Implants with Sensing Capabilities

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Abstract: Due to the aging human population and increased numbers of surgical procedures being performed, there is a growing number of biomedical devices being implanted each year. Although the benefits of implants are significant, there are risks to having foreign materials in the body that may lead to complications that may remain undetectable until a time, at which the damage done becomes irreversible. To address this challenge, advances in implantable sensors may enable early detection of even minor changes in the implants or the surrounding tissues and provide early cues for intervention. Therefore, integrating sensors with implants will enable real-time monitoring and lead to improvements in implant function. Sensor integration has been mostly applied to cardiovascular, neural and orthopedic implants, and advances in combined implant-sensor devices have been significant; yet there are needs still to be addressed. Sensor-integrating implants are still in their infancy; however, some have already made it to the clinic. With an interdisciplinary approach, these sensor-integrating devices will become more efficient, providing clear paths to clinical translation in the future.

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1 Introduction

The body normally functions autonomously, controlled by the interplay of "smart" and integrated chemical, electrical and mechanical mechanisms that act within, between and among cells and tissues in the body.[1,2] These biological communication networks and repair mechanisms maintain homeostasis and manage problems associated with threats by pathogens and malignancies, damage due to wounds and other pathophysiologic disturbances.[3] Using clinical examination and various diagnostic modalities, physicians can pick up some of the signs and signals associated with these processes, which can be used to guide appropriate therapy in the form of medical or surgical treatments that augment the body's intrinsic healing properties.[4]

Although the number and types of implants used in medicine have increased dramatically due to significant advances in microelectronics,[5] biotechnology,[6] materials,[7] and improved surgical techniques,[8] these interventions are still associated with a number of complications that can lead to implant failures; the subsequent impact of implant failure on patient health and life and healthcare costs is significant.[9,10] Therefore, an ability to monitor implants more closely is required.[11] With advances made in sensor,[12] communication[13] and related technologies,[14] implants can be watched more closely, and any unwanted issues can be identified and addressed early. In this manner, early signs of infection or inflammation can be recognized, e.g. by using microsensor strips in hybrids of the thin film,[15] and signs of integration or failures can be monitored using the electro-mechanical impedance of piezoelectric materials that work as both sensors and actuators.[16] Implant-incorporated sensors can also report to, and communicate with, external devices.[13,17] By integrating various technologies, patient-controlled or autonomous smart implants and advanced devices will, ultimately, be developed for improved human health.

The development of implants with incorporated sensors was spearheaded by devices designed for the treatment of conduction block in the heart, a condition that results in slow heart rate, fainting spells and death.[18] These devices were initially stimulators that lacked synchrony with the heart's spontaneous action, so-called fixed-rates pacemakers. It was soon realized that at a minimum, a pacemaker needs to sense spontaneous heart contractions to prevent it from producing a pacer impulse that could induce dangerous arrhythmias by stimulating the heart in a vulnerable phase, potentially leading to cardiac arrest. Pacemaker implants have since undergone dramatic developments with multiple sensors incorporated.[18]

Most non-cardiac implants, such as orthopedic implants, have not had incorporated sensors and their function has remained mechanical and nonadaptive or sensing. Progress in micro- and nano-electronics,[5,19] transcutaneous energy transfer[20] and transfer of information[17] changed in the landscape of implant monitoring and has led to a future of early detection and intervention.[11] The vision is to have implants that, in addition to their primary function, can sense locoregional environmental changes and relay relevant information to the patient or the care provider. Ultimately, implants will be autonomous, correcting themselves independently.[4] To achieve this, implants should have actuator, sensor, communication and control components. This review focuses on implants with integrated sensors for monitoring of various parameters related to the implant itself or its microenvironment, in order to detect implant-related problems and failures (**Figure 1**). We focus on the sensing domain, and, in particular, on evolving implants with sensing capabilities which is the central part to achieve this vision. Implants that have sensing as the only function or part enabling their function, such as vestibular implants or glucose measurement implants, are therefore not included in this review.

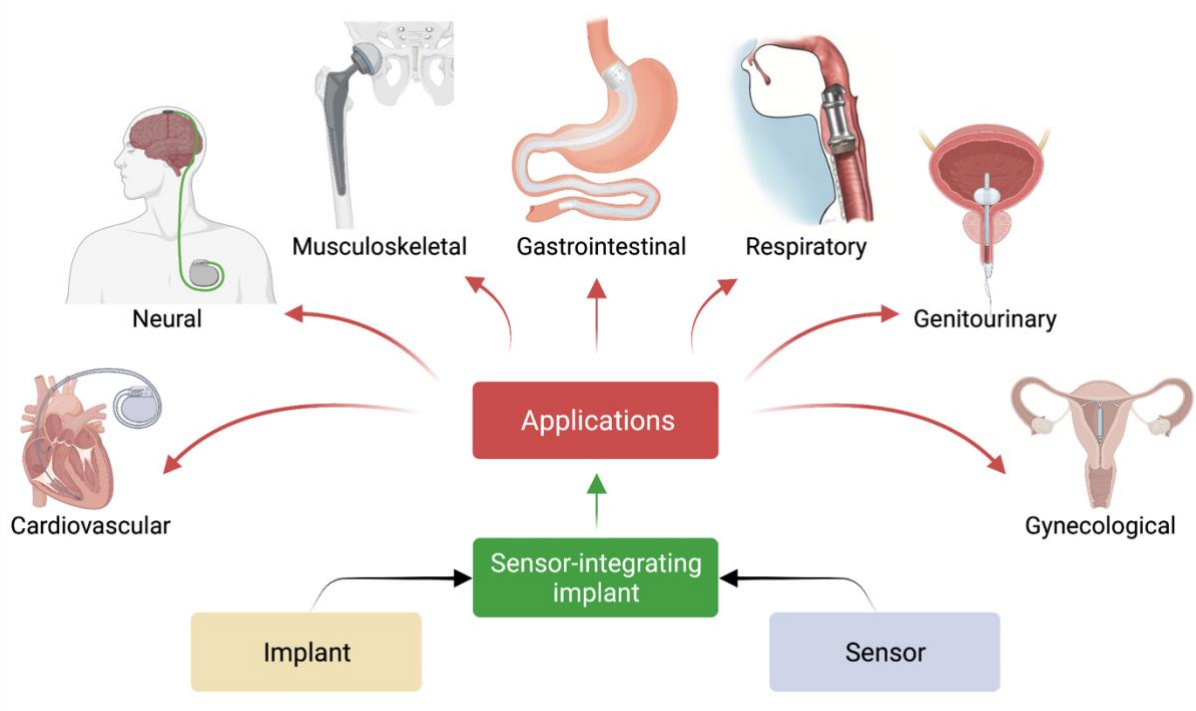

Figure 1. An illustration showing development of new generation of multifunctional sensor-integrating implants and their common applications. The illustration was created using BioRender.com. Gastrointestinal implant is reproduced.[21] Copyright 2017 Korean Society of Gastrointestinal Endoscopy under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/3.0/). Laryngeal implant is reproduced with permission.[22] Copyright 2014 Wiley.

2 Current Implants, Problems and Limitations

2.1 Current Implants

With the global increase in the aging population, and associated trauma and disease,[23] the use of implants is increasing, with the implant market accounting for USD 157.97 billion in 2021 (**Figure 2**). Implants are used for mending,[24-26] reconstruction,[27-30] repair[31-37] and regeneration[29,38,39] of tissues (**Figure 3**). They can also be used as stents, shunts and tubes. Implants evolved from bioinert[40-43] to bioactive,[44-46] biodegradable[47-49] and multifunctional,[50,51] and they can be integrated with sensors to move to the next generation.

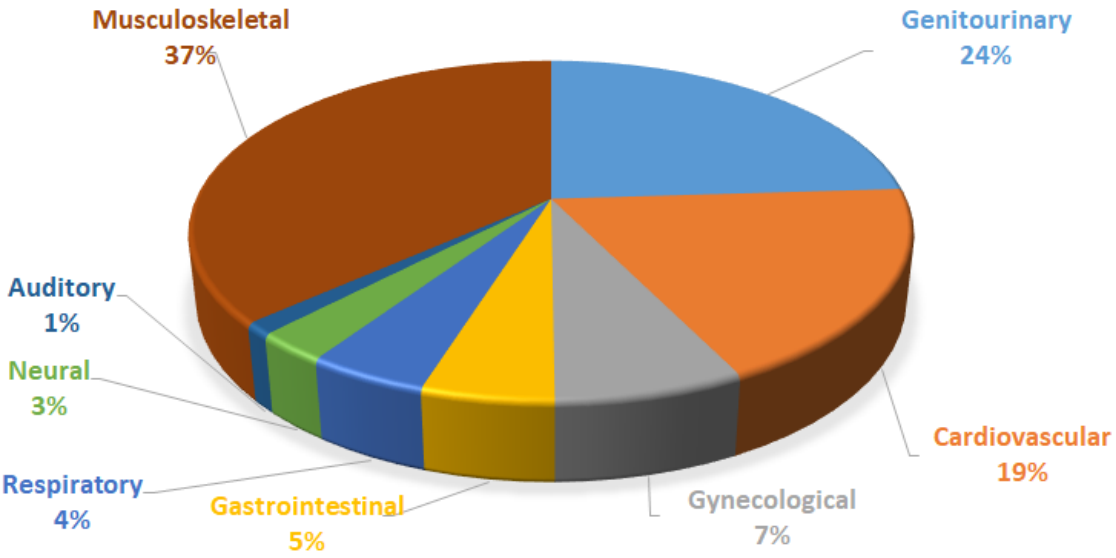

Figure 2. **The global market share of implants.** Projection of the implant global market share in USD for 2021 by implant categories.

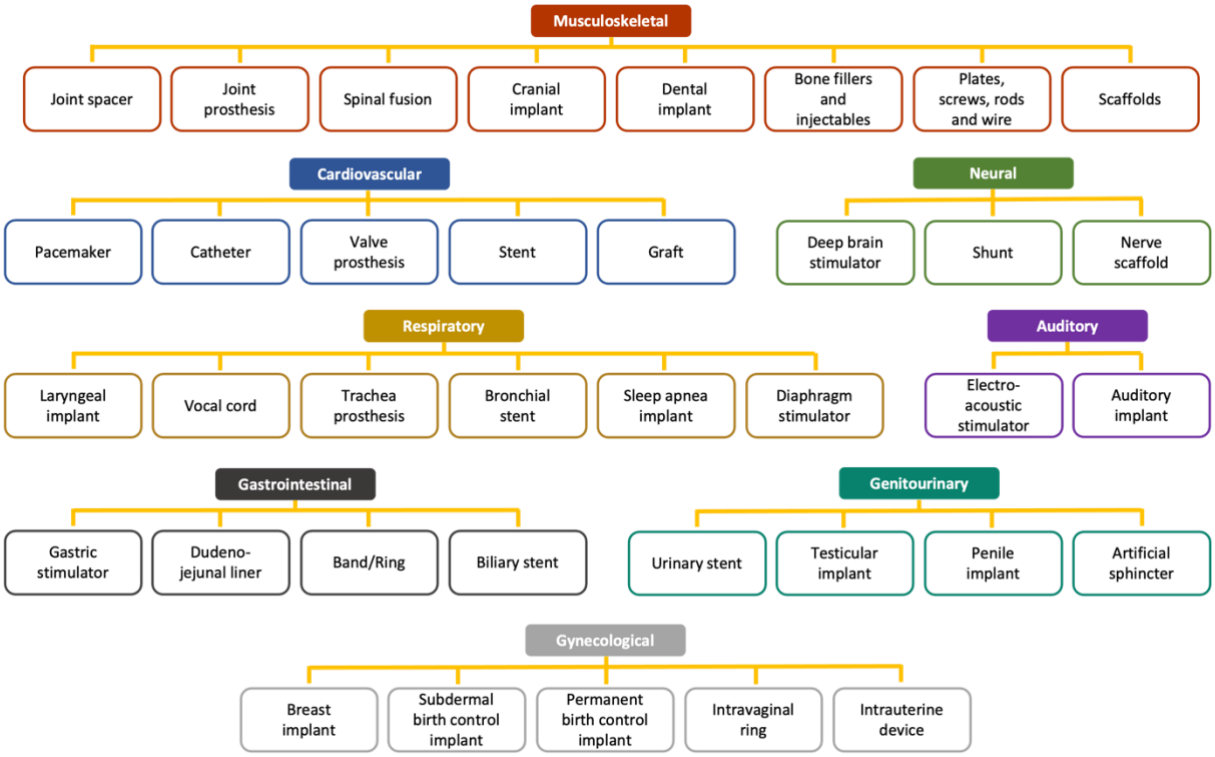

Figure 3. **Commonly used relevant implants.**

2.2 Problems and Limitations of Current Implants

Although measures are taken to prevent complications, implants may be associated with chronic inflammation,[23,52,53] infection,[54-56] failure of integration,[57] fatigue, implant failure,

leak, degradation and particle release,[58-64] migration,[65-69] and thrombosis, obstruction and occlusion,[70-73] and lack of remodeling, responsiveness and sensing capability (**Figure 4**, **Table 1**), and these can benefit from integrating appropriate sensors to implants to enable their early detection (**Table 2**).

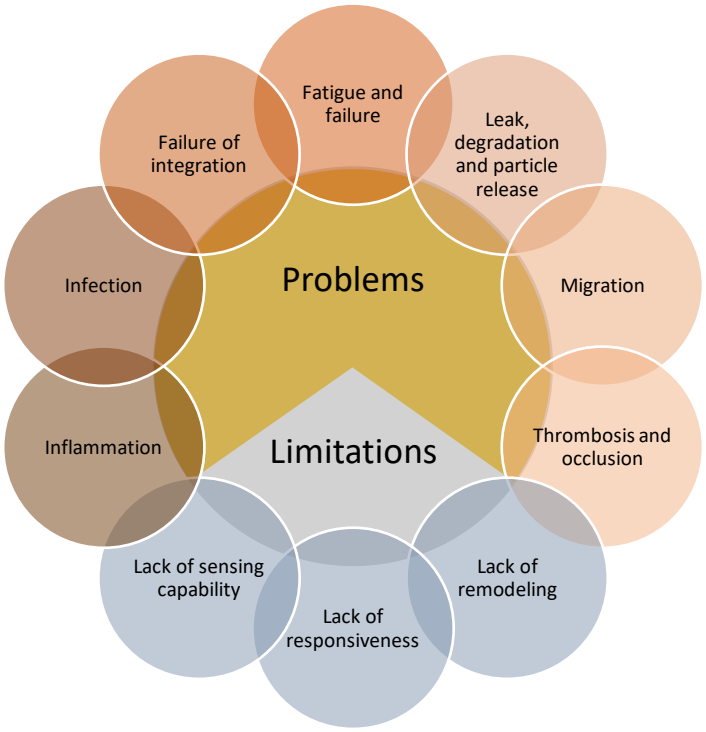

Figure 4. Common problems and limitations associated with implants.

Table 1. Current strategies to prevent and detect issues associated with implants.

No.	Implant issue	Strategies to prevent issues	Strategies to detect issues
1	Inflammation	Anti-inflammatory drugs, anti-inflammatory coatings (micro- and nano-patterning), controlled material stiffness	Imaging, blood tests, clinical examination
2	Infection	Antibiotics, surface patterning, surface charge, functionalized surfaces, antimicrobial components, drug release	Imaging, blood tests, clinical examination
3	Failure if integration	Osteoconductive material, e.g. bonding with tissue using bioactive glass or oxidized surface layer on titanium, graduated materials, matching stiffness, biodegradable and smart materials, e.g. stimuli-responsive materials, growth factors	Imaging, functional assessment
4	Fatigue, implant failure, leak, degradation and particle release	Durable materials, composite materials, reinforced materials, natural materials, flexible materials, adaptive materials	Clinical examination, imaging, blood and other tests
5	Migration	Biodegradable materials	Functional assessment, clinical examination, in vivo visualization and monitoring

6	Thrombosis, obstruction and occlusion	Hematocompatible materials, biomimetic surfaces, cellular implants, anti-coagulant releasing	Continued monitoring using imaging techniques, clinical examination
7	Lack of remodeling	Biodegradable materials, smart materials	Imaging
8	Lack of responsiveness	Stimuli-responsive materials, shape-memory materials, self-healing materials	Imaging (positron emission tomography and functional magnetic resonance imaging)
9	Lack of sensing	-	Sensors in limited number of implants

Table 2. Summary of current implants showing main mechanisms of failure, consequences they may have and sensors that can possibly be used to monitor mechanisms of failure.

No.	Implant	Mechanism of failure	Consequences	Sensors to detect failure	Refs.
A	**Musculoskeletal**				
	Cranial implant	Infection, bone resorption	Sunken cranioplasty, neurologic deficits and hydrocephalus	Force and temperature distribution sensors	74-77
	Dental implant	Fracture, cement failure, tissue reactions, bone loss and loss of integration	Loosening	Bacterial detection sensors and DNA biosensors	78-81
	Spinal fusion	Failure of integration, infection	Nonunion, bacterimia and septecemia	Resonance frequency and dampening sensors, and force sensors	82-84
	Joint prosthesis	Infection, fracture, migration, wear, osteolysis, and implant fracture	Instability, implant loosening, revision operation and death	Chemical, force and temperature sensors	85-87
	Joint spacer	Implant dislocation and fracture and allergic reactions	Femoral fracture	Temperature sensors and DNA biosensors	81,88-90
	Bone fillers and injectables	Bone resorption, fracture and infection	Failure and bacterimia	Temperature and strain sensors, and DNA biosensors	81,91-93
	Plates, screws, rods and wires	Infection	Nonunion and bacterimia	Optical and pH sensors	94-97
	Scaffolds	Fracture, inflammation, infection and dislocation	Failure and allergic reactions	Strain and pH sensors	98-100
B	**Cardiovascular**				
	Pacemaker	Mechanical failure	Cardiac and respiratory arrest, acute coronary syndrome, cardiac perforation, pneumothorax, hemothorax, stroke, infection, hemodynamic instability and death	Heart rate sensors	18,101,102
	Catheter	Thrombosis	Retroperitoneal bleeding, pseudoaneurysm, arteriovenous fistula, dissection, embolism, myocardial infarction, stroke, atheroembolism, arrythmias and radiation injury	Chemical and pH sensors	103
	Valve prosthesis	Thrombosis and structural valve dysfunction	Endocarditis and hemolysis	Blood flow sensors	102,104-106
	Stent	Thrombosis, perforation and stent failure	Closure	Vessel pressure capacitive resonator sensors	107-109
	Graft	Thrombosis, infection and graft failure	Embolism, stroke, myocardial infraction, atrial fibrillation and pulmonary hypertension	Inertial (with accelerometer and gyroscope) and pressure sensors	110-113
C	Neural				

	Deep brain stimulation	Migration, component fracture, failure and infection	Loss of effect	Motion sensors	114-119
	Shunt	Mechanical failure, obstruction, infection and inflammation	Loss of function	Flow and resistance measuring sensors	24,120,121
	Nerve scaffold	Calcification, migration, infection and allergy	Aberrant regeneration	Electrical activity sensors	29,39,122
D	Gastrointestinal				
	Gastric stimulators	Inflammation and infection	Device failure, erosion, tissue damage, stomach wall perforation, lead penetration and lead obstruction	Electrical activity sensors and three-axis accelerometer	25,123-129
	Duodeno-jejunal (DJ) liners	Migration and pancreatitis	Bleeding and cholestasis	Glucose sensors	25,130-133
	Bands/rings	Erosion into the esophagus	Ulcers and bleeding	Impedance and pH sensors	25,35,134-138
	Biliary stents	Infection and blockage	Pancreatitis, cholangitis, bleeding, device failure and duodenal perforation	Magnetoelastic resonator and pH sensors	25,36,139-141
E	Respiratory				
	Laryngeal implant	Infection and migration	Implant revision, suboptimal voice and airway obstruction	Temperature and pH sensors	142-145
	Vocal cord	Extrusion and infection	Airway obstruction	Temperature, moisture and pH sensors	146-149
	Trachea prosthesis	Inflammation (Granuloma) and migration	Dehiscence, pulmonary insufficiency and pneumonia	Micro-electro-mechanical and volatile organic compounds (VOC) sensors	150-154
	Bronchial stent	Migration, restenosis, granulation tissue formation, stent fracture, infection and mucus plugging	Airway obstruction	Flow sensors	37
	Sleep apnea implant	Fracture and decementation	Loosening	Thoracic impedance sensors	155-157
	Diaphragm stimulator	Infection	Pain	Temperature, bacteria and pH sensors	158
F	Genitourinary				
	Urinary stent	Infection and encrustation	Hematuria and tissue irritation	Encrustation sensors	159-161
	Testicular implant	Extrusion and infection	Pain and hematoma	Displacement sensors	30,162,163
	Penile implant	Mechanical failure, infection and migration	Pain and erosion	Pump speed, leak, electrical shorts and temperature sensors	164-166
	Artificial sphincter	Infection, erosion and silicone shedding	Urinary retention, stricture, hematuria and urinary frequency	Pulse oximeter saturation sensors	167-170
G	Gynecological				
	Silicone implant	Hematoma, migration, infection, capsular contracture and implant buckling	Wound dehiscence, pain, leakage and rupture	Reflective photoplethysmography (PPG) sensors	171,172
	Subdermal birth control implant	Infection and implant expulsion	Menstrual disturbances and lower abdominal pain	pH and inertial sensors	173-177
	Permanent birth control implant	Immune reactions and migration	Chronic pain, perforation and bleeding	Pulse, respiratory and heart rate sensors	178,179
	Intravaginal ring	Vaginal irritation and infection	Bleeding	Gravimetric biomedical micro-electro-mechanical sensors	180-182

	Intrauterine device	Implant expulsion and inflammation	Uterine perforation, ectopic pregnancy and pelvic inflammation	Distance sensors	183-186
H	Auditory				
	Electroacoustic stimulator	Infection and flap necrosis	Bleeding, swelling, tinnitus, meningitis, dizziness and balance issues	pH and paper-based bacterial sensors	43,187-191
	Auditory implant	Infection	Meningitis, balance issues and headache	pH and electrochemical sensors	188,192-195

2.2.1 Inflammation

Inflammation is a normal body response to injury or contact with foreign materials.[196] Uncontrolled, inflammation can significantly hamper the function of the implant,[197] lead to implant degradation, and chronic cellular response (e.g. osteolysis) that leads to tissue loss in the immediate vicinity of the implant.[23,52] Therefore, the problem of chronic inflammation must be identified and managed before it becomes irreversible, and the implant is loosened or fails.[53]

2.2.2 Infection

Implant-associated infections comprise 25.6% of healthcare-related infections in the USA alone,[56] costing USD ~100,000/patient.[198] Bacteria tend to adhere to inanimate objects and form biofilms, a structured microbial community that creates a barrier, which excludes antibodies, immune cells and antibiotics. Untreated, infections may lead to septicemia and death.[23] Therefore, signs of infection need to be identified early to enable early interventions that prevent biofilm formation and progression. If infections are not eradicated early, implant removal becomes unavoidable.[23,199]

2.2.3 Failure of integration

Implant-to-tissue integration is key to ensuring a result of normal physiological loading of implants and healing.[28,200] For example, failure to integrate orthopedic implants into the bone leads to implant loosening, loss of mass in the surrounding bone, loss of implant function and the need for revision surgeries, which are extensive.[57]

2.2.4 Fatigue, implant failure, leak, degradation and particle release

Implants may undergo wear, corrosion, degradation, fatigue and fracture.[58] Implants may fail due to the effect of the surrounding environment, which includes chemical, mechanical and temperature challenges.[23] Implants can also fail due to malfunction of individual components, especially in joint arthroplasty cases, which is a significant concern due to the increased numbers of elderly recipients and a variety of available devices.[58] Degradation of the implant may lead to crevice corrosion and the release of corrosion products,[59] ultimately leading to inflammation and loss of function. The dislocation of components of an implant can also lead to implant failure and warrant intervention.[61] Implant fracture may, in some instances, result in catastrophic outcomes leading to death, as was reported with arterial vascular stent fracture.[62-64] Leak is also a problem that may complicate, e.g. vascular implants such as stents (endoleak).[201]

2.2.5 Migration

One of the major problems of implantation is migration or displacement from the initial implantation site.[67] For example, hip replacement displacements occur in about 4% of first-time surgeries and about 15% of revision replacements.[202] Implant migration may also result from the foreign body reaction, which leads to movement of the implant or its parts,[66-68] and even exteriorization of the implant in extreme cases.[203] Implant migration in pediatric cases can also be passive resulting from normal patterns of tissue growth, where the growth of the skull occurs by laying of new bone externally and resorption from the intracranial side.[69] Migration may also occur because of external factors such as the application of magnetic resonance imaging (MRI)[204] or trauma such as may occur with cochlear implants.[205] Initial factors such as infection can also contribute to implant migration and externalization.[206] Therefore, attending to causative factors and monitoring for early signs of implant displacement are required.

2.2.6 Thrombosis, obstruction and occlusion

Devices that come in contact with blood, such as stents and ports may be complicated by thrombosis,[70] in 18% of patients.[71,72] Thrombosis may lead to complete occlusion of vessels,[73] with subsequent distal ischemia[207] that leads to death of the downstream tissue or patient death, such as may occur in myocardial infarction.[208] Although stents have been laced with drugs that can prevent tissue growth and thrombosis,[31] studies have revealed that thrombosis may still occur.[31] Detecting signs indicative of thrombosis that enable early intervention would have a significant impact on both safety and efficacy of stents.

2.2.7 Lack of remodeling

Most of the implants are made of rigid materials that have different mechanical and elasticity properties,[209] which may affect the loading of the surrounding tissues and remodeling.[210] Remodeling will always allow for improved tissue-implant bonding, and it is influenced by biomechanical stresses.[211] For example, in dental implants, continuous remodeling is required to replace the regions damaged by implant fatigue.[212] Although the development of biodegradable devices[48,213,214] have, to a large extent, affected the loading and remodeling in the surrounding tissues, current implants themselves remain static and unable to adjust or react to varying stresses and loading forces.[23]

2.2.8 Lack of responsiveness

Lack of responsiveness in implants contributes to the failure of their integration and remodeling and may also be associated with failure in the short and long term. To develop responsive implants, attempts have been made to develop biologically mimicking materials and to build smart devices that can react to external factors.[6,215] Therefore, the use of stimuli-responsive materials,[216-218] shape-memory materials[219,220] and self-healing materials has been explored and continue to be developed.[221,222]

2.2.9 Lack of sensing capability

Conventional implants cannot sense changes in the surrounding environment and tissues. Therefore, the development of implants with sensing capability will help in detecting changes in the implant or its microenvironment early on before damage or problems become irreversible.

3 Sensing

Sensors,[12] in general, have different components which are designed to reduce errors, size and cost (**Figure 5**). Sensors are typically categorized by what they sense,[223] or how they sense (**Figure 6**).[223] In this section, we discuss sensors relevant to sensor-integrating implants, including their working principle, and applications.

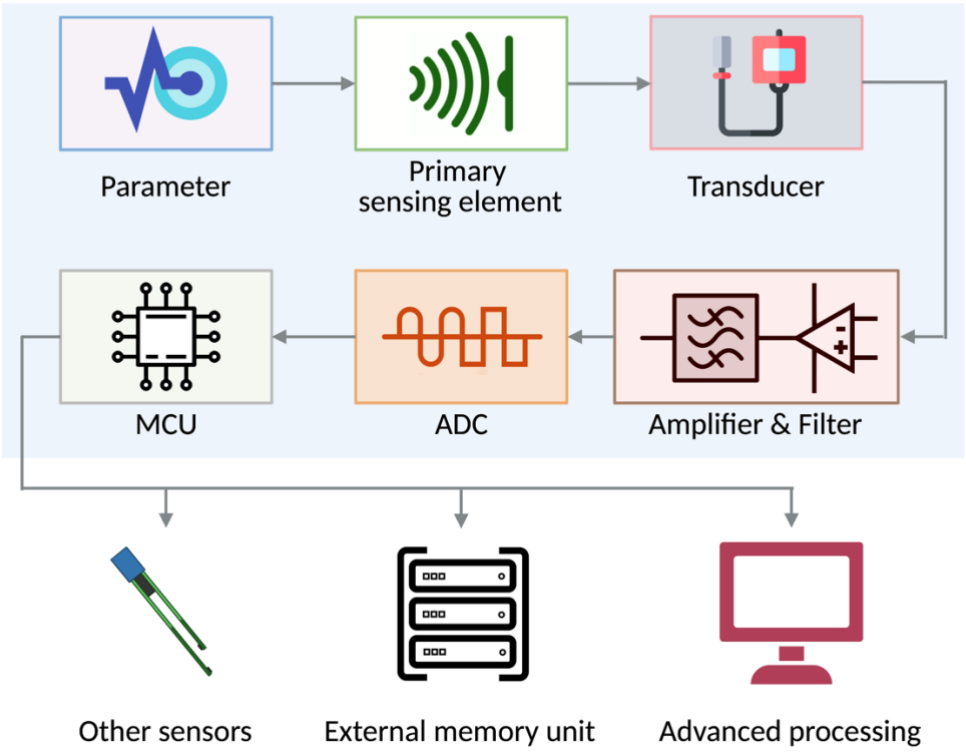

Figure 5. Block-schematic of the sensor-integrating units for signal conditioning and processing. The first unit is a primary sensing element which senses parameters such as temperature, pressure, force, etc. The primary sensing element is connected to a conversion element (transducer). The transducer converts the sensing output by amplification and filtering to a signal suitable for further processing [analog-to-digital converter (ADC) and microcontroller unit (MCU)] and transmission. The MCU can be connected to other sensors

or an external memory unit, or a PC for advanced data processing. The illustration was created using BioRender.com.

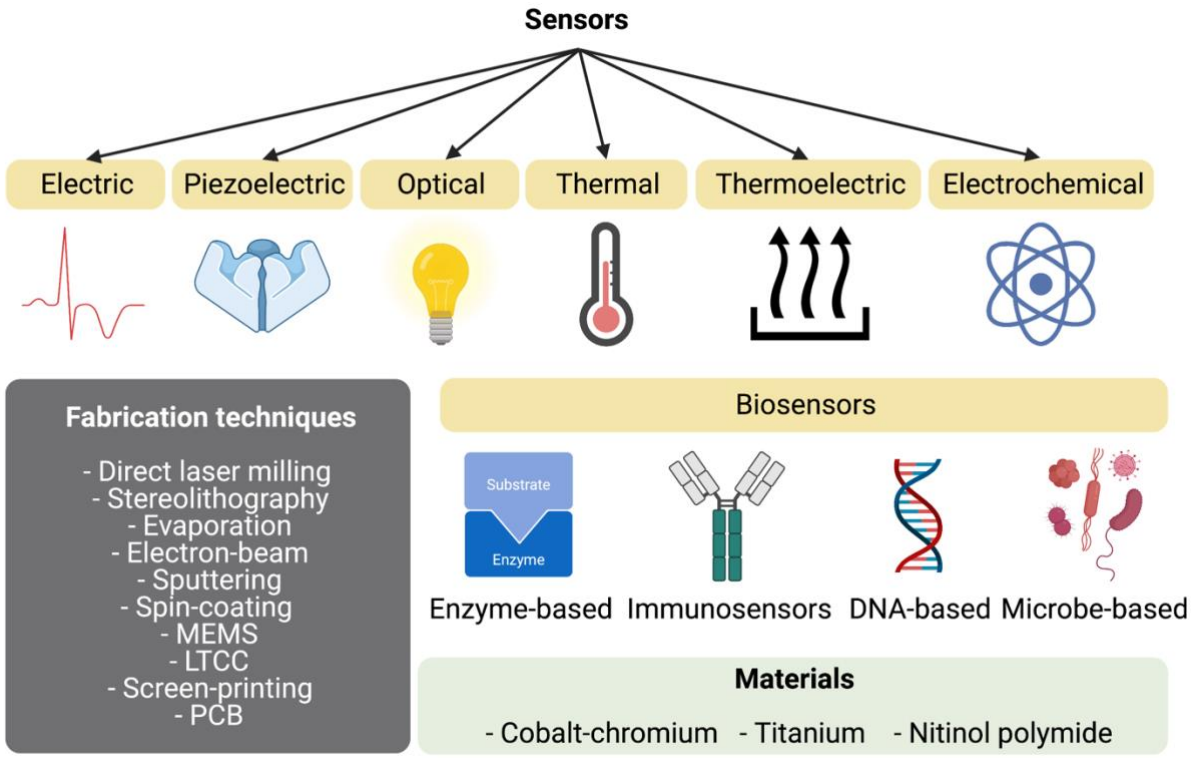

Figure 6. **Types of sensors, materials they are made of and their fabrication techniques**, which include direct laser milling, stereolithography, microelectromechanical systems (MEMS), low temperature co-fired ceramics (LTCC), printed circuit board (PCB), etc. The illustration was created using BioRender.com.

3.1 Electric Sensors

Electric sensors change either resistance, capacitance, or inductance upon applying a physical stimulus.

3.1.1 Resistive sensors

Resistive sensors are based on the principle that a change in resistance can be produced by a change in a physical variable. They are useful for detecting temperature and strain because of their simple construction, durability, dynamic range and low cost. The most common resistive sensors are resistance temperature detectors (RTDs), thermistors and strain gauges. Temperature dependence of resistivity is linear or close enough to linear for some materials, making them as very good choice for temperature sensing. The typical measurement range of

RTD and thermistors associated with implants is from 20 °C to 100 °C, with accuracy of ±0.2 °C, with the reported response time of 130 °C/min.[224] Therefore, RTD and thermistors are predominantly used for temperature sensing,[225] e.g. to have real time diagnosis of infection of dental implants.[224] Polydimethylsiloxane (PDMS) and polyethylene terephthalate (PET) based strain sensors have functional operation of three hours in liquid environment.[226] The sensitivity and resolution are 2.5 times better for PET-based sensors (2.5 mV/kPa) when compared to the PDMS-based sensors (1 mV/kPa). The dynamic range of the PET sensor is at least 100 kPa with the response time of 1.5 seconds.[226] Accordingly, a wide range of applications of strain gauge sensors have been reported and they include displacement measurement to monitor fracture healing (e.g. the measurement range of 2.25 mm displacement under a force of 100 N),[227] force on dental implant prostheses at various occlusal heights,[228] *in vivo* test monitoring of bladder pressure[226] and acceleration monitoring for musculoskeletal applications.[229]

3.1.2 Capacitive sensors

Capacitive sensors are formed by two small conducting plates, separated by a dielectric material. A change in physical variable produces a change in either the distance between electrodes, their overlapping area, or dielectric properties of the material. They are generally used for level (change of overlapping area between electrodes), strain, force, and pressure (change in distance between electrodes), or humidity monitoring (change in dielectric properties of the material between electrodes). Their high sensitivity even with small force magnitudes makes them useful for applications such as histomorphometrical evaluation of dental implants and bone growth around them over time.[230] Sensor capacitance during bone development ranges from 20 nF to 1.57 µF.[230]

3.1.3 Inductive sensors

Inductive sensors usually consist of a magnetic core with an air gap and a coil. Due to the much higher permeability of the core when compared to the air, magnetic resistance (reluctance) is mostly determined by the length of the air gap. Therefore, a very small change in air gap size leads to a large change of the inductance. The durability of these sensors makes them advantageous for use in bone implants. Therefore, they are used for measurement of displacement and strain,[231] e.g. to monitor strain response of bone prostheses,[232] where an inductive strain sensor placed in an LC circuit reported shift of resonant frequency of 4.555 Hz/με.[232] Inductive sensors can also have wireless communication and power transfer. These advantages will enhance their applications and enable their use in future to monitor bone implants remotely.

3.2 Piezoelectric Sensors

Piezoelectric sensors employ a direct or reverse piezoelectric effect. In the former, electric charge is produced when the material is deformed. This is the basic mechanism for sensors used in detecting stress in knee implants.[233] This is suitable for this application because sensors can be self-powered (e.g. 12 μW of energy can be harvested with four sensors)[233] and can provide feedback about the alignment and balance of the knee prosthesis during surgery and recovery periods. In the reverse piezoelectric effect, the material deforms when voltage is applied, which can be employed for obtaining genetic information of a pathogen such as, *S. aureus*[234] which can be implicated in implant related infections.[235] Specific applications for piezoelectric pressure sensing also comprise synthetic skin.[236] As regards integrating with implants, these sensors can be useful to integrate with cochlear implants, to detect acoustic vibrations and acceleration characteristics with sensitivity of 391.9 mV/Pa at 900 Hz.[237] Size limitations, biological compatibility, and flexibility of these sensors are challenges that are being investigated.[236]

3.3 Optical Sensors

Optical sensors can detect changes in optical properties of environment that are a consequence of the interaction between the photodetector of the sensor and analyte.[238] Optical sensors are usually integrated with eye implants.[239] However, optic fiber-based sensors can also be used with dental implants because of their high sensitivity and electrical passivity, which helps to measure bite forces with relative errors lower than 7% and sensing resolution of 0.017 μ-strain.[240] Their immunity to electromagnetic interference is useful especially when, e.g. MRI imaging of the head and neck area is carried out. Their chemical inertness helps to avoid inducing inflammatory response and corneal edema, which is of particular importance during the first 1–2 weeks after surgery after intraocular lens implantation.[241] The increase in the pixel density is still a challenging issue because the number of interconnecting wires is proportional to the number of pixels.[239] Although optical sensors have several advantages, unfortunately they have low immunity to environmental interference, and they are relatively costly.

3.4 Thermal and Thermoelectric Sensors

Thermal or calorimetric sensors work by changing their properties in response to a change in temperature, while thermoelectric sensors work by changing the voltage produced in response to a difference in temperature between two electrodes (Seebeck's effect). A well-studied example of thermal sensors is the thermistor.[242] Thermistors are used with long-term dental implants for real-time diagnosis of inflammation and infection.[224] Thermistors are suitable for this application because they are sensitive to small rises in temperature (e.g. temperature coefficient of resistance value is 3.33×10^{-3} /°C[224]), which usually accompany inflammation and infection. An example of thermoelectric sensors is the thermocouple-based sensor. Its use offers economical and simple measurement of a wide range of temperatures.[243] As regards implants, thermoelectric sensors can be integrated with dental[224] and transfemoral[244] implants

for detecting inflammation and infection. However, both sensor types are associated with challenges such as efficient localized monitoring, flexible sensor design, elimination of additional calibration and long-term safety,[224] which still need to be addressed. Moreover, thermocouple-based sensors have low sensitivity requiring additional conditioning and amplifying circuit, and nonlinear transfer function.

3.5 Electrochemical Sensors

Electrochemical sensors record electrical response to target chemicals. Based upon how they respond to chemical stimuli, they are divided into conductometric and potentiometric sensors. Conductometric sensors change resistance or impedance when a chemical stimulus is present. Their sensitivity is high (e.g. -4.61 ± 0.84 nA/μM when measuring oxygen *in vivo*). Therefore, they can be used to monitor clinically relevant analytes such as electrolytes and metabolites,[245] or for intracochlear monitoring.[246] Potentiometric sensors are based on generating voltage from the exchange of electrons between the sensing element and a species in solution. Therefore, they are useful for monitoring pH changes that usually accompany biodegradation of magnesium implants,[247] that are becoming increasingly investigated and introduced to the clinic in the form of vascular stents,[248] bone screws[249] and orthopedic implants.[250] They can also potentially be used with other implants, e.g. joint prostheses to detect drops in pH, which can occur during inflammation or infection. Once such problems are detected, combined with other signs and symptoms patient may have, they will help making proper diagnosis and institute timely intervention.

3.6 Biosensors

Biosensors can employ any of the transduction mechanisms discussed above. However, because they require special attention, they are discussed on their own in this section. Biosensors are defined as sensors that have a biological sensing element connected to a transducer to detect certain biological elements.[251] A sensor having no biological component

can still detect biological target variables, i.e. perform biosensing. Some of the most popular types of biosensors include enzyme-based biosensors, immunosensors, DNA biosensors, and microbe-based biosensors,[252,253] of which details are given below.

3.6.1 Enzyme-based sensors

Enzyme-based biosensors have adsorbed enzymes used for monitoring of target molecules in biological fluids.[254] An important class of enzyme-based biosensors is amperometric biosensors,[255] which have already been integrated with retinal prostheses.[256] Enzyme-based biosensors can potentially be used with drug delivery implants because they can provide feedback in a closed-loop glucose control,[257] monitoring glucose levels of 4-7 in blood, 0.1-4 in sweat and 0.01-0.2 in saliva. The effective *in vivo* lifetime of amperometric enzyme-based sensors ranges from a few days to a month.[257] Their greatest challenges are oxygen deficit, increase of *in vivo* current when compared to *in vitro* current due to the current produced by electrochemical interferents, and time-lag associated to the substrate mass transfer rate in tissue.[256]

3.6.2 Immunosensors

Immunosensors employ antibodies to bind to specific pathogens or toxins and biomarkers in body fluids.[258] Moreover, *in vivo* monitoring of early failure stages (small-scale localized changes in the implant and surrounding environment) of implants such as bovine-derived xenografts is possible with immunosensors.[259] Their use for this specific indication is appropriate because of their specificity, reliable operation with high sensitivity (1-50 ppm), fast response (around 30 minutes), portability, and inherent miniaturization.[259] Low power density and high cost of required power harvesters to maintain the functionality of immunosensors integrated with implants remain the limiting factors facing the commercialization of these devices.

3.6.3 DNA biosensors

The working principle of DNA biosensors is based on specific DNA hybridization,[260] which takes place directly on the surface of transducer. Such an approach enables quicker and less expensive data collection for pathogen recognition and diagnostics. Therefore, DNA-based coatings are used with dental implants,[261] which is very important for diagnosis and early interference to preserve implants. This type of sensors is very specific in fields where nucleic acid identification is included with sensitivities as low as 0.05 nM of doxorubicin, 0.1 nM of daunorubicin and 0.5 nM of idarubicin.[261] Therefore, they can be useful when specific type of infection is suspected or wanted identified and treated, e.g. *Vibrio cholerae*[262] or viruses.[263]

3.6.4 Microbe-based biosensors

Microbe-based biosensors contain a transducer that generates a signal proportional to the specific analyte concentration. In general, microbe-based biosensors are used for monitoring of biofilm formation,[264] which may occur with implants as they provide a substrate for bacteria to adhere and grow biofilm that protects them from the immune system. Therefore, an electrical current-based approach for detection and control of bacterial infections of orthopedic implants has been investigated.[265] The main limitations of microbe-based biosensors are poor selectivity, low sensitivity (caused by cell population size), and impractical portability.[266]

3.7 Sensor Fabrication Techniques

There are several techniques for the fabrication of primary sensing elements. However, for the fabrication of sensors that are combined with implants, methods are limited to those suitable for use with biocompatible and mechanically reliable materials.[267]

For some materials, such as metallic foams, deposition techniques (direct laser milling, stereolithography,[268] evaporation, electron-beam and sputtering,[269] spin-coating[19]) are

applicable, while for other materials etching techniques are required as they cannot easily be patterned into microfabricated structures during deposition. The availability of microfabrication of silicon-based structures enabled the development of microelectromechanical systems (MEMS).[5] In addition to silicon, germanium (Ge) and gallium arsenide (GaAs) are used as substrates. MEMS building blocks are made by deposition, patterning, lithography, etching and die preparation.[270] MEMS sensors were reported as suitable for wireless and battery-less cardiovascular implants[271] and knee implants.[272] Another popular technique where multilayer circuits from ceramic substrate tapes or sheets are produced is low temperature co-fired ceramics (LTCC) technology.[273] LTCC technique is used for the fabrication of implantable sensors for continuous glucose monitoring[274] and biosensors.[275] Another common method used for thick film deposition is screen printing technology which enables simple, rapid and low-cost production. Small size and connectivity to portable instruments make screen-printed electrodes appropriate for on-site determination of target analytes, e.g. in implantable intravascular pressure sensors used in ventricular assist devices.[276] Finally, printed circuit board (PCB) technology has been recently used for the fabrication of amperometric glucose sensors,[277] and it can be suitable for fabricating parts of more sophisticated MEMS sensors for liquid characterization.[278]

3.8 Sensor Powering

Regarding powering, common limitations in the design of sensor powering units are related to dimensions, economical aspects, longevity, and the need to function continuously without maintenance.[23] Chronic applications such as pacemakers, cardiac defibrillators, cochlear implants, or drug delivery implants require lithium batteries.[279] Pacemakers require low currents, while drug pumps and neuro-stimulators require moderate power and implantable defibrillators and cardioverters require extremely high power.[280]

3.8.1 Generators

Thermoelectric generators

Thermoelectric generators (TEGs) convert temperature difference between two parts into electrical energy. TEGs are based on Seebeck's effect with advantages in terms small size and lack of moving parts. TEGs can be used, e.g. in brain stimulation implants,[281] and sensors but they usually can provide only a low microwatt power.[282]

Piezoelectricity generators

Piezoelectricity generators can also be used to power sensors and they convert mechanical energy into electrical energy. They rely on continuous motion, but they have to be large to produce reasonable energy levels;[283] hence, they are usually used for powering sensors integrated into orthopedic implants with reported 12 μW of energy that can be harvested with four piezo transducers.[284] The main advantage of piezoelectric generators is their energy harvesting capability.[284]

Electrostatic generators

Power generation can also be achieved by using electrostatic generators that use mechanical motion to generate energy, but they can produce only a small amount of energy. An additional limitation of electrostatic generators is the high output voltage they produce with very low current.[285] However, tens of microwatts are reported as suitable for powering devices such as pacemakers,[286] and self-powered capacitive sensors for detection of tiny mechanical impacts and measurement of human finger bending.[287]

Electromagnetic generators

These generators represent another option for powering sensors, and they rely on relative motion between a permanent magnet and a coil to generate voltage.[288] Their basic principle is Faraday’s law of electromagnetic induction. They can be linear or rotating generators. Linear

electromagnetic generators are more convenient to harvest energy from human activity, e.g. vibrations caused by walking, or cardiac vibrations.[288] Electromagnetic generators usually generate up to five watts of output power.[289] This should be enough for powering sensors (accelerometer[289] or temperature[290]) incorporated into implants, such as orthopedic prosthesis,[291] or electromagnetic hip-mounted generator.[292]

3.8.2 Charging systems

In many applications, sufficient levels of electrical energy cannot be produced or harvested, therefore, requiring permanent energy source such as battery or supercapacitor. However, both elements have limited energy resources, requiring recharging after prolonged operation. There are three major charging systems, optical, mechanical and electromagnetic.

Optical charging systems

Optical charging systems are composed of internal and external units, where the external unit transfers energy by lasers in the near-infrared (near-IR) or IR-region of the spectrum in the direction of the internal unit. However, generated power is in the order of hundreds of microwatts,[293] usually suitable for powering cardiac pacemakers.[294]

Mechanical charging

Mechanical charging is usually based on ultrasonic transducers, where the acoustic wave is transmitted from an external unit to an implanted ultrasonic generator. The power output is dependent on the frequency of the excitation wave.[295]

Electromagnetic charging

Electromagnetic charging is based on inductive coupling between the coil outside the body and the inner integrated with an implantable device.[296] The external coil acts as an antenna transmitting varying electromagnetic signals and causing voltage induction in the inner coil. The main drawback is related to the dependence of power efficiency on distance, coil

orientation and frequency. Output power in the order of few hundreds of milliwatts has been reported.[297] The use of ultrasound power to charge implanted medical devices has also been investigated.[298]

3.9 Sensor Communication

Sensing requires also the communication of data with external equipment, which remains a challenge.[299] This is in part due to problems associated with the use of wires and leads, which can lead to infection,[300] and the limited ability of wireless communication; electrical signal transmission through tissues is inefficient.[17] On the other hand, wireless communication, whether optical[301] or ultrasound[302] based, has low-efficiency transmission through the body and is difficult to miniaturize. Communication is also hindered by the lack of an appropriate power supply to record and transmit signals.[303] Furthermore, foreign body reaction to sensors and implants may hamper communication.[17]

Recent developments are based on the use of dedicated RF band for medical implants communication systems (MICS) in the range of 401 MHz to 406 MHz. RF systems have good performances with low latency and attenuation, which enable higher transmission rates and distances up to few meters.[304] Modern MICS band transmitters and receivers are designed according to strict rules in terms of radiated mission and effective isotropic radiated power, which can be challenging when losses (because of propagation through tissues, skin and air) are not always predictable as receiver/transmitter can be positioned in different locations according to its specific application. Another approach is one-way telemetry where data is only transmitted from implanted device to the external unit. However, lack of synchronization in such realization caused that one-way telemetry devices are still not fully supported,[304] with reported works in fields of camera pills,[305] implanted devices in human head,[306] or implant in-body localization.[307]

Still an open question is the variable data transmission rate required for different applications, causing that communication protocols must be adopted for specific use, from 600 bits per second (bps) in case of heart rate monitoring, to 1200 bps for blood pressure sensors implantable near the right ventricular outflow tract,[308] and 250 kbps in ECG monitoring[309] with cranial-mounted implants.[310] Research continues to explore new methods such as electromagnetic-based readout in temperature monitoring with hip implants,[311] measurement of intra-articular tibial forces with sensor mounted on prosthesis,[312] and Bluetooth low energy-based mechanics monitoring of bone repair.[100]

3.10 Limitations, Challenges and Future Aspects

Modern sensor solutions are capable of monitoring biological variables in real time, with high level of reliability. Ongoing development of sensor technologies is improving sensor performances in terms of sensitivity, linear response and long lifetime, making monitoring of various critical parameters possible.[313] However, even though huge research efforts were made during the last few decades, implants integrating sensors are rarely used in clinical practice, due to numerous challenges that need to be addressed.[253,314] To enhance regular clinical use, sensor-integrating implants need to have low power consumption and long period of maintenance-free and stable operation,[255,315] as well as reliable communication.

As discussed in Subsection 3.8, various power supply and energy harvesting options are available. However, the main challenge is development of low-power circuits that will be reliable under these energy constraints imposed by small battery size, and low energy available via harvesting. There are also recent developments of passive LC sensors that are battery-less and have wireless readout of various parameters such as pH,[316] temperature,[317] strain,[318] and force.[319] However, sensor small dimensions requirement for enabling reliable integration with implants results in higher resonant frequencies of these sensors. Signals containing higher frequencies are more absorbed by body tissues, which in addition to signal

attenuation increases temperature of the surrounding tissues. Therefore, strong barrier in sensors integration with implants is caused by need to have structural changes of implants to deploy sensors and electronics, without impact on implant performance. This will also add costs and thus may deter consumers from purchasing sensor-integrating implants, since current ones are functional, although they lack monitoring capability using. There will be a need for much of marketing to convince users of the advantages of sensor-integrating prostheses. Market penetration will need some time and sustained investment before this generation of prostheses can enter clinical trials and becomes accepted as a part of routine clinical practice. Development of biodegradable and stretchable sensors[320-322] and biodegradable batteries[323] may create new opportunities for new sensor designs and find new clinical indications.[324]

4 Implant Integrating Sensors

Most of the sensor-integrating implants that are in clinical studies comprise cardiovascular implants such as pacemakers,[325-328] defibrillators,[329] blood pressure implants[330] and endografts.[201] However, because we focus on sensors that detect implant related problems, we discuss the most commonly developed ones (**Table 3**), which are orthopedic sensor-integrating implants,[331-337] followed by another section that comprises cardiovascular, neural and other implants.[34,338-341] There are several reports that include sensors used for testing implant performance in the lab, but these are not intended for their use as part of the implant itself,[342-344] hence they are not discussed here.

Table 3. Summary of combination (integrated) implant-sensor devices, type of combinations and phase of their development up to their translation to the clinic [in clinical studies (CS), preclinical animal studies (AS), or prototypes and *in vitro* studies (PT)]. These include applications in the cardiovascular system (CVS), neural system (NS), orthopedics (Orth), gastrointestinal (GI) system, gynecology (G), and auditory (A) system. Combination devices include pacemakers (PM), total knee arthroplasties (TKAs), and total hip arthroplasties (THAs), among others.

No.	Category	Phase	Combination type	Refs.

1	Orth	CS	TKA and mechanical sensor	331-333
			Plate and pressure sensor and temperature sensor	334
			Plate and mechanical sensor	335-337
		PT	THA and mechanical sensor	345
			THA and temperature sensor	311
			Fixator and/or THA and magnetoelastic sensor	346
			THA and inductive proximity sensor	347
			THA and spring-mass oscillators	348,349
			Knee tibial implant and mechanical sensor	350
			TKA and mechanical sensor	233,272,351-354
			Distraction osteogenesis and mechanical sensor	355
			Distraction osteogenesis and carbon-nanotube based thin films	356,357
			Total joint arthroplasty and mechanical sensor	358
			Artificial bone and magnetoelastic sensor	359
			Plate and magnetoelastic sensor	360
			Total shoulder arthroplasty and pressure sensor	361,362
			Tibial implant and eddy current sensor	363
			Limb prosthesis and implantable myoelectric sensor	364
			Upper extremity prosthesis and implantable myoelectric sensor	365,366
			Interference screw and temperature sensor	367
2	CVS	CS	Blood pressure implant and telemetric pressure sensor	330
			Endograft and blood pressure sensor	201
		AS	Flow pump and piezoresistive sensor	368
		PT	Coronary stent and pressure sensor	369
			Coronary stent and piezoelectric microcantilever	370
			Valve and blood flow sensor	371
			Valve and dedicated electrodes for electric field alteration detection	33
			Flow pump and eddy current sensor	372
3	NS	CS	Shunt and intracranial pressure (ICP) sensor	34
4	GI	AS	Biliary stent and resonating magnetoelastic sensor array to detect possible obstruction	141
5	G	PT	IUD and position sensor	373
6	A	PT	Cochlear implant and force sensor	374

4.1 Orthopedic Implants

Orthopedic implants that integrate sensors enable close follow-up of implant function and early detection of any complications that may arise (**Figure 7**). These smart implants,[314] can wirelessly transmit information to externally placed control equipment. Early detection of any

deterioration in implant function and subsequent institution of appropriate intervention[4] will help to shorten recovery time, reduce readmissions and revision procedures and save healthcare resources. However, significant challenges related to reliability, biocompatibility and customization of the implants in conjunction with sensors need to be overcome before they become integrated into clinical practice. In this section, we provide an in-depth analysis of devices currently used in clinical and experimental studies. To the best of our knowledge, there is no sensor-integrating orthopedic implant device that is currently in routine clinical use.

4.1.1 Clinical studies

Following joint replacement, detailed information about the loading of the joint is needed. To achieve this, a sensor-integrating joint prosthesis can be used. In one example, total knee arthroplasty was combined with 6-strain gauges to measure force and torque/moment during level walking and stair climbing by two patients who were followed for 6–10 months.[331] In these prostheses, a 9-channel telemetry unit with an RF transmitter was encapsulated hermetically. Fatigue testing showed no failure (after 10 million loading cycles).[375] A similar system with 12-strain gauges was also used in one patient,[333] and five patients who received total knee replacement.[332] At 12 months postoperatively, measurements were obtained with the patients walking. Peak axial and medial forces obtained from sensors of 15 to 20 gait cycles were recorded. Two maxima of the axial force during the stance phase of the gait cycle were observed, with typical values of 215% of body weight at the first peak and 266% at the second peak; and the medial load share was 73% at the first and 65% at the second peak. Ultimately, data were obtained from nine patients, during ergometer cycling and walking, 15 ± 7 months after total knee arthroplasty.[376] Tibiofemoral forces during cycling at power levels between 25 and 120 W, cadences of 40 and 60 rpm, and 2 seat heights were smaller than those during walking. In addition to following patients themselves, obtained data can also be

used in mechanical simulators, which can be programmed according to realistic load profiles in patients. The data can also be used for validation of musculoskeletal models, which could not predict the load values such as varus-valgus and internal-external moments.[331]

Further, an internal osteofixation plate was integrated with force and temperature sensors for the evaluation of bone healing.[334] The system also had a telemetry module, an external reader device and a computer. The study was performed on 39 patients, 36 femoral fracture nonunions, one nonunion following an Ilizarov segmental transport, one osteotomy, and one revision bone fixation for primary fracture. It was found that the device can be used for the assessment of bone healing.[377]

The concept of strain monitoring was applied using nail plates and plates employed for the treatment of femoral fractures.[335] Four different implant types were proposed and clinically tested: 1) implants that integrate a strain gauge, which is connected to an external recording unit with a wire; 2) implants that can be expanded with telemetry to allow the patient to move;[336] 3) implant that integrate a strain sensor, interface circuit and RF data transmitter, with a power receiver placed into a different location in the body to avoid field shielding effects;[337] and 4) sealed one-piece implants that integrate a sensor, interface circuitry, data transmitter and power receiver. A two-piece nail plate was implanted in a 39-year-old patient who had a pertrochanteric fracture.[335] Monitoring of implant deformation (indicative of failure) was carried out using a histogram of the amplitude of the daily deformation. The results indicated that obtained data can help in the evaluation of rehabilitation exercises, tracing overloads, assessing the risk of implant failure and observing the healing process. Results also indicated that improvements in device packaging are required to avoid sensor drift due to failing insulation.

4.1.2 Experimental studies

Hip implants

No animal studies on hip implants integrating sensors existed at the time of writing this paper. In the following, phantom studies and computational simulation studies involving sensor-integrating hip implants are reviewed.

Information about forces and moments affecting sensor-integrating implants is needed for their development and optimization of their friction properties. To measure these forces, e.g. head and cup of a hip prosthesis, the prosthesis was integrated with a small coil for the inductive power supply and a 9-channel telemetry transmitter.[345] Information about implant heat up due to friction is needed for the optimization of implant materials, and for identification of patients at risk of implant loosening. Therefore, a sensor-integrating hip implant with telemetric data transfer capability to measure the increased implant temperatures, which may also rise during installation, cementing, as in cases of inflammation and infection, was developed.[311] The signal from the implant is detected by a giant magnetoresistive sensor fixed near to an external energy coil. Data obtained from simulations demonstrated that the implant temperature could be measured with an accuracy of 0.1°C in the range of 20°C to 58°C and at a sampling rate of 2–10 Hz. The low power consumption (7 mW) prevents rises in temperature due to the inductive power supply.

In another study, contact-free magnetoelastic smart microsensors (thin film-based microsensors) were introduced.[346] The sensor could be combined with hip implants or external fixation implants, of which loading generated a thin film magnetoelastic response which was detected as a voltage by the coil. Two sensor-integrating implants effectively diagnosed damage to implant inflicted during simulations using the experimental setups (one with hip prosthesis and one with external fixator for fractured ovine tibia).

To diagnose hip prosthesis loosening (failure of integration) , an electromagnetic-based inductive proximity sensor-integrating system was proposed and tested.[347] In this system, positional change of the implant can be assessed using sensors that can detect parallel resistance, inductance and resonance frequency change due to the electromagnetic field that induces eddy currents at the surface of the implant. This then generates another field in the opposite direction of the original one. Modeling and simulation of the sensor carried out using COMSOL Multiphysics® software and finite element analysis together with phantom experiments showed that the biological material (blood and bone) had little impact on the resolution of the sensor. The proximity sensor is found to be capable of detecting movement, with high accuracy, over a reasonable range of distances. Similarly, a novel radiation-free method to diagnose implant loosening (failure of integration) was proposed,[348,349] investigating a passive sensor array that has a coil outside the body and excites magnetic oscillators located in the hip prosthesis to impinge on thin membranes and produce a sound and vibration signal. The system is composed of several spring-mass-oscillators, which are assembled using a flat spring and a magnetic sphere to measure magnetic induction. Simulations proved that the sensor array can detect reproducible and selective excitation of sound emission inside the total hip replacement.

Knee implants

All existing solutions for sensor-integrating knee implants are based on the use of force sensors. For example, a vibration-based system to detect possible loosening of the cemented knee tibial component, in an objective, facile and repeatable way, was developed.[350] The system has a vibrator for transcutaneous stimulation of the bone in a repeatable manner, and a sensor integrated into the implant to measure the propagated vibration. Cadaveric experiments using 14 human fresh-frozen lower limb specimens (from the upper third of the thigh) proved that the proposed coherence-based technique loosening (failure of integration) detection

performed better than the technique based on new peak appearance, peak shift, and peak flattening in power spectra. The inter-subject differences in soft tissue density and volume, bone quality and the type of the implant may minimally affect the detection of implant loosening. Therefore, this technique can be translated into clinical practice.

To power sensor-integrating implants, a triboelectric energy-harvesting load measurement system was integrated between the polyethylene bearing of a total knee replacement implants and tibial component.[351] The triboelectric generator converts mechanical energy derived from axial loading to electrical energy that can be used to power the electronic circuit. Phantom experiments demonstrated that the system could generate an average power of six μW under an equivalent gait load of 2.3 KN at the frequency of 1 Hz. It is predicted that load digitization and harvesting circuitry consume 4.46 μW. An instrumented knee implant based on piezoelectric ceramics to measure tibiofemoral axial forces was also developed.[352] The system evaluates axial load distribution among the four quadrants of the tibial baseplate via a center-of-pressure (COP)-based approach and as a function of ligament imbalance level at predetermined flexion angles. Finite-element analysis and simulations showed a relationship between the displacement of COP (recorded by instrumented tibial baseplate and computed by finite element modeling throughout an entire gait cycle) and the level of ligament imbalance (simulated by different offsets of the axial force applied to the knee prosthesis during gait cycle).

An implantable telemetry device to measure intra-articular tibial forces with 12 strain gauges was explored.[353] The prosthesis was also integrated with a microtransmitter for wireless data transmission. Remote powering of the electronics was achieved by employing magnetic coil induction. Experiments with tibial trays mounted on a fixture designed for cantilever testing on Shore Western Fatigue Frames showed that the prosthesis accurately measured all six components of tibial forces. About 40 mW of power (adequate to power the strain gauges and

the telemetry system) was consistently generated by the internal coil. Measurements of tibial forces can be used to determine soft tissue balancing and assess the effects of rehabilitation and daily activities.

To improve the alignment and balance of the knee prosthesis, force sensors (piezoelectric ceramic transducers) were embedded into the polyethylene bearing part of knee prosthesis to act as self-powered sensors that can provide both intraoperative and postoperative feedback to the surgeon.[233] Biomechanical and electrochemical modeling, finite element analysis, and phantom experiments (including MTS 810 servo-hydraulic load frame and prototype bearing) provided results that are promising for the development of autonomous, self-powered force sensors for knee implants. To achieve accurate sensing of force amplitude and location, it was envisioned that the design should include four or more transducers embedded in the polyethylene bearing.

Monitoring of strain associated with knee imbalance and applied forces can also help in the development of knee replacement implant biomechanics, improve intraoperative prosthesis alignment and enable follow up of the state of the implanted prosthesis. Therefore, a polyimide-based MEMS strain-sensing device for monitoring of knee prostheses was developed and evaluated in a knee simulator employing static and dynamic axial load conditions similar to those occurring in the body.[272] Applied forces could be estimated from the measured strain. The sensor could measure strain associated with the total axial forces in the range of approximately four times bodyweight with good sensitivity and accuracy for events taking place within the one-second time interval.

A “smart patella” for the measurement of force magnitudes and distributions across the patellofemoral joint was examined.[354] Designed force sensing system can be used to measure

forces across a simulated patellofemoral joint, and it has the potential to be implanted into the patellofemoral joint with minimal need for alterations in implant design.

To monitor implant osseointegration, an approach that relies on the reception of the ultrasonic wave by the sensing elements situated in the adjacent and distant struts of the implant was presented.[355] Piezoelectric elements were bonded onto a surrogate implant to provide actuation and sensing functions. Actuating piezoelectric elements positioned on an extramedullary strut were excited with a 1 MHz pulse signal. The reception of the waves by the sensors was used to assess the integration of implant and bone-like surrogate. The findings showed that the osseointegration index **(**O-Index) cab be used for monitoring of osseointegration. Another noncontact, noninvasive sensing approach was also investigated for *in situ* monitoring of infection in osseointegrated prostheses.[356,357] This approach is based on the use of multi-walled carbon nanotube (MWCNT)-based thin films for measuring force and polyaniline (PANI)-based thin films for detecting drops in pH as an indicator of infection.[356,357] An electrical capacitance tomography (ECT) measurement method and algorithm were employed to realize noncontact implant strain sensing. The nanocomposite thin film employed along with ECT could be used to quantify the strain- and deformation-states of osseointegrated prosthesis phantoms in a noncontact way. The results also indicated that thin film pH sensors used in conjunction with ECT exhibit changes in their dielectric property due to changes in pH.

General design ideas

Several sensor-integrating orthopedic implant prototypes have been reported. For example, a working principle of magnetostrictive sensor material, design, analysis and fabrication processes were described.[358] The sensor can potentially be implanted *in vivo* to monitor the force information of bones and joints to prevent failure due to overloading. Finite element analysis and phantom experiments showed that the sensor prototype achieves an effective

measurement range of 0-40 N for the tension force, and a 0-4 NM for the torque. The sensing error after calibration and decoupling for the tension force is 3.4% and for the torque is 4.2%. In another study, a magnetoelastic sensor was designed to monitor the magnesium-based artificial bone (MBAB) degradation rate.[359] The sensor was made of a magnetoelastic material, which exhibits vibrates when exposed to a magnetic field. The magnetoelastic-based sensor enables a wireless and passive monitoring of *in vitro* degradation rate of magnesium-based implants. Phantom experiments were conducted by immersing MBABs in modified simulated body fluid and alkaline media, and monitoring with magnetoelastic-based sensors. It was found that average implant degradation rates were 0.027 dbm/day and 0.012 dbm/day in alkaline and modified simulated body fluid media, respectively. Further, another magnetoelastic-based sensor was designed.[360] This sensor could be used to measure strain in a plate used for the fixation of fractured artificial bone. It was thought that this system can also be used in monitoring of the healing of various fractures.

To analyze loads in orthopedic implants, a three-dimensionally (3D)-printed sensor array (composed of PANI structures embedded in a polymeric parent phase) was developed.[361,362] Linear outputs following fractional changes in resistance occurring during incrementally applied loads, were obtained. For the detection of micro-motion, eddy current sensors and factors that affect the sensitivity and range of sensors implanted in the tibia beneath the metallic plate were also investigated.[363] The sensor was tested using a bovine bone. It was found that sensor resistance is associated with higher sensitivity than inductance, where the resistance-based range of the sensor peaks at 20 MHz and the inductance-based range of the sensor is constant over the frequency of 10 to 200 MHz.

For replacing external electrodes, which are often embedded in the prostheses and extend to the skin, fully implantable myoelectric sensors (IMES) which include the use of a wireless interface to the prosthetic limbs were designed.[364] The prototype meets the size and power

requirements necessary to for implantable neuro-prosthetic sensors. IMES is anticipated to become a critical element in the neuromuscular interface.[365,366]

In another study, an upper-extremity prosthesis control system based on the use of implantable myoelectric sensors was developed.[366,378] The prosthetic hand/arm controller system integrates IMES and was envisioned to receive and process signals from up to 16 implanted bipolar differential electromyography (EMG) electrodes. EMG signals from different muscles can be used to provide simultaneous control of various degrees of freedom in the prosthesis. Besides, wireless telemetry of EMG signals obtained from sensors can eliminate problems associated with percutaneous wires. An external prosthesis controller deciphers user intent from telemetry sent over a transcutaneous magnetic link; telemetered signal waveforms were captured on the prototype, with a significant amount of wild-point noise.

In another study, a wireless and battery-independent temperature sensor that can be embedded into orthopedic implants, e.g. in interference screws, was developed.[367] This sensor can potentially be used to monitor internal wound temperature, which employed for the detection of any developing implant infection.

Summary

Orthopedic implants integrated sensors to monitor forces on the implants,[272,331-333,345,352-354,375,376] integration[335-337,355] and bone healing,[334] possible complications such as heating up,[311] damage,[346] loosening[347-350] or infection,[356,357] by using mechanical (force), proximity, temperature, pH and magnetoelastic sensors. A major constraint of orthopedic implants has been the use of wire-based systems, which are being replaced by wireless data communication modules.[331,334,336,345,353,366] In addition, powering has been a challenge and ways to develop energy harvesting and battery-free systems have been explored.[233,351] The integration of

advances in these frontiers should lead to the development of smarter sensor-integrating orthopedic implants. Despite extensive research, only a few of such implants have reached the phase of clinical studies, which include temperature and mechanical sensor-integrating knee implants and bone plates.[331-337] Currently, most research and development-related activities are focused on hip[311,345-349] and knee[233,272,350-354] sensor-integrating implants, some of which are now in the stage of preclinical animal studies, and are expected to reach the clinic within the next 5-10 years.

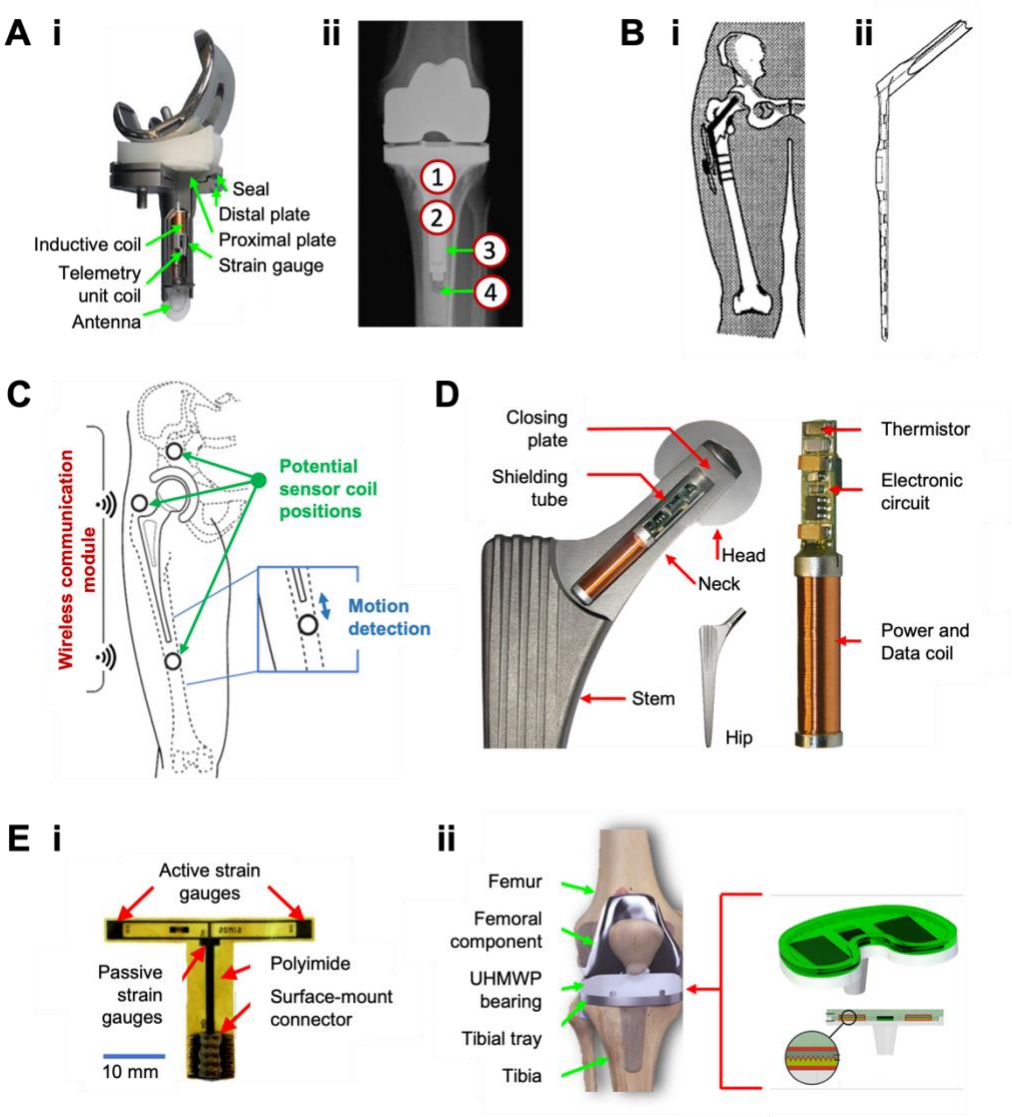

Figure 7. <u>Sensor-integrating orthopedic implants.</u> <u>Clinical application:</u> **A) i)** Sensor-integrating tibial tray. Reproduced with permission.[331] Copyright 2009 Elsevier Ltd. **ii)** Postoperative radiograph showing the sensor-integrating tibial prosthesis, showing hollow

strain-gaged portion of the stem (1); location of microprocessor (2); internal coil (3); and transmitting antenna (4). Reproduced with permission.[333] Copyright 2007 Elsevier Ltd. **B)** Pictures of sensor-integrating implant showing: **i)** the location, and **ii)** design. Reproduced with permission.[335] Copyright 2000 IPEM, Elsevier Ltd. In experimental stage: **C)** Hip loosening detection using inductive proximity sensor (simulation experiment). Reproduced with permission.[347] Copyright 2020 IEEE. **D)** Temperature sensor, electronic circuit and power/data coil are placed inside the neck of the hip implant. Reproduced.[311] Copyright Bergman et al. 2012 under the terms of the Creative Commons Attribution License. **E) i)** Polyimide-metal-polyimide micro-machined sensor. Reproduced.[272] Copyright 2013 The Authors under the terms of the Creative Commons Attribution License. **ii)** Diagram of the triboelectric system of knee prosthesis. For load measurements, the triboelectric generators are placed between the tibial tray and the ultra-high molecular weight polyethylene (UHMWPE) bearing. Reproduced with permission.[351] Copyright 2019 IOP Publishing.

4.2 Other Implants

4.2.1 Cardiovascular implants

There have been major advances with integrating sensors with cardiovascular (CVS) implants, some of which made it to clinical studies,[201,325-330] and more are in the experimental stage.[33,368-372,379] Details of the implants that integrate sensors to detect related problems are discussed in the following sections (**Figure 8**).

Clinical studies

The most commonly sensor-integrating implants used in clinical studies comprise pacemakers.[325-328] However, these were mostly used for monitoring heart rate,[328] change in heart rate during exercise,[325] apnea/hypopnea index,[326] or sleep respiratory disturbance monitoring.[327]

For the monitoring of aortic aneurysm, a telemetric pressure sensor integrated with battery-less blood pressure implants was deployed within the aneurysm sac and kept in place using a surrounding metallic basket.[330] The implant was used as a simple inductive-capacitive tank, with the fixed inductive component and the capacitive component consisting of flexible plates whose position depends on blood pressure. In simulation models and clinical trials, the sensor detected type I endoleaks (leaks that occur around the top or the bottom of the stent graft) and

type III endoleaks (leaks that occur through a defect in the stent graft) but demonstrated less sensitivity in detecting type II endoleaks (leaks that occur when blood flows into the aneurysm sac from branches of the aorta). In another study, an endograft integrating a blood pressure sensor was clinically investigated for the safety and efficacy of intraoperative endoleak detection in 76 patients.[201] The sensor measured full pressure waveforms and data were transmitted to an external unit. Recorded initial sensor pressure measurements agreed with the angiographic catheter pressure measurements of the type I endoleak equivalent.[201] The overall sensitivity of the device was 0.94 and the specificity was 0.80 for detecting type I or III endoleaks.

Experimental studies

Sensor-integrating CVS implants that are still in the experimental study stage comprise stents,[369,370,379] heart valves[33,371] and pumps.[368,372] At the time of writing this paper, only one heart pump made it to the level of animal studies,[368] where MEMS-based devices which provide accurate blood pressure measurements for the regulation of pump speed and output have been designed, fabricated and tested in a sheep. More extensive *in vivo* validation of the proposed MEMS sensor is needed to investigate its performance in blood.

In stents, monitoring of flow is required to assess clinical outcomes of arterial grafts and arteriovenous fistulas used for dialysis.[380] Several studies have discussed the incorporation of pressure sensors within aneurysm grafts to detect occlusion,[369] and a piezoelectric microcantilever within coronary stents to detect endothelialization (implant integration).[370] However, the full integration of a sensor, stent and wireless communication module that allows constant patient monitoring remains to be the next evolution step of stent technology.

Sensors were developed for heart valves to monitor valve opening and detect any thrombosis or malfunction that may occur, at an early stage.[371] Dedicated electrodes were also embedded

in the structure of the heart valve prosthesis to generate a local electric field that is altered by the valve leaflets during their cyclic opening and closure movements.[33] This can be used to measure electric impedance and detect any thrombus formation that may alter the motion of the leaflets. Preliminary results obtained using the prototype that was applied to a simplified circulatory mock loop system, built to reproduce hydrodynamic working conditions for the sensorized valve, showed that the device provided repetitive and stable impedance measurements during the normal cyclic valve opening/closure. The recording reflected the induced alterations in leaflet motion that could be further associated with the early diagnosis of valve thrombosis.

Ultimately, integration of an eddy current sensor into the axial flow pump that consists of an impeller, a motor and a magnetic bearing has been suggested.[372] To control the gap between the impeller and other parts, continuous non-contact gap sensing was prototyped; sensors were tested with various gaps, temperatures, and materials, but no integration with the implant was reported.

Summary

Although challenging due to size, power and functionality constraints, integrating sensors such as pressure[201,330,369] and eddy current[372] sensors into cardiovascular implant designs has already been implemented and clinically used, e.g. in endografts to aid clinical decisions and offer a personalized medical diagnosis and therapy. Of particular interest is the research and development of self-reporting cardiovascular stents.[369,370] This is expected to increase to benefit a large number of patients undergoing the implantation of CVS implants.

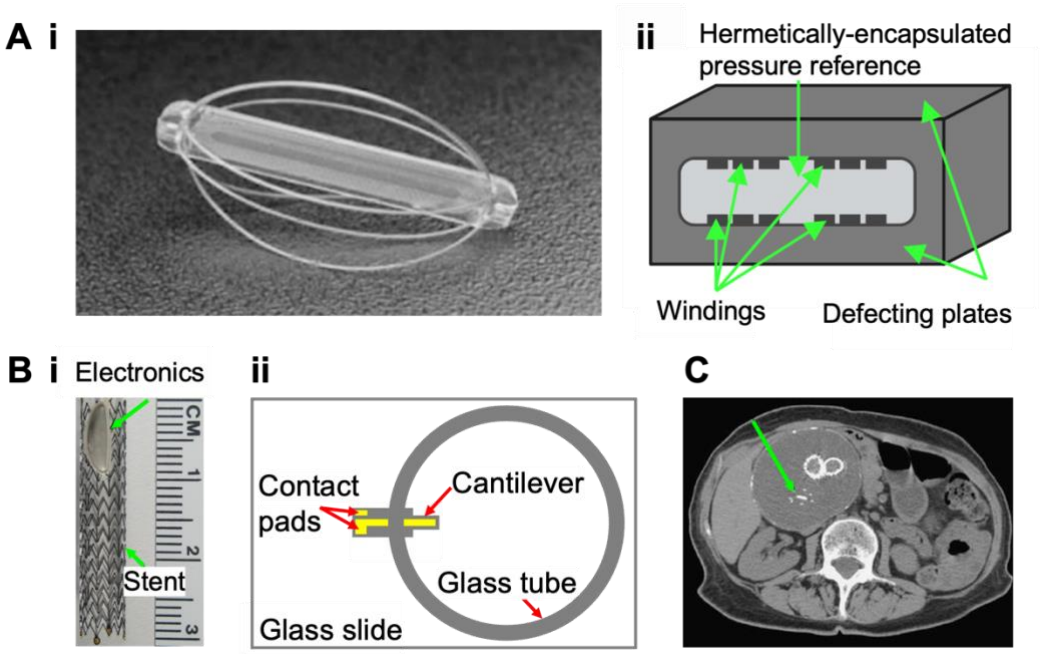

Figure 8. **Sensor-integrating cardiovascular implants.** **A) i)** EndoSure pressure sensor with a nitinol basket surrounding the electronic components. The sensor is (~5 mm wide and 30 mm long). Reproduced with permission.[369] Copyright 2006 Elsevier Inc. **ii)** Cross section of the sensor. Reproduced with permission.[201] Copyright 2007 The Society for Vascular Surgery. **B)** Sensors in experimental stage: **i)** Active electronics sealed in a liquid crystal polymer package and integrated with a stent. **ii)** Top view of cantilever cell chamber for performing sensor measurement in fluid. The sensor can be placed along the struts of a coronary stent, represented with a glass tube (1 cm in diameter). Reproduced.[370] Copyright 2010 Musick et al; licensee BioMed Central Ltd. under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0). **C)** Computed tomography scan demonstrating the EndoSure sensor and an endograft whose two limbs are visualized within the aneurysm sac. Arrow points to the sensor residing in the mural thrombus separately from the endograft which is clearly visualized within the aneurysm sac. The sensor is surrounded by the nitinol cage. Reproduced with permission.[369] Copyright 2006 Elsevier Inc.

4.2.2 Neural implants

The integration of sensors to neural implants provides the treatment of sensory and neurological disorders, rehabilitation of the body after an injury,[381] improvement of memory, and communication with prosthetic limbs. An ever-increasing number of neuron recording electrodes means recordings from far more neurons.[382] Some of the sensor-integrating neural implants are already in clinical studies,[34,338-341,383,384] while others are in the experimental studies stage.[385-388]

Regarding implants that integrate sensors to detect related problems, only one intracranial pressure (ICP) sensor-guided shunt valve which detects occlusions was investigated in the clinic.[34] The test cohort consisted of 25 patients (age of 13-81 years). ICP-guided valve adjustments provided clinical improvement in 18 patients over 12 months. Measurements were performed with a sensor-integrating drug reservoir. The implant could detect and localize occlusions in the ventricular drainage system but could not be used for the determination of default valve settings or universal target ICP values. Magnetic resonance imaging (MRI)-related artifacts, heating and functional disturbances on the sensor-reservoir were investigated to evaluate magnetic field interactions.[389] It was found that magnetic field interactions were not substantial and at 3T showed that the sensor-reservoir is "MR conditional" for patients undergoing MRI examinations.

4.2.3 Gastrointestinal implants

Gastrointestinal (GI) stents are used for several applications to keep tubular structures patent, as their obstruction may lead to serious complications. For example, the blockage of biliary stents leads to the development of cholangitis, which may result in liver damage, sepsis or even death.[390] The current diagnosis of biliary stent obstruction involves the use of invasive endoscopic retrograde cholangiopancreatography which can be associated with various complications.[390] Therefore, a strategy that enables a timely, non-invasive obstruction monitoring system that avoids the risk of complications is required.

A system that includes wireless monitoring of the accumulation of biliary sludge in plastic biliary stents was developed and tested in a pig[141] (**Figure 9**). The system involved the integration of a sensing element to the stent; the element is composed of a passive array of magnetoelastic resonators and is activated by a wireless electromagnetic signal. The array was anchored into a 2.8-mm inner-diameter stent using a thermal staking method. Information was received and sent by an external non-implanted interrogation module. After the stent was

endoscopically installed into the porcine bile duct, it was found that the monitoring system can provide sufficient wireless range (7.5 cm). Further studies are required in this case to demonstrate the robustness of the integration of sensor-arrays to stents and its preservation during implantation. Further animal studies are required to gain wider information about safety and efficacy of the system. This will help to translate this technology to the clinic, which is currently lacking.

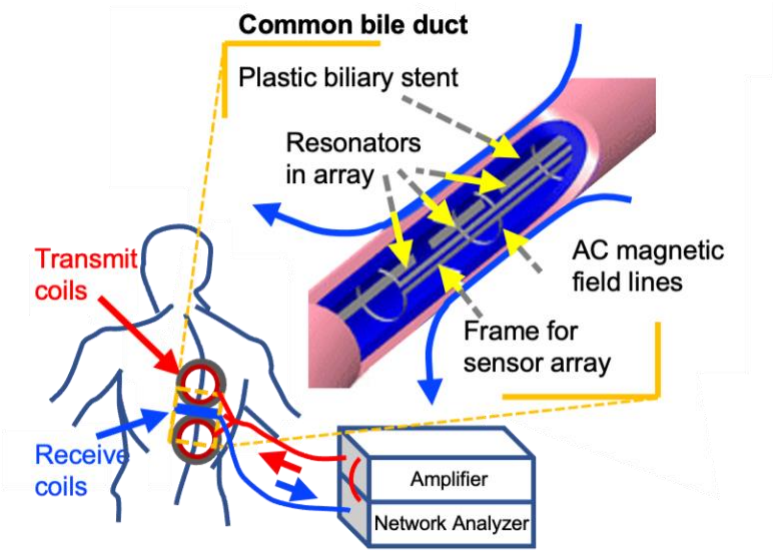

Figure 9. Sensor-integrating gastrointestinal implants. Magnetoelastic sensor-integrating biliary stent for monitoring of the accumulation of biliary sludge in the biliary duct: Conceptual diagram. Adapted with permission.[141] Copyright 2013 Springer Science Business Media New York.

4.2.4 Gynecological implants

Since intrauterine device (IUD) is a favorable mode of contraception, especially for women who have completed their childbearing period, a "smart IUD" could increase the acceptance of this method and decrease the reliance on hormonal drugs and avoid their side effects. Therefore, a sensor-integrating IUD was developed to enable the detection of device position in the uterus and thereby ensure that the contraceptive measure is functional.[373]

4.2.5 Auditory implants

The application of MEMS technology for the fabrication of high-density thin film cochlear electrode arrays with onboard circuitry for neural stimulation, recording and position measurement was proposed.[374] The implant is based on strain gauges that allow real-time imaging of array shape during implant insertion and a tip sensor that measures forces on any structures contacted in the scala tympani. Developed microsystem is not a final cochlear implant, but it rather provides a platform for the investigation of implanted electronics such as electrode arrays.

5 Challenges and Future Perspectives

5.1 Challenges

Attempts to include sensors into implants are hindered by many factors that can be classified as common problems shared by all types of implants and specific problems shared by some types of implants or tissues. Among the common ones is the foreign body tissue reaction leading to fibrous tissue[391] (or glial tissue, in the case of the central nervous system)[392] encapsulation. Following implantation, inflammatory cells (macrophages) generate and release various pro-fibrotic factors, leading to the formation of a fibrous capsule around implants and sensors.[393] The fibrous tissue capsule, combined with the foreign body giant cell formation, creates a barrier surrounding the implant, leading to limited access to interstitial fluid and impaired function of the sensor.[394,395] To address this, different strategies have been investigated (**Figure 10**), including surface modification (implant coatings,[396,397] that may have micro- and nanopatterning,[397] with or without surface functionalization),[398,399] use of fibrotic reaction inhibitory molecules (biomolecules[400] or drugs).[401,402] It was also thought that implant coating can provide the necessary physical, biochemical, structural and mechanical buffer zone,[403-405] which may help to address challenges facing sensor-integrating implants. For example, it was shown that electrospun membranes with optimized fiber diameter, pore

size and permeability could play a critical role in achieving long *in vivo* sensing lifetime of implantable glucose biosensors.[404] The membranes, which were infiltrated by fibroblasts that deposited collagen in the membrane's pores, prevented the formation of dense fibrous capsule around the sensor.

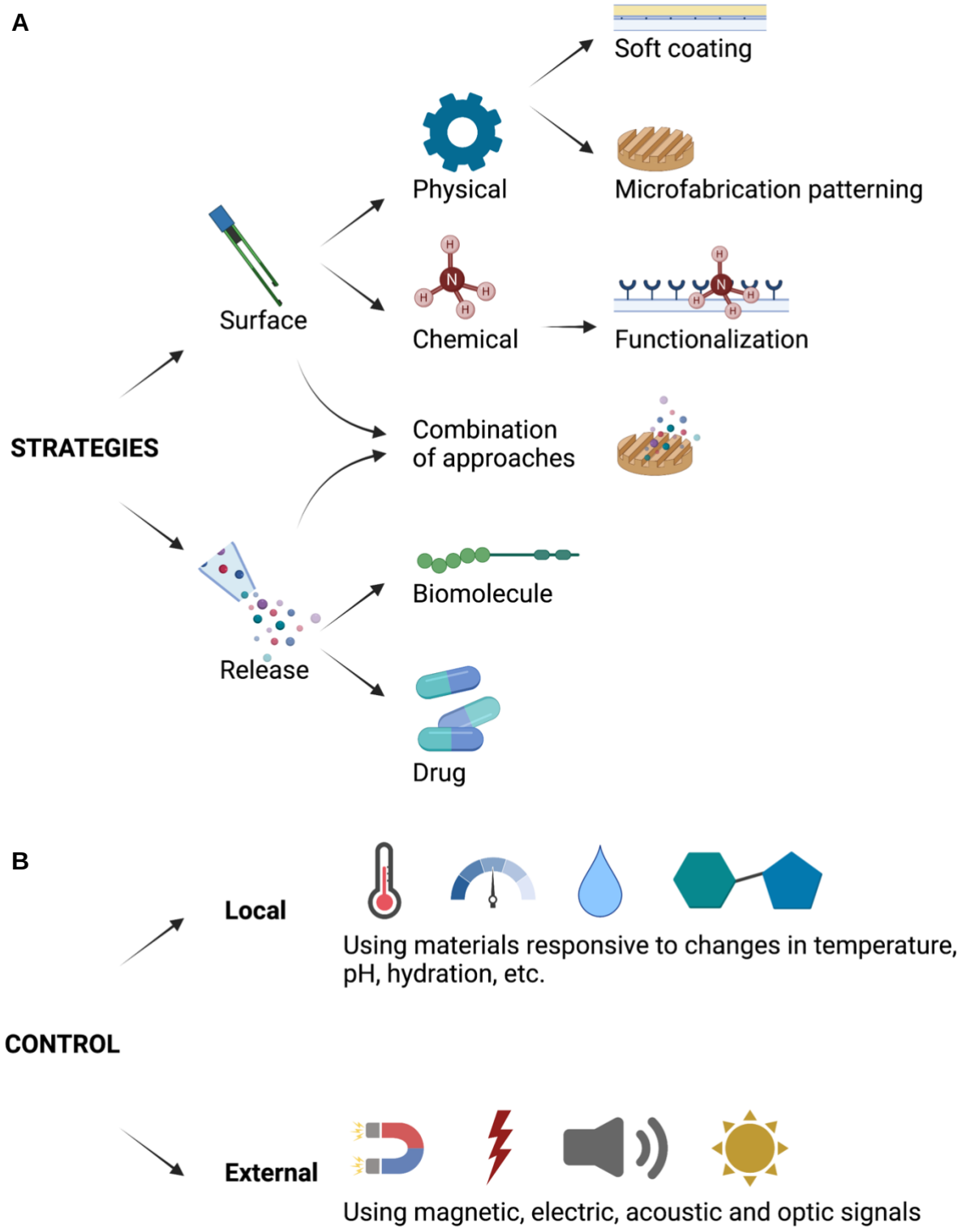

Figure 10. <u>Strategies for modulating tissue reactions and modes of their control</u>. A) Illustration summarizing important strategies for possible modulation of tissue responses toward sensor-integrating implants that can be used to address this major challenge currently facing the application of these devices. **B)** Proposed modes of control of tissue modulation locally or remotely in future. The illustration was created using BioRender.com.

Most recently, it was suggested that the combination of soft coating and release of integrin-binding inhibitory molecules can tremendously reduce the thickness of fibrous tissue capsule around silicone implants.[406] Stiff extracellular matrix (ECM) enhances the activation of integrins, and the release of active TGF-β1, which with other mechanisms, drive pro-fibrotic programs, myofibroblast activation and encapsulation of stiff implants with a stiff ECM capsule. Therefore, reducing implant surface stiffness and/or inhibiting α_v integrin-binding attenuate implant encapsulation.[406] This is expected to help with enhancing implantable sensor function and longevity.[407]

In addition, technologies bring about new possibilities to control these approaches through the use of stimuli responsive materials[408] that can actuate (release active agents) in response to changes in the local microenvironment,[409-412] or externally exerted control (via magnetic,[413-417] electric,[418-421] acoustic,[422-424] or optic stimulation)[425-430] the release of loaded molecules. This will enhance the function of both the sensor and implant components of the system and will be valuable in developing future implants that can sense and actuate, controlled by an operator in the first-generation and using self-adjusting mechanism in smarter second-generation implants.

Infection is a significant risk shared by implants of all types,[23] by offering a surface for bacterial attachment and biofilm formation,[54] and sensor-integrating implants are not an exception. Having sensors as a part of the system will, however, confer an extra capability to detect infection early and enable instituting proper treatment and avoid the development of more complicated consequences.

It remains, however, to consider variations in challenges facing different types of implants depending on their anatomical location, sensor type they contain, and variables intended to measure. For example, pacemakers implanted in the CVS to pace cardiac rhythm have been successfully combined with sensors[325-328] but integrated sensors can face specific problems, e.g. the accelerometer sensor might not respond during very intense exercise that involves fewer body movements or in emotional stress moments[431] and the volume sensor might not be reliable in patients with hyperventilation and obstructive pulmonary disease.[432] In addition, lead insulation failures seen in implantable cardioverter-defibrillator (ICD) endocardial sensing leads represent a significant challenge. This is a likely cause of inappropriate shocks seen in patients with BT-10 sensor leads.[433] Device diagnostics may detect an impending lead failure in nearly 50% of cases,[434] where sensor-based remote monitoring may be a potential solution and prevent failure-related adverse events.

In the central nervous system, glial tissue reaction is an important factor. Glial tissue encapsulation of implants creates a passive barrier to signal detection by recording electrodes.[435,436] In addition, there is evidence that chronic glial response is associated with a neurodegeneration close to implanted electrodes.[437] This makes challenges in sensor-integrating implants of the brain more difficult and innovative solutions to modulate glial tissue reaction are needed.

Fatigue is another problem more specific to sensor-integrating implants applied in locations where continuous and probably high loading is applied, such as in orthopedic and craniomaxillofacial areas, or where continuous movement can be an issue, such as in the case of heart, major vessels and the gastrointestinal tract. Sensors may, therefore, fracture or fail.[438] In the case of sensors made from biodegradable materials,[322,439] degradation is a targeted advantage that enables having sensors only temporarily as required.[322] However,

biodegradation will be accompanied by an inflammatory reaction[213] that needs to be kept controlled with no chronicity, and ultimately subsides.

The impact of tissue reaction also varies with the type of sensor. For example, an electrical sensor may be still active with some fibrous tissue encapsulation, while a pH or glucose sensor may lose effectiveness due to limited access to interstitial fluid.[440] Electrical sensors can be more robust and durable as compared to biosensors, as the latter may suffer from the loss of attached molecules due to mechanical challenges during implant installation or due to inflammation occurring during the healing process. Also, neurochemical sensors can be affected by the electrochemical stability of the interface,[441] as their performance is dependent on effective diffusion of target chemical species,[442] which can be affected by the astrogliosis.[443]

There has been a trend to produce devices with small size and low weight. Implants that weigh less than 2% of the body weight are usually desired.[23] When used, batteries largely increase the weight and size of the implant. Battery-less implants, therefore, can further be miniaturized and can rely on energy harvested from natural or artificial sources. Utilization of nano- and molecular-scale technologies can lead to new advancements in integration density and dynamic power dissipation of new implants.[23] However, current nanotechnologies are still faced with relatively high stand-by power consumption, electron leakage due to insufficient insulation and the thermal energy dissipated within the implant circuitry.

The choice of fabrication techniques is limited by the number of biocompatible materials that can be used. Additionally, materials must have appropriate mechanical properties. Many biocompatible materials, such as inorganic semiconductors, are fragile even for very small strains.[444] Therefore, stability of the sensing output upon stretching and strain, as well as the biocompatibility of sensing and packaging materials must be ensured. Unfortunately, these

requirements exclude many materials which are commonly used for non-implantable sensor fabrication. Search for novel materials with improved properties suitable for the fabrication of implantable sensors should, therefore, continue.

The telemetric link can be used for: 1) bi-directional transfer of information, including sensed data about the patient and indwelling module, 2) wireless re-programming and communication between the implanted modules, and 3) powering. To enable the use of the same link for powering and data transfer, magnetic field modulations can be utilized to impress data signal onto the carrier signal used for powering of the device.

The operation time of the implantable sensors is defined by battery longevity and the period between battery changes. Therefore, efforts to develop wireless battery charging systems are required.[20,300] Although non-rechargeable batteries can be used, they have a limited lifetime, after which they must be surgically replaced. Rechargeable batteries can be recharged either transcutaneously using, for example, RF, infrared light, ultrasound and low-frequency magnetic field,[293,445] or powered internally using the energy produced by the body environment or motion.[20]

Sensor drift and artifacts due to motion must be expected especially following continuous use and it represents a challenge to systems reliant on the use of single sensors. On the other hand, the use of a sensor arrays[446] for monitoring of the same target can provide data immune to noise and patient-related artifacts resulting from differing metabolism and patterns of motion.[447]

Sensor-integrating implants have very big demands related to memory constraints and data processing capabilities. All operations and long computations which require long cycles have to be avoided due to high power consumption. Challenges associated with achieving the optimal function of electronics integrated to implants should be addressed. Effective wireless

links for data transmissions are among the most challenging parts in the design of implantable devices. Implantable devices are surrounded by a conductive medium which increases signal attenuation and makes antenna design very demanding. Dimension constraints, as well as biocompatibility of the antenna casing, are on the top of priorities. Additionally, regulation of effective power output to meet safety limits must be satisfied. However, occasional power dropouts due to inaccurate geometrical alignment can be expected due to body motion and flow of body liquids. In addition to the above-mentioned challenges, implantable systems must be robust to provide long-term operation with a strong rejection of noise generated by the body.

One of the major challenges of implants is their adaptability, functionality and biocompatibility followed by cleaning and sterilization procedures, which impose special challenges. The purpose of implant cleaning is to remove or reduce superficially visible soils, including blood, protein contents, fat, and debris on its surface. This process is followed by sterilization.[448] Researchers have been studying the effects of sterilization on the implant's functions, physical and mechanical properties;[449] biomaterials must be sterile before implantation. Titanium (Ti) has been routinely used as an implant material, and it has been shown in one study that cleaning and sterilization affected the Ti surface's hydrophobicity and roughness, which altered the osteogenic differentiation of human MG63 osteoblast-like cells. Also, osteoblast differentiation was correlated with modified surface wettability and roughness. In addition, sterilization of electronics such as pacemakers was also developed and it includes washing devices in an enzymatic detergent, component replacement, brushing, inspection, and sterilization in ethylene oxide.[450] The combination of implant and electronics sterilization methods poses a challenge on the choice of sterilization method for sensor-integrating implants. One possibility is to sterilize each component separately using the preferred and efficient method and then combine them in a sterile environment.

Accurate and cost-effective imaging techniques are required for post-operative surveillance and diagnosis of implant-related complications. MRI ensures high spatial and contrast resolution and is thus suited for imaging implants. However, metal implants can pose risks during MRI scanning because of exposure to a strong magnetic field. Developments of novel technologies that can be useful in imaging of sensor-integrating devices are required.

The regulatory hurdles facing the introduction of implantable medical devices are considerable. The European Union implemented in 2021[451] the so-called Medical Devices Regulation legislation that requires extensive testing and documentation prior to the approval of a new device.[452] The new legislation made an introduction of devices to the European market more difficult. In the US, FDA is responsible for medical device approval. According to FDA Medical devices are divided into three classes: Class I to III. Most implantable devices (including sensor-integrating ones) will be classified in Class III. Devices in this category require extensive testing often including an early feasibility study which can be used to show essential features and give an indication of safety. Before approval for marketing on a wider scale, a premarket approval study is required, involving a much higher number of patients and frequently a randomized design.[453]

The use of implanted medical devices with sensing and communication capabilities can help many patients, but it will also introduce different societal and ethical challenges. Traditionally, if the surgeon implants a device such as an orthopedic prosthesis, the surgeon is responsible for the procedure while the manufacturer is responsible for the implant itself. The patient reports to the doctor if there is a problem and the doctor may investigate the device and its function according to a predetermined schedule or when problems occur. With implants that have sensors and communication capabilities, new issues appear. The sensor may have a constant connection to the patient, healthcare company, manufacturer or specialized centers. The streams of data generated can point to potentially dangerous state, but

in some situations, such information may not reach the patient or the treating doctor before a major complication has occurred. In such cases it may be difficult to define responsibilities shared between the patient and the doctor, the communication system transmitting the information, the cloud provider, or the datacenter receiving the data. Most sensors will have alarms that give notifications about abnormal data. Who will be responsible for the response to such alarms? To make it even more complicated, processing of the data will probably soon utilize machine learning and artificial intelligence (AI) and the question is how such processes will be brought into the picture. We believe that society will, at least initially, solve it in a similar fashion, used in a self-driving car, where the driver remains responsible, and the algorithms are only facilitators. A patient who requires a pacemaker to prevent sudden death may be constantly connected to a data center in Germany or Australia. Is such a data center responsible for immediate contact with the patient, family or the health care system in the patient environment? If such processes are not organized, remotely monitored implants may drastically increase the use of resources. In this relation, the role of healthcare personnel is also critical. These functions must be properly designed. An implant with a sensor in which data is reviewed intermittently mostly will not cause problems. The physician will receive sensor data during office visits or on scheduled occasions and respond to the received information. When we consider implants with important sensor data which is received 24/7/365, the issue becomes more important to understand and address. Diabetes control devices and pacemakers belong to this type of devices, where abnormal data may require immediate attention. This may be solved by transmission or automatic warnings from the device itself or the remote data center. The patient or family members will then be responsible for taking appropriate action.

For most implanted devices with sensors, the patient or family members will be the ultimate responsible persons for managing data provided by the sensors. Fortunately, many patients are

already using sensor-devices for self-management of conditions such as hypertension and diabetes. Certain patients may become obsessively involved in the data retrieved, which can then affect the sense of well-being. For most patients, the use of implants with sensors will have the potential for improving their quality of life. Concerning remote communication and handling of patient data, the benefits, as well as the risks, may increase dramatically. Security breaks and hacking may in a worst-case scenario lead to corruption of data, reprogramming of the device leading to inappropriate action and ultimately potential death.[454]

Technologies that support individualized out-of-clinic automated monitoring and patient status-responsive treatment will be an area of great interest to the research community. Nonetheless, monitoring and remotely controlled reprogramming of indwelling electronic modules can also be hindered by the regulatory and legislative restrictions that may prohibit remote reprogramming outside of the clinic that makes implants vulnerable to malicious interventions.[23] Further miniaturization of the sensing and stimulating devices will soon enable organ monitoring and the delivery of specific treatment.[23]

5.2 Future Perspectives

New advances in life sciences and engineering are required to expand and redefine the concepts related to material biocompatibility and safety of implants. New biomaterials such as bioceramics, biopolymers, biometals, biomimetic materials and hybrid biomaterials, as well as new implant morphologies, designs, geometries, porosities, mechanical properties and testing regimes are needed to optimize implant characteristics and ensure a high benefit-risk ratio for the patients. Combinations of materials offers endless possibilities given the range of mutually compatible materials. New composites are constantly being developed, e.g., such as those comprising natural and synthetic polymers, and they attain mechanical properties close to those of native tissues.[455] Moreover, biomaterials with surfaces that are resistant to bacterial attachment cells are required to reduce the risk of infections associated with these

materials.[456] This would negate revision surgeries, lower the financial burden for the healthcare provider and significantly improve the patient experience. Then, the fabrication techniques employing novel biomaterials should improve to enable fast and cost-effective implant fabrication (**Figure 11**).

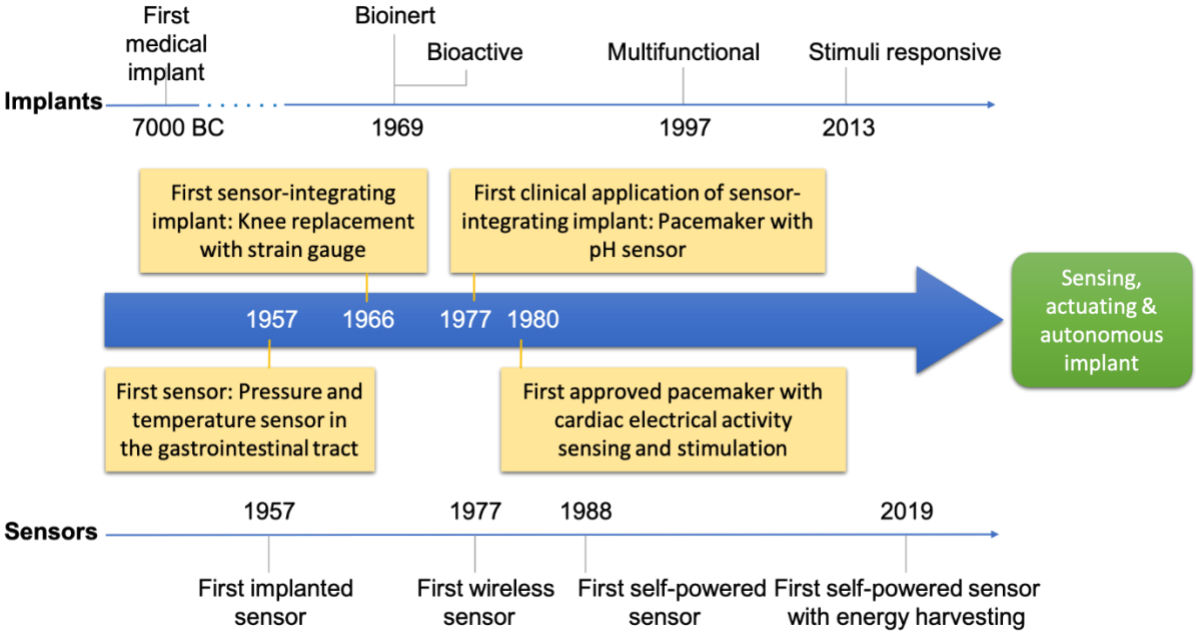

Figure 11. <u>Overview of milestones in sensor-integrating implants development.</u> Developments made in implants (bioinert,[457] bioactive,[458] multifunctional[50,401] and stimuli-responsive[459]), sensors (implanted,[460] wireless,[461] self-powered with battery[462] and self-powered with energy harvesting[439]) and their integration [first sensor-integrating implant,[463] first clinical application of a sensor-integrating implant[464] and first approval (by the Institutional Review Board at the Newark Beth Israel Medical Center) of a sensor-integrating pacemaker[465]] toward realizing future vision of having multifunctional sensing, actuating and autonomous implants.

The next-generation of medical implants are expected to use a closed-loop system, and contain sensors, actuators and algorithms to enable a link between the two. These implants will be able to communicate with devices such as smartphones to display their operating status and transmit sensor data either to the smartphone or directly to the cloud and the attending physician. By adding components such as MEMS/nanoelectromechanical (NEMS), the implants will be fabricated to sense, interpret and then act or treat, thus being autonomous. An interesting example is a neurostimulator implant with an exceptionally high number of

electrodes (a few thousand),[382] fine-grained electrical recording and stimulation that can provide the patient either with intuitive control of prosthesis movements combined with a sensory feeling or permanent reduction of severe, chronic pain.

Developments of a new generation of sensors will include the use of flexible, stretchable and biodegradable materials.[322,466] It is realistic to expect that battery-less solutions will be available in near future, which will increase the output power of thermoelectric, piezoelectric, electrostatic and electromagnetic generators described above. More advanced fabrication techniques, combination of 3D printing with other methods[467,468] will help to develop new and personalized implants, that may integrate sensors. It also is possible to load cells isolated from the patient into the biomaterial to form the bioink and print them together to form 3D constructs.[469-471] Robust technologies have already made it possible to produce customized implants by using 3D images and 3D printing.[472] *In situ* 3D printing[471] and 4D printing of stimuli responsive constructs[473] that can also integrate sensors, will also be possible in future.

The recent expansion of chronic obstructive pulmonary diseases due to pollution[474] increases the need for research of sensors for monitoring of progression of such conditions. For example, monitoring of the nitrogen dioxide in the body, rather than bulk outside monitoring, will enable more precise risk assessment and future developments of the condition. It is also expected that the use of implantable sensors in neuroprostheses will increase due to the demands for myoelectric control, and further developments in providing almost natural control by tapping into the signals used for control of body movements prior to sustained injury and implantation.[475]

Implantable pumps have been available for years and have been used for chronic conditions that require continuous administration of drugs.[476] Most of such devices do not have any sensing mechanism, but large efforts are undertaken since drug administration without patient

intervention is probably more desirable to ensure safety and increase patient compliance. An implantable drug delivery device with sensing function which can steer algorithms incorporated in the infusion control system of the device will be ideal for the ultimate management of diseases such as diabetes, where.[257] A number of other conditions could also significantly benefit from a sensor-controlled implantable drug delivery system. Although implantable sensors have been developed[477] and potentially could be combined with an implantable insulin pump, the limitation in sensor stability has kept diabetic management still being maintained by wearable glucose sensors and infusion pumps.[478] It has been demonstrated that the Eversense® implantable sensor functioned for up to 180 days before needing replacement. Implantable insulin pumps have been designed for intraperitoneal administration of insulin. If combined with a long-lasting glucose sensor a closed-loop system for the management of diabetes or a so-called artificial pancreas could become a reality.[479] A large number of implantable pumps for controllable drug delivery have been designed, with many of them in clinical practice. Such pumps will be of importance for the management of chronic disease, but the vast majority have sensors,[480] and this new generation is expected to evolve in future.

The deployment of body area networks (BANs) in terms of energy management and safety aspects is going to gain a huge attention. Sensor nodes need to be developed in smaller dimensions and with enhanced security protocols. It is expected that pacemakers will receive new functionalities so they can monitor patient's vital information. For example, drug pumps and hemodynamic monitoring can be incorporated to detect and treat irregularities in the cardiac rhythm. Moreover, in the near future, new sensors for continuous monitoring of blood pressure, glucose level and oxygen concentration are expected to be incorporated with pacemakers.

In addition to the above-mentioned functionalities of the implantable devices and sensors, it is also expected that new services towards health data tracking will be developed. Due to the availability of smartphones, automatic data capturing, storage and transmission will be possible. Moreover, recorded lifestyle habits and biometric data will be used for predictive models toward the estimation of potential health risks. A more precise definition of treatment and therapy will be possible.

The internet of things (IoT) paradigm opens new avenues in the monitoring of the implant functionalities from a centralized remote location.[481] However, several challenges remain to be addressed. From the technological viewpoint, cyber-physical-biological capabilities, computing, body channels and intra-body and extra-body communication systems need to go beyond classical and well explored over-the-air radio communication. Communication between the implant and receiving devices need to be optimized in respect of operating bandwidth and low power operation while complying with laws and regulations. The classical modes of over-the-air radio communication need to be revised, as the human body channel is a different medium. The signals used for communication may range from RF signals in the kilohertz band, megahertz band, MICS, wireless medical telemetry service (WMTS), gigahertz band, and terahertz band, to non-RF signals such as ultrasound, inductive coupling, molecular communication (leading to the paradigm of the so-called Internet of BioNano Things (IoBNT)), and optical technology. Data integrity and security are in the focus due to the need to implement lightweight methods that require a minimum of additional components that will not increase power consumption above the capabilities of the implemented power supply unit. Low-power microcontrollers are favored for the implementation of security schemes, where cryptography protocols must be optimized for available data processing units and memory space. Additional challenges are related to the implementation of services that aim at increasing the operational efficiency of the devices, i.e., preventive or predictive

maintenance of the device, and remote diagnostics and software upgrades. From the patient viewpoint, the adoption of new technology is slow. Thus, novel services that offer comfort of use, maintenance of the implant and troubleshooting, application, and the network need to be developed.

By directly sending information from the patients to the healthcare providers, patient health can closely be monitored, circumventing physical visits. Personalization of products and services that leverage IoT, today estimated at 12 billion devices already connected to the Internet, is growing and it is expected to generate a market of up to USD 11.1 trillion per year by 2025.[14]

6 Conclusion

The vision to have implants that can perform their primary function, sense changes in the implant and its microenvironment, and communicate relevant data to the healthcare giver has been conceptualized. To this end, there is much work that has been done in developing a new generation of implants that integrate sensors enabling them to closely monitor implant primary function, integration and early indicators of failure or complications. Most of the implants that have sensors to detect problems are still in the preclinical or experimental developmental phase, but many are expected to move to the clinic in the future. The main challenges that currently prevent sensor-implant combinations comprise the durability of sensors and maintaining their function despite tissues reactions. The integration of various approaches that comprise chemistry, biology, electronics, engineering and surgical approaches is required to circumvent current challenges and introduce more implants with sensing capabilities that will have an impact on implant long-term function, complications, patient life and care providers. This will eventually take place because of rapid advances made in the fabrication of small, robust and inexpensive sensors suitable for integration into the next generation of implants. A key issue that may affect faster industrial production and

clinical translation is ensuring that the integration of such sensors with the implant requires little to no modification to existing implant designs. Increased clinical and industrial interest, as well as new investments, are expected to influence the development of this new generation of smart implants and their use in the clinic.

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Biographies

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