronic diseases capable of receiving care at home. Of course, the main disadvantage of wireless medical technology is the increased challenges in designing and fabricating wireless medical devices. Wireless physiological measurements have not only found applications in healthcare, but have also been applied in the areas of military, security, sport, and fitness monitoring (Hao and Foster 2008).

Clearly, a wireless physiological measurement system is meant to alert the medical emergency system if vital signs drop below certain threshold (Hao and Foster 2008). In this scenario, the exact location of the patient needs to be transmitted, along with any useful medical information that could assist the emergency team. For example, in the United States, each year, about 1.1 million Americans suffer a heart attack. About 460,000 of those heart attacks are fatal. About half of those deaths occur within 1 h of the start of symptoms and before the person reaches the hospital (Hao and Foster 2008). The use of wireless physiological measurement systems could help save lives, in that they could detect and warn of early symptoms.

Fig. 1 An illustration of various bodily functions measured by wireless medical monitors
of impending cardiac (or other) problems, enabling the patient to receive potentially life-saving treatments earlier (Hao and Foster 2008). Of course, identification of a health problem is only part of the solution. Designing sensors that can treat the medical problem after it has been identified is necessary.

A wireless physiological measurement system measures in real-time, a bio-signal for local processing (Hao and Foster 2008). A good example is an automatic internal cardiac defibrillator (AICD, also known as an implantable cardioverter defibrillator or ICD), which acts to restore the regular heart rhythm by delivering an electric shock if abnormal behavior is detected, potentially averting sudden cardiac death (Hao and Foster 2008). Another example is implantable drug delivery systems, which deliver medication more efficiently for chemotherapy, pain management, diabetic insulin delivery, and AIDS therapy, by locally processing wireless physiological measurements (Jones et al. 2006).

A wireless physiological measurement system can also provide real bio-signal information for post-processing (Hao and Foster 2008). In the military, a WPMS implementation can facilitate remote noninvasive monitoring of vital signs of soldiers during training exercises and combat. For example, it can be used to remotely determine a soldiers’ condition by medics in a combat situation, without exposing first responders to increased risks, or to quickly identify the severity of injuries and continuously track the injured condition until they arrive safely at a medical care facility (Hao and Foster 2008). Such devices can keep track of an injured person’s vital signs, allowing rapid distribution of the information to medical providers and assisting emergency responders in making critical, and often life-saving, decisions in order to expedite rescue operations (Mendelson et al. 2006). Examples of wireless physiological measurement systems can be found in Table 1 while those being used commercially and researched academically can be found in Tables 2 and 3, respectively (Hao and Foster 2008).

<table>
<thead>
<tr>
<th>Critical monitoring</th>
<th>Noncritical monitoring</th>
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<tbody>
<tr>
<td>Monitoring chronically ill patients with heart disease, diabetes, and epilepsy</td>
<td>Monitoring physical conditions and efficiency of a sport athlete during exercises</td>
</tr>
<tr>
<td>Monitoring at home and nursing home for elderly and demented people</td>
<td>Control and feedback during athlete training</td>
</tr>
<tr>
<td>Monitoring vital signs of soldiers in battle</td>
<td>Crime investigation with wireless lie detectors</td>
</tr>
<tr>
<td>Vehicles such as ambulances when transporting patients</td>
<td>In the hospital to reduce discomfort and restriction of wires</td>
</tr>
<tr>
<td>Monitoring the consciousness of drivers, pilots, and operators of heavy machinery</td>
<td>Monitoring employees to identify those who are engaged in unlawful activities</td>
</tr>
<tr>
<td>Medical research teams can carry out unobtrusive patient studies and clinical field trials over an extensive period</td>
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<td>Remote telemedicine</td>
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3.1 Treating Bone Defects

As mentioned above, while monitoring human health through the use of wireless technologies is important, so is using that information to treat a medical problem (should it be diagnosed). A great example of this approach is through the use of implantable wireless medical devices for diagnosing and treating orthopedic problems. In the United States, annually an estimated 1.5 million people suffer a bone fracture caused by various bone diseases, resulting in 165,000 hip joints and 326,000 knees replacements in 2001 (Smith 2004; Bren 2004). The number of orthopedic implant surgeries is increasing. For example, according to the American

| Table 2 | Some current commercial applications of wireless physiological measurement systems |
|-----------------|---------------------------------|-----------------|
| Commercial applications/vendor | Description | Market |
| TeleMuse Biocontrol Systems | This is a mobile physiological monitor for acquiring ECG, EMG, EOG, EEG, and GSR data from wireless sensors using ZigBee technology | Medical care and research |
| VitalSense Integrated Physiological Monitoring System | This is a chest-worn wireless physiological monitor that incorporates an ECG-signal processor and offers wireless transmission of heart rate and respiration rate to a handheld monitor | Fitness and exercise |
| The Security Alert Tracking System, Third Eye Inc. | Wrist-mounted surveillance monitors blood oxygen saturation and heart rate fluctuations noninvasively; the information is transmitted wirelessly to a central monitoring system. It can assist in apprehending employees engaged in unlawful activities in casino and banks | Security and safety |
| The Alive Heart and Activity Monitor, Alive | This Bluetooth device monitors the heart rate and activity, including ECGs, blood oximeters, and blood glucose meters. It communicates with software on your mobile phone to log and upload information to a central Internet server | Medical care, research, fitness, and exercise |
| Polar Heart Rate Monitor/Watch S625X Polar | This is a watch combined with a heart rate monitor, altimeter, and speed/distance monitor. It communicates wirelessly with a chest belt | Fitness and exercise |
| PillCam® Capsule Endoscopy Given Imaging | The tiny camera contained in the capsule captures images of the gastrointestinal (GI) tract as it travels through the body and transmits the images to a computer, so the physician can view them and make a diagnosis | Medical care |
Table 3 Examples of on-going academic research on wireless physiological measurement systems

<table>
<thead>
<tr>
<th>Research applications/vendor</th>
<th>Description</th>
<th>Market</th>
</tr>
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<tbody>
<tr>
<td>CodeBlue: wireless sensor networks for medical care, Harvard University</td>
<td>Exploring applications of wireless sensor network technology to raise alerts when the vital signs of patients fall outside the normal range</td>
<td>Medical care/military</td>
</tr>
<tr>
<td>Wireless physiological sensors for ambulatory and implantable applications, Tampere University of Technology</td>
<td>The study and development of a new wireless sensor technology for ambulatory and implantable human psychophysiological applications. The goal is to develop commercially mass-produced physiological measurement systems, based on patch-type sensors and implantable smart wireless devices</td>
<td>Medical care, research, and military</td>
</tr>
<tr>
<td>Wireless implantable sensors with advanced on-body data processing, Queen Mary College, University of London</td>
<td>The proposed feasibility study aims to deliver a clinically viable strategy that can provide a wireless connected system for implantable electrophysiological and metabolic monitoring sensors, enhancing existing capabilities in both wireless and sensor technology</td>
<td>Medical care</td>
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Academy of Orthopedic Surgeons, there was an 83.72% increase in the number of hip replacements performed from nearly 258,000 procedures in 2000 to 474,000 procedures (including 234,000 total and 240,000 partial hip replacements) in 2004. The total hospitalization costs for knee replacements doubled to $11.38 billion in 2003 compared with $5.67 billion in 1999 (American Academy of Orthopedic Surgeons 2010). Despite the increasing demand and cost of orthopedic implants, the durability of implants has not risen as most of the current implants serve only 10–15 years (Webster 2003).

All of these statistics bring a challenge of developing durable, affordable, and better orthopedic implants to the bone community, but the question is how? And, can the design and use of wireless orthopedic medical devices help? Integrating materials science and bone biology is probably one of the best solutions and most importantly, can create better interfaces between the implant and bone. More excitingly, the emergence of nanomaterials (materials with size scales within 1–100 nm, i.e., $10^{-9}$–$10^{-8}$ m) and nanotechnology (the research and development related to nanoscale materials) during the last two decades has brought more anticipation to solve the chronic challenge of creating better bone implants and wireless orthopedic devices. Here, we will introduce the frontier of exploring biological responses on implant materials, especially nanoscale materials and wireless devices, and how the design and fabrication of implant surfaces based on these explorations can ultimately aid in bone health. But first, we must discuss what biological events would need to be controlled by wireless orthopedic medical devices to treat bone problems.
3.2 Fundamentals of the Interface Between Sensors and Bone

3.2.1 Events at the Sensor–Bone Tissue Interface

Bone is a very complicated biological system that consists of both hierarchical structures and living bone remodeling units. The architecture of bone is composed of nanofibrous collagen matrices, noncollagenous proteins, and nanocrystalline calcium phosphate (mainly hydroxyapatite). Bone remodeling units involve three major types of bone cells: osteoblasts (bone forming cells), osteocytes (bone-maintaining cells), and osteoclasts (bone-resorbing cells). Therefore, one can expect the interactions at the interface of bone tissue and implant materials are very intricate events, as illustrated in Fig. 2.

Basically, all of these events can be categorized as host responses toward the implant and, conversely, material responses to the host (Puleo and Nanci 1999). In the present context, it is important to realize that an implanted wireless sensor will interact in all of the events in Fig. 2. It is also important to mention that for this application, an optimal sensor will not only sense new bone growth (and whether it is occurring), but it will also improve new bone growth. Though all of these events described in Fig. 1 are of great importance when designing a wireless medical device, there are several body responses that are of particular interest since such information can be used to determine bone health next to the sensor. (1) Protein adsorption is the immediate event once a material is implanted. Also, the type and density of the adsorbed proteins can regulate cell adhesion and subsequent cellular activities. (2) Adhesion of osteogenic cells, subsequent bone deposition, and bone remodeling are crucial factors at a successful orthopedic sensor–bone interface. (3) Sensor surface properties are also important events closely related to biomaterial cytocompatibility, immune or inflammatory responses that may ultimately cause implant failure. Immune and inflammatory cell responses are not introduced

![Fig. 2 Events at the bone–implant interface. (a) Protein adsorption from blood and tissue fluids, (b) protein desorption, (c) surface changes and material release, (d) inflammatory and connective tissue cells approach the implant, (e) possible targeted release of matrix proteins and selected adsorption of proteins, (f) formation of lamina limitans and adhesion of osteogenic cells, (g) bone deposition on both the exposed bone and implant surfaces, and (h) remodeling of newly formed bone (adapted from Puleo and Nanci (1999))](image-url)
in this chapter; however, the reader is cautioned to bear in mind that they are of exceptional importance at the bone–implant interface because if the sensor is encapsulated in scar tissue, it will not be able to “sense.”

Understandably, the bone–sensor interface is difficult to characterize because of the complexities of the various biological responses and in vivo environment. Therefore, in vitro bone cell culture models become practical and effective tools to initially investigate biological responses and cell functions on sensor surfaces. Most of the experimental results discussed in this chapter are, thus, based on bone cell culture models. Importantly, nanotechnology (or more specifically, nanomaterials) has been shown to control such events and, thus, should be an integral part of an implantable wireless sensor.

### 3.2.2 Novel Properties of Nanomaterials/Nanotechnology

Nanoscale materials are defined as materials (e.g., particles, fibers, tubes, etc.) with size scales within 1–100 nm in at least one dimension. The research and development aimed at understanding and working with (e.g., detecting, measuring and manipulating) these kinds of materials has been called nanotechnology (Balasundaram 2007). Nanotechnology emerged in the last century and has shown extraordinary potential in biomedical research applications. This potential originates from unique properties of nanomaterials compared to bulk conventional (e.g., micron grain size) materials, such as: (1) more surface reactivity as a result of much larger surface areas; (2) greatly enhanced mechanical properties (such as high ductility and high yield strength) due to various mechanisms such as increased grain boundary sliding and short-range diffusion-healing; (3) exceptional magnetic, optical, and electrical properties because of stacking, alignment, and orientation of nanoscale building blocks (grains, supermolecules, etc.); and (4) homogeneity and high purity in composition or structure thanks to reacting or mixing at the molecular or atomic level.

Furthermore, nanoscale materials or structures provide the bone community with not only novel properties to utilize but also a wide landscape to understand the biological responses on a material surface. One important reason behind this is that the comparable size of nanoscale materials enables researchers to really detect, interact, and analyze biomolecules or bio-microstructures. The other reason is that nanostructured materials can be readily tailored to reveal extraordinary variations in surface properties, which leads to accurate observations of their effects on cellular or tissue responses.

### 3.3 The Role of Sensor Surface Chemistry, Topography, and Energetics on Promoting Cell Recognition and Function

The surface properties of sensors that cells and tissues recognize (through initial protein interactions) in vivo or in vitro are chemistry, topography, and energy. As surface chemistry and topography both contribute to surface energy, which is directly
related to surface wettability, many researchers have been using surface energy to characterize the interface between materials and cells. Figure 3 summarizes the sensor (or implant)–cell interface and interactions between cells, proteins, and sensor surface properties. It is worth remembering that proteins always dictate the interactions between surface properties and cells in an aqueous environment (body fluids, culture media, etc.). Therefore, understanding the impact of surface properties on protein adsorption and activity can also be an effective tool to explore biological responses on different sensor surfaces. In this section, we follow these rationales to explain the roles surface chemistry, topography, and energetics play on cellular functions, emphasizing how nanotechnology is promoting such interactions.

### 3.3.1 Surface Chemistry

There are many factors of surface chemistry that affect biological responses on sensors, such as the inherent chemistry (i.e., the chemical or phase composition and crystallinity of materials), possibly conjugated functional groups/molecules on the surface, and surface charge/polarity due to the configuration of such chemical groups. Different types of implant materials have been shown to be either bio-inert or bioactive, which results in either morphological fixation or bioactive fixation to the host tissue (Cao and Hench 1996). The different states of fixation indicate that the inherent chemistry of materials alters the responses of biological systems, and this information has guided researchers to seek a variety of implant materials. For example, the materials for orthopedic implants range from metals (CoCrMo alloys, titanium (Ti) and its alloys, and stainless steel), ceramics (alumina, zirconia, titania, and hydroxyapatite), ultra high molecular weight polymers (polyethylene, polyurethane, and poly-lactic-co-glycolic acid [PLGA]) to biologically
synthesized substances (such as mineralized complexes of collagens, calcium, and phosphate) (Balasundaram 2007).

On the other hand, modifying surfaces with functional groups have demonstrated a crucial role in influencing cell responses regardless of the underlying inherent chemistry. For instance, a wide range of peptides (most notably, arginine–glycine–aspartic acid (RGD)) have been conjugated on various material surfaces (Ti and its alloys, hydrogels, polymers, etc.) to improve bone cell functions in vitro and in vivo (Schuler et al. 2006; Kroese-Deutman et al. 2005; Picart et al. 2005). In addition, it is also believed that electrostatic interactions play a role in biological responses to implant materials since cell membranes carry charges and virtually all interfaces are charged in aqueous solutions (Haynes and Norde 1994; Wilson et al. 2005). An observation conducted by Qiu et al. (1998) revealed that positively charged indium tin oxide enhanced the adhesion of rat marrow stromal cells but impaired subsequent cell spreading and differentiation. Itoh et al. (2006) created electrically polarized hydroxyapatite with pores and reported increased bone growth and decreased osteoclast activity. They attributed these effects to the electrical polarity on surfaces with pores.

Clearly, one aspect of how nanotechnology has been used to improve bone growth has been through altered surface chemistry. Nanotechnology exhibits a great potential to improve implant efficacy by manipulating the discrete surface chemistry regions of nanomaterials. There are several reasons for this:

1. Nanomaterials can provide much larger surface areas, more substructures (such as grain boundaries), and more active surfaces for chemical modification. For instance, nano-fibrous poly(l-lactic acid) scaffolds modified by entrapping a large amount of gelatin molecules on the scaffold surface demonstrated improvements in osteoblast adhesion, proliferation, and compressive modulus (Liu et al. 2006).

2. A variety of novel nanomaterial shapes (dots, rods, tubes, cages, etc.) can be used for patterned, anisotropic, or multiple functionalizations. One example is that incorporating segments of growth factors and antibiotics into anodized nanotubular Ti can further enhance new bone formation and inhibit infection (Yao and Webster 2006).

3. Controllable assembly of nanomaterials can be realized or adjusted to certain chemical effects by a bottom-up strategy that establishes structures from tiny building blocks (e.g., atoms, molecules, etc.). For example, layer-by-layer nano-assembly of poly(lysine)/alginate above a gelatin (or extracellular matrix) surface resulted in a 200-fold decrease in the adhesion of human fibroblasts (cells that contribute to soft, not hard, granulation tissue formation) compared to the untreated surfaces (Ai et al. 2003).

3.3.2 Topography and Roughness

Another predominant surface property that can be easily modified through nanotechnology to build better interfaces between sensors and bone is surface topography.
Among several ways of describing surface topography, roughness is a major parameter; its effects on bone tissue/cell responses has been studied intensely during the last two decades (Thomas and Cook 1985). Biologically inspired by the hierarchical micron-to-nanostructure of bones, which osteoblasts are naturally accustomed to in the body, an approach of creating nanometer roughness or nano-scale features on orthopedic implant surfaces can increase the efficacy of many orthopedic implant chemistries. This rationale has been applied to a variety of nanoscale materials (including metals (Webster and Ejiofor 2004), carbon nanofibers/nanotubes (Price et al. 2003), polymers (Washburn et al. 2004), ceramics (Webster et al. 2000), and polymer/ceramic composites (Webster and Smith 2005)), and increased osteoblast functions (such as adhesion, proliferation, differentiation, and calcium deposition, etc.) on these nanostructured materials have been reported. Meanwhile, a general positive correlation between nanoscale roughness and biological responses (i.e., increased roughness corresponds to enhanced osteoblast functions) has been established (Anselme et al. 2000; Linez-Bataillon et al. 2002). One explanation of the nanometer roughness-enhanced osteoblast functions is that large surface areas associated with increased roughness can adsorb more proteins (fibronectin, vitronectin, etc.) important for osteoblast adhesion. However, other studies suggested that proteins adsorb differentially with variations in nanoscale surface roughness (Wilson et al. 2005), perhaps relating nanometer surface features to changes in surface energetics important for controlling selective protein adsorption.

Several other nanoscale topographical features that cannot be described simply by roughness may also mediate bone cells responses at the bone–sensor interface. Texture and alignment of surface patterns have been reported to influence both osteoblast functions and orientation on materials. For example, Biggs et al. (2007) reported a decrease in osteoblast adhesion and spreading on highly ordered nanopits (120 nm in diameter and 100 nm in depth) than randomly distributed ones, noticing that surface roughness on both substrates was similar because the number of pits per area on each was approximately the same. Zhu et al. (2005) created nanoscale polystyrene grooves with spacings of 150 nm and a depth of 60–70 nm and observed alignment of osteoblast-like cells and cell-produced collagen fibers along nanogrooves. Recently, thickness gradients of coatings in the nanometer regime have also been found to influence bone cell responses. For instance, a poly(3-octylthiophene-2,5-diyl) film with thickness gradients (120–200 nm) showed a higher proliferation ratio compared to tissue culture polystyrene controls after 1 day of incubation, while cell adhesion after a period of 4 h was not affected by changes in thickness over 10–60 nm (Rincon et al. 2009).

### 3.3.3 Wettability and Surfaces Energetics

To further understand the effects of nanoscale surface topography and roughness on osteoblast responses, researchers have defined surface energy. Surface energy is
closely related to wettability (hydrophobicity or hydrophilicity) of a surface, and
the basic relationship is given by Young’s equation:
\[
\cos \theta = \left( \frac{\gamma_{SV}}{\gamma_{SV} - \gamma_{SL}} \right) \frac{1}{\gamma_{LV}},
\]
where \(\theta\) is the contact angle, \(\gamma_{SV}\) is the interfacial tension (or surface energy)
between the solid and vapor, \(\gamma_{SL}\) is the interfacial tension between the solid and
liquid, and \(\gamma_{LV}\) is the interfacial tension between the liquid and vapor.

It has been widely observed that hydrophilic surfaces are energetically favorable
for the adhesion and subsequent activities of osteoblasts as well as many other types
of cells, probably relating to the increased adsorption of several hydrophilic
proteins than hydrophobic proteins less important for cell adhesion. Measuring
surface energy demonstrates an association of the relatively high surface energy on
hydrophilic surfaces compared to hydrophobic ones, and the criterion of \(\theta=65^\circ\)
that differentiates between the two regimes has been suggested (Vogler 1999; Lim
et al. 2008). One clear study created both hydrophilic (high surface energy) and
hydrophobic (low surface energy) surfaces by modifying chemistry on quartz sur-
faces and showed that hydrophilic surfaces induced homogeneously-spaced osteo-
blastic cell growth and mineral deposition, and enhanced the quantity (e.g., area) and
quality (e.g., mineral-to-matrix ratio) of mineralization by osteoblasts (Lim et al.
2008). The authors suggested that surface energy effects on osteoblast differentia-
tion, especially mineralization, could be correlated with surface energy dependent
changes in spatial cell growth. Roughness also alters surface energy and resultant
wettability, which establishes critical connections between topography and surface
energetics. Although it has not been well substantiated, a trend of increased surface
energy resulting from the increased presence of nanometer surface features enhances
osteoblast functions has been shown in a number of studies (Anselme 2000; Das
et al. 2007; Khang et al. 2008).

In summary, surface energy is closely related to surface wettability and can be
modified through both surface chemistry and roughness. An idea of integrating sur-
face chemistry, topography (roughness), and wettability into a unified expression of
surface energetics and correlating such properties with biological responses will be
of great importance to the understanding and mediation of protein, cell, and tissue
responses on nanotechnology-created sensor surfaces.

### 3.4 Novel Sensor Surfaces: Better Biological Responses and Better Performance

Although the reasons for enhanced osteoblast functions on nanostructured materials
are under intense investigation, the evidence that osteoblasts perform better on
nanostructured surfaces is overwhelming. As one example, osteoblast responses
to carbon nanotubes (CNTs) have been studied. Due to their excellent electrical
conductivity, great mechanical strength, and unique chemical–biological proper-
ties (Iijima 1991; Lin et al. 2004; Webster et al. 2004; Smart et al. 2006; Zanello
2006), many studies have shown that CNTs are promising for bone sensor applications.
CNTs are macromolecules of carbon, classified as single walled carbon nanotubes (SWCNTs), diameter 0.4–2 nm, and multiwalled carbon nanotubes (MWCNTs), diameter 2–100 nm. In theoretical and experimental results, CNTs have an electric-current-carrying capacity 1,000 times higher than copper wires (Avouris et al. 2003). Thus, CNTs have been considered to improve the electrical properties of such sensors as well. For instance, CNT-TiN nanocomposites, composed of 12% CNTs by volume, exhibited a 45% increased electrical conductivity over TiN materials (Jiang and Gao 2005). Since bone regenerates under electrical conduction, many researchers have used CNTs to promote bone growth. For example, nanocomposites of polylactic acid and MWCNTs have been shown to increase osteoblast proliferation by 46% and calcium production by greater than 300% when an alternating current was applied to the substrate in vitro (Supronowicz et al. 2002).

Also, CNTs have been used to increase the mechanical strength of nanocomposite scaffolds for bone tissue engineering. SWCNTs, functionalized with phosphates and poly(aminobenzene sulfonic acid), can substitute as collagen to direct the anisotropic crystallization of hydroxyapatite (HA) reaching a thickness of 3 mm after 14 days of mineralization, resulting in composites that can be used as supporting scaffolds for orthopedic applications (Zhao et al. 2005). MWCNTs improve the mechanical properties of the as-aligned HA composite coatings (Chen et al. 2007). Balani et al. (2007) showed that a MWCNT reinforced HA coating promoted human osteoblast proliferation in vitro compared to a normal HA coating, and osteoblasts were observed near MWCNTs regions.

CNTs exhibit a large surface area to volume ratio, which may support and promote cell attachment. It has been investigated that a large number of human osteoblasts adhered more on carbon nanofiber (CNF) micro-patterns than polycarbonate urethane (Khang et al. 2006). The morphology of osteoblasts extended in all directions within CNT scaffolds formed on polycarbonate membranes (Aoki et al. 2005). Nanophase poly(lactic-co-glycolic) acid (PLGA) casts of CNF (average diameter = 60 nm) compacts possessed a higher degree of nanometer surface roughness by approximately 50%, which increased osteoblast adhesion after 1 h compared with PLGA casts of conventional CNFs (average diameter = 200 nm) (Price et al. 2004).

Moreover, osteoblast-like cells also significantly enhanced their adhesion on vertically aligned MWCNTs arrays on substrates another great sensor, which were prepared by lithography. It was observed that the periodicity and alignment of vertically aligned MWCNTs considerably influenced the growth, shape, and orientation of the osteoblasts (Giannona et al. 2007). Zanello also showed that single/multi-walled CNTs scaffolds with/without surface modifications are suitable for osteosarcoma ROS 17/2.8 cell proliferation. Lastly, the cell densities and transforming growth factor-β1 secreted by human osteoblast-like (Saos2) cells were higher on MWCNT scaffolds compared with polystyrene and polycarbonate scaffolds.

Importantly, in the studies mentioned above, CNTs were synthesized by a number of different techniques, yet all showed greater osteoblast functions. CNTs can be produced by a laser furnace, the arc, and chemical vapor deposition (CVD). However, CVD is a scalable and controllable method to obtain high purity CNTs. Sato et al. (2005) revealed that cobalt (Co) particles could extend their catalytic ability by combining with Ti particles when growing MWCNTs by CVD and forming
a strong contact between Ti and MWCNTs. All of these techniques speak well for creating a sensor composed of electrically active CNTs that can also positively interact with bone cells.

Importantly, for such sensor design, cell responses transduce and transmit a variety of chemical and physical signals to produce specific substances and proteins within specific tissues and organs. The in situ sensing of proteins from specific cell induction processes can be employed as a signal of specific cellular responses or bone regeneration. For example, in a previous study, MWCNTs grown by the CVD technique out of anodized Ti nanotubes (Fig. 4) exhibited excellent electrochemical properties and stability. An in vitro study showed the redox of proteins could be enhanced on MWCNTs grown from an anodized nanotubular Ti (MWCNT-Ti) electrode in order to sense bone growth (Sirivisoot et al. 2007; Sirivisoot and Webster 2008), and such a sensor can promote osteoblast proliferation and differentiation after 21 days on MWCNT-Ti. MWCNT-Ti can thus be used as a bio-sensing material to generate electrical signals, which can be interpreted later as information.

Moreover, coupling drug delivery to implantable wireless sensors enables on-command diffusion-controlled drug delivery systems by using radio-frequency, which is a new approach in the orthopedic field. There is a need for new technology for the delivery of soluble/insoluble or stable/unstable therapeutic compounds locally to improve the bioavailability of drugs. Polypyrrole is a conductive electroactive polymer, which has been shown to be biocompatible and has been proposed

Fig. 4 SEM micrographs of multiwalled carbon nanotubes (MWCNTs) grown out of an anodized nanotubular surface: (a) currently implanted conventional titanium (Ti) which has no sensing capabilities; (b) anodized nanotubular Ti which has no sensing abilities; and (c) side and (d) top views of MWCNT grown out of anodized nanotubular Ti which has bone growth sensing abilities
for several in vivo applications, such as a conductor for the electrical stimulation of cells. PPy can be synthesized on Ti for local drug delivery, promoting bone regeneration, and carrying therapeutic drugs. Typical doses of antibiotic/anti-inflammatory drugs need to be large for hip/knee implants. Improvement in the delivery efficiency and localization may also result by controlling the thickness and the area of the polypyrrole membrane. Thus, sensors are being developed that can sense new bone formation, and if that is not happening, release drugs to promote new bone growth. Similar attempts are being attempted for decreasing orthopedic implant infection and inflammation.

In summary, this exciting new nanomaterial, or CNTs, may become a powerful tool in bone sensor applications in terms of their nanofeatures, superior mechanical properties, and higher electrical conductivity to sense and control cellular behavior. Continuing the careful studies on CNTs may discover additional potentials for this novel biomaterial for engineering biocompatible nanomaterials and nanodevices for various sensor applications.

4 Summary and Remaining Challenges for Wireless Monitoring and Sensing Medical Devices

Wireless physiological measurement systems, like other innovations, seek to reduce risks (Hao and Foster 2008). However, all new technologies have unanswered questions. The major remaining questions concerning all wireless medical devices (whether implantable or not) are as follows (Hao and Foster 2008):

- **Reliability** – the main challenge is to make sure that information reliably gets to its destination. The reliability of a wireless physiological measurement system relies on many aspects, such as reliable wireless communication between nodes, efficient computation in each sensor node, and stable software programming (Hongliang et al. 2006).
- **Biocompatibility** – the shape, size, and materials are restricted for sensors that directly act on the human body. One solution is to package the sensor nodes in biocompatible materials and use nanomaterials, which appear to optimally interact with biological tissues (Hongliang et al. 2006).
- **Portability** – the size of the sensors used in wireless physiological measurement systems and in implantable sensors needs to be small and lightweight.
- **Privacy and security** – there are big security issues to be considered, such as eavesdropping, identity spoofing (i.e., the assumption of a trusted user’s security credentials during a communication session), and redirection of private data to unauthorized persons. Security can be improved using data encryption. It is necessary to protect private data from improper access and alteration.
- **Lightweight protocols for wireless communication** – must support self-organizing networks (including security aspects) and be able to perform data collection and routing.
• Energy-aware communication – it is desirable for sensors to transmit at low power. An energy-aware protocol is necessary to allow sensors to negotiate their transmission power to a minimum.

• RF radiation safety – the electromagnetic radiation must be within the recommended SAR limits. In the United States, the FCC has set the safe exposure limit to a SAR level at or below $1.6 \text{ Wkg}^{-1}$ in 1 g of tissue. In Europe, the European Union Council has adopted the SAR limit of $2 \text{ Wkg}^{-1}$ in 10 g of tissue.

However, in light of these high demands for sensors, the excitement concerning developing more efficient and effective medical devices based on wireless medical sensor technology makes this journey worth every effort.

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