A Review of In-Body Biotelemetry Devices: Implantables, Ingestibles, and Injectables

Asimina Kiourti, Member, IEEE, Konstantina S. Nikita, Senior Member, IEEE

Abstract— Objective: We present a review of wireless medical devices that are placed inside the human body to realize many and different sensing and/or stimulating functionalities. Methods: A critical literature review analysis is conducted focusing on three types of in-body medical devices, i.e., a) devices that are implanted inside the human body (implantables), b) devices that are ingested like regular pills (ingestibles), and c) devices that are injected into the human body via needles (injectables). Design considerations, current status and future directions related to the aforementioned in-body devices are discussed. Results: A number of design challenges are associated with in-body devices, including selection of operation frequency, antenna design, powering, and biocompatibility. Nevertheless, in-body devices are opening up new opportunities for medical prevention, prognosis, and treatment that quickly outweigh any design challenges and/or concerns on their invasive nature. Conclusion: In-body devices are already in use for several medical applications, ranging from pacemakers and capsule endoscopes to injectable micro-stimulators. As technology continues to evolve, in-body devices are promising several new and hitherto unexplored opportunities in healthcare. Significance: Unobtrusive in-body devices are envisioned to collect a multitude of physiological data from the early years of each individual. This big-data approach aims to enable a shift from symptom-based medicine to a proactive healthcare model.

Index Terms—biotelemetry, implantables, injectables, in-body devices, wireless telemetry

I. INTRODUCTION

WIRELESS medical devices used to sense physiological parameters (sensors) and/or stimulate the nervous system (stimulators) are becoming increasingly popular nowadays [1]-[5]. A comprehensive overview of related technologies, systems, application areas and research challenges is presented in [6]. In fact, statistics show that 27% of Americans already use some sort of wearable device, such as a smart watch that records heart rate and number of steps, or smart socks that track speed, calories, altitude, and distance [7]. Nevertheless, wearable devices are limited to monitoring

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A. Kiourti is with the ElectroScience Laboratory, Department of Electrical and Computer Engineering, The Ohio State University, Columbus, OH, 43212 USA (e-mail: kiourti.1@osu.edu)

K.S. Nikita is with the School of Electrical and Computer Engineering, National Technical University of Athens, Athens, Greece (e-mail: knikita@ece.ntua.gr)

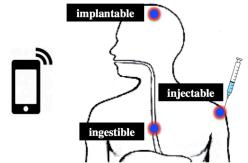


Fig. 1. Definitions of implantable, ingestible, and injectable devices for wireless biotelemetry.

only specific types of physiological parameters that are readily accessible from outside the human body. Along these lines, wireless in-body medical devices that are placed directly inside the human body are promising an entire new realm of applications [8]-[10].

As shown in Fig. 1, wireless in-body medical devices are divided into three categories based on the way of insertion into the human body, i.e., implantables, ingestibles, and injectables. Herewith, the term 'wireless' refers to in-body that communicate wirelessly with monitoring/control equipment (e.g., a smart phone) without the need for wires that would otherwise penetrate through the tissues to ensure a connection. Specifically, implantable devices are placed inside the human body by means of a surgical operation, and entail the most traditional type of inbody devices [11]. Over the years, they have evolved from bulky pacemakers to miniature deep brain implants [12]. Ingestible devices are capsule-looking devices that are ingested and swallowed like regular pills [10]. The most traditional ingestible device is the wireless endoscope that was first discovered in year 2000 [13]. Today, wireless ingestible capsules are integrated with advanced capabilities that can even monitor reactions to pharmaceuticals [14]. Finally, injectable devices are micro-devices that are injected into the human body by means of needles. They have been reported very recently for both sensing and neuro-stimulation applications [15]. As technology continues to evolve, in-body devices are becoming more powerful and concurrently more unobtrusive. In doing so, new resources are opening up for medical prevention, prognosis, and treatment that quickly outweigh any concerns about their invasive nature.

In the past, we presented an overview of implantable and ingestible devices, focusing on the challenges related to design and fabrication of the corresponding in-body antennas [16]. In

this paper, we take a step forward, and discuss in-body devices from an application point of view, addressing design challenges related to communication, powering, and biocompatibility. Beyond implantables and ingestibles, the recently introduced area of injectable devices is also included in this review. Section II will address design considerations related to wireless in-body devices. Section III will discuss research and commercial applications of in-body devices, providing the current status and indicating future directions.

II. DESIGN CONSIDERATIONS FOR IN-BODY DEVICES

Design of in-body devices is typically performed using analytical models of the human body and advanced electromagnetics (EM) simulation software. Experimental validation is further performed in-vitro using phantoms that emulate the electrical properties of biological tissues, and/or in-vivo using animals (rats, pigs, etc.) and potentially human subjects. Detailed overviews of numerical simulation and experimental validation concepts used to accurately emulate real-life scenarios for in-body devices are provided in [11], [17], [18]. Herewith, we will focus on specific challenges associated with the design of in-body devices, and specifically: selection of operation frequency, wireless interface design, powering, and biocompatibility. These considerations are discussed next, and are applicable to all types of in-body devices, including implantables, ingestibles, and injectables.

A. Operation Frequency

As shown in Table I, several frequency bands have been employed for in-body devices [19]-[45], with the most commonly used ones being the Medical Device Radio Communication Service (MedRadio) band of 403.5 MHz, and the Industrial, Scientific and Medical (ISM) band of 2.4 GHz. In general, selection of operation frequency involves several trade-offs. Specifically, low frequencies tend to be more attractive as they are associated with lower loss through the biological tissues. As an example, high frequencies in the order of 3-5 GHz imply attenuation as high as 20-30 dB for every 2 cm of biological tissue [10]. On the other hand, low frequencies limit the communication speed and imply large antennas and circuit components, which, in turn, increase the size of the in-body device. In fact, ingestible devices typically employ high-frequency telemetry links to achieve high data rates, better image resolution, and device miniaturization.

B. Wireless Interface: from Inductive Links to Antennas

Integration of wireless capabilities into the in-body device is highly critical as it enables unobtrusive and ubiquitous communication with the exterior monitoring/control equipment. Today, such equipment may be a smart phone, a smart watch, or another type of smart wearable garment. Data can further be wirelessly transmitted to remote physicians, family members, etc.

The first wireless implants integrated inductive coupling technology at a frequency of 20 MHz or lower. This technology employed inductors within the implant and

TABLE I FREQUENCY BANDS USED FOR IN-BODY DEVICES

	Operation Frequencies		
Implantable Devices	402 MHz [19]-[27]		
	433 MHz [19], [22], [28]		
	868 MHz [25], [28]		
	915 MHz [25], [28]-[30]		
	1.4 GHz [31]		
	2.45 GHz [19], [21]-[23], [27], [31]		
	UWB around 6 GHz [32], [33]		
Ingestible Devices	433 MHz [34]		
	500 MHz [35], [36]		
	800 MHz [34]		
	1.2 GHz [34]		
	1.4 GHz [37], [38]		
	2.4 GHz [39], [40]		
Injectable Devices	132 kHz [41]		
	2 MHz [42], [43]		
	13.56 MHz [44]		
	915 MHz [45]		

TABLE II
ANTENNA DESIGNS USED FOR IN-BODY DEVICES

	Antenna Designs	
Implantable Devices	PIFA [19], [21]-[27], [30], [31]	
	Patch [20]	
	Loop [28]	
	Monopole [32], [33]	
Ingestible Devices	Helical [34], [37], [39], [40]	
	Spiral [35], [36]	
	PIFA [38]	
Injectable Devices	Loop [42], [44]	
	Dipole [43], [45]	

exterior device that were brought in close proximity to realize wireless communication via coupling between the two. However, inductive coupling has typically been associated with several limitations, including slow data rates and high sensitivity to misalignments between the inductors. As such, inductive coupling has recently given its place to wireless antenna communication. In-body antennas alleviate the aforementioned issues, and are becoming increasingly popular nowadays. Their design entails several challenges that are mainly related to miniaturization while achieving wide operation bandwidth, and have been extensively addressed in [16]-[18]. Antenna designs for in-body devices reported to date are summarized in Table II [19]-[45], and are further illustrated in Fig. 2. As seen: a) Planar Inverted-F Antennas (PIFAs) are typically employed for implantable devices as they provide several degrees of freedom for miniaturization, b) helical antennas are typically employed for ingestible devices as they provide circular polarization, omnidirectional radiation pattern, and consistent bandwidth across a range of tissues surround the device, and c) loop or dipole antennas are employed for injectable devices depending on the size and shape of the device.

C. Powering

In-body devices have been traditionally powered via batteries [46]. Drawbacks in this case are that batteries increase the size of the in-body device, raise patient safety and biocompatibility concerns, and require frequent replacement and/or recharging. In fact, despite recent advances in

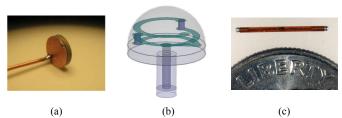


Fig. 2. Example antenna designs for in-body devices: (a) Planar Inverted-F Antennas (PIFAs) typically employed for implantable devices [17], b) helical antennas typically employed for ingestible devices [39], and c) loop or dipole antennas typically employed for injectable devices [45].

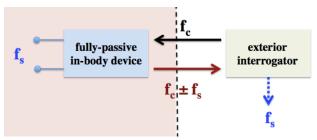


Fig. 3. Concept of fully-passive operation to realize batteryless in-body devices.

electronics and powering/charging technologies, batteries still occupy the majority of space in existing in-body devices. With these in mind, batteryless in-body devices are envisioned. The latter can be achieved via power harvesting techniques, or by enabling fully-passive operation, as outlined below.

- 1) Power harvesting. Power harvesting technologies imply harvesting energy from environmental or bodily sources. Among others, this includes harvesting electromagnetic energy (RF [47], [48], ultrasound [49], etc.), tissue motion and heartbeat [50], thermal gradients in the body [51], human motion [52], and glucose oxidization [53]. Extensive research is currently being carried out to improve the efficiency of the aforementioned methods and make them suitable for powering in-body devices out of thin air.
- 2) Fully-Passive Operation. A novel technology that aims to completely eliminate power storage requirements of any sort is related to fully-passive operation of the in-body device [12], [54]. Fully-passive in-body devices operate very much like an RFID and require an exterior interrogator in close proximity (e.g., exterior interrogator could be part of a hat in the case of brain implants, or part of a T-shirt in the case of pacemakers). As shown in Fig. 3, the interrogator sends a carrier signal (f_c) that is wirelessly received by the in-body device. The in-body device, in turn, mixes the carrier signal with the sensed physiological parameter (f_s) and immediately backscatters the mixing products ($f_c \pm f_s$). The latter are received and further demodulated by the exterior interrogator to retrieve the sensed signal (f_s).

D. Biocompatibility

Biocompatibility implies that a device operating inside the body won't react with the surrounding tissues. A number of techniques have been explored to achieve biocompatibility for in-body devices, including use of biocompatible materials [55], coating with thin biocompatible polymers [23], addition of superstrates to cover the exposed metal parts [56], etc. For

example, authors in [57] developed a coating that allows low-cost silicon sensors to be inserted inside the human body for up to 24 hours. Nevertheless, these solutions typically provide for short-term biocompatibility, as eventually the body will wrap the device in a fibrous cocoon and try and push it towards the outside. To survive inside the biological tissue environment, devices must eventually be enclosed inside a steel jacket, as is the case with existing pacemakers.

III. APPLICATIONS OF WIRELESS IN-BODY DEVICES: CURRENT STATUS AND FUTURE DIRECTIONS

A. Implantable Medical Devices

Implantable medical devices are typically placed inside the human body by means of a surgical operation, and may serve all sorts of sensing and stimulating functionalities. Example applications for wireless implantable medical devices reported to date are summarized in Table III. Some of the most representative implantable applications are further discussed below.

- 1) Pacemakers: One of the most popular implantable medical devices is the pacemaker, a miniature device placed inside the chest or abdomen to help control cardiac arrhythmias [58]. The first pacemaker was implanted in 1958, and, since then, advances in electronics, electromagnetics, and wireless communications have significantly improved the pacemakers' physical size and performance. In fact, most modern pacemakers do not exceed 1.2" in size, and some may additionally communicate critical diagnostic information about the patient and themselves (device status) to exterior devices. As an example, the world's smallest pacemaker, the Medtronic Micra [59] (see Fig. 4(a)), is about the size of a large vitamin and can actually be implanted inside the heart. This pacemaker delivers an estimated average 12-year battery longevity, and can be safely scanned using either a 1.5T or 3T full-body Magnetic Resonance Imaging (MRI).
- 2) Intra-Cranial Pressure (ICP) monitors: Elevated ICP is typically a result of cerebral edema, cerebrospinal fluid disorder, head injury, and/or localized intracranial mass lesion. In turn, elevated ICP increases the risk of severe brain damage and may cause disabilities or even death. With these in mind, a number of unobtrusive implantable solutions have been reported for measuring the IOP. For example, in [60], [61], a MEMS pressure sensor was reported to detect changes in ICP and wirelessly transmit them to an exterior device (see Fig. 4(b)). The system's operation frequency was set to 2.45GHz, and indicated a maximum pressure error of only 0.8mmHg. In [62], an RF oscillator was employed that was designed to detect changes in the ICP based on changes in its oscillation frequency. This device operated at 2.4GHz and was demonstrated to accurately identify pressures in the 10-70mmHg range. Both of the aforementioned sensors were battery-powered, which, in turn, increased the overall size of the implant and required frequent replacement and/or recharging. To avoid batteries, [63], [64] introduced a passive capacitive MEMS ICP sensor that was powered via inductive RF coupling. The sensor formed an LC tank with a coil placed on the skull, and the tank's resonance frequency changed as a function of changes in the ICP. The latter was eventually

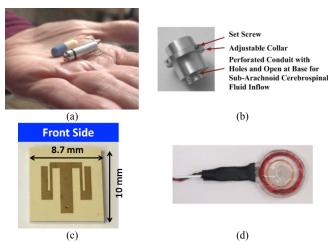


Fig. 4. Example implantable devices reported to date: (a) Medtronic Micra pacemaker placed next to a large vitamin for comparison [59], (b) intra-cranial pressure monitoring sensor [60], (c) deep brain neurosensor [12], and (d) subretinal neurostimulator [76].

detected by an exterior reader device. In-vitro measurement

results proved the capability of these sensors to detect ICP variations ranging from 0 to 70mmHg at 2.5mmHg intervals. 3) CardioVascular Pressure Monitors: Chronic blood pressure monitoring is of utmost importance for continual assessment of various conditions of the cardiovascular system (e.g., restenosis, hypertension, heart failure), as well as for tracking the progress of surgical interventions (e.g., monitoring repaired aneurysms) [65] However, the traditional gold standards of blood pressure measurement, such as external pressure cuffs or intra-arterial catheter-based systems, exhibit several drawbacks. Examples include lack of patient comfort, infrequent measurement, possible occlusion of blood flow, and long-term complications (trauma and infection). As such, fully implantable devices are becoming quite popular for long-term monitoring of blood pressure. The latter allow for continuous monitoring without hindering the individual's daily activities, and have no associated risks of infection as would typically be the case for catheters or wires. Rapid progress in microfabrication technologies has enabled the production of low cost, highly accurate sensors that may be safely implanted into patients for chronic pressure monitoring. Implantable blood pressure monitors based on MEMS capacitive sensors [66], a Surface Acoustic Wave (SAW) resonator [67], and Pulse Transit Time (PTT) measured by using an accelerometer [68] have been proposed. Recent industry developments include a pressure sensor fabricated by Boston Scientific for measurement of pressures within an aneurysm sac following endovascular aneurysm repair (EVAR) [69], as well as the first FDA approved implantable blood pressure device from CardioMEMS for detection of heart failure within the pulmonary artery [70]. Moreover, the

4) Neurosensors: Deep brain neurosensors have recently attracted significant interest for several applications, including epilepsy, Parkinson's, Alzheimer's, addictions, etc. In one case [48] RFID-inspired neural tags were considered for wireless brain-machine interfaces. Batteries were avoided, and

potential of a device, originally developed for energy

harvesting from arterial motion, to monitor cardiovascular

system parameters has been demonstrated [71].

power storage was performed via RF energy harvesting techniques. In another case [72], a wireless neurosensor was presented for recording neural signals from the cortex of monkeys. The sensor in employed a head-mounted device with a 'screw-on' interconnect to the implant, and integrated a head-mounted battery. Recently, wireless fully-passive implanted neurosensors have been reported (see Fig. 4(c)) [12], [73]-[75]. These devices operate without internal power supply elements and exhibit a highly simplified implant circuit topology. Also, no intra-cranial wires or cables are used. As an example, one of the latest fully-passive brain neurosensors occupies a footprint of 10 mm \times 8.7 mm, and can read emulated neuropotentials as low as 20 μVpp [75]. This is a 25 times improvement in sensitivity compared to previously reported fully-passive configurations [73].

5) Neurostimulators: Several implantable neurostimulators have been reported to stimulate the nervous system and recover functionality for Parkinson's, dystonia, depression, stroke, artificial limbs, spasticity, Alzheimer's, sleep apnea, chronic pain, obesity, epilepsy, hypertension, heart failure, incontinence, auditory and visual impairments, etc. For example, retinal neurostimulators may restore vision [76] [77] (see Fig. 4(d)), cochlear implants may improve hearing [78], stimulators in the subthalamic nucleus may manage Parkinson's disease [79], brain-computer interfaces may develop robotic hands/arms/legs that can be controlled by thoughts [80], and stimulators in the grey matter may inhibit chronic pain [81].

A number of future applications are envisioned for implantable devices that will take advantage of breakthroughs in electronics, materials, power harvesting, etc. Examples include heart stents capable of wirelessly transmitting the health of an artery, implants that can detect performance-enhancing drugs, closed-loop glucose meters and insulin pumps that monitor and correct blood sugar levels, and implants capable of detecting the presence of oral cancers.

B. Ingestible Medical Devices

Ingestible medical devices are miniature capsule-looking devices, and are taken through the mouth like regular pills [10], [13]. While traveling through the gastrointestinal tract and digestive system, ingestible medical devices may collect images, transmit real-time video, sense several physiological parameters, deliver drugs, etc. Collected data are eventually transmitted to a nearby monitoring/control device for display and further post-processing. Example applications for wireless ingestible medical devices reported to date are summarized in Table III. Some of the most representative ingestible applications are further discussed below.

1) Imaging Capsules: Smart endoscopy capsules used for imaging the gastrointestinal tract and digestive system are the most well-known form of ingestible medical devices. For example, Given Imaging provides pill-sized disposable capsules that can visualize the small bowel, esophagus, and colon without sedation or invasive endoscopic procedures [82] (see Fig. 5(a)). To date, prototyping systems with data rates as high as 2 Mbps have been reported for wireless capsule endoscopy that employ advanced compression techniques to achieve up to 15-20 frames per sec [83]. To obtain clearer

TABLE III. EXAMPLE REPORTED APPLICATIONS OF IMPLANTABLE, INGESTIBLE, AND INJECTABLE WIRELESS MEDICAL DEVICES.			
Implantable Devices	Ingestible Devices	Injectable Devices	
Pacemakers [58], [59]	Imaging of the digestive system [82]-[84]	Neurostimulators [15]	
Defibrillators [16]	Medication adherence [14]	Glucose sensors [44]	
Intra-cranial pressure monitors [8], [25], [60]-[64]	Heart failure detection [85]	Oxygen sensing sensors [89]	
CardioVascular pressure monitors [65]-[70]	Gastrointestinal disorder detection [86]	Peripheral artery disease monitors [89]	
Deep brain neurosensors [12], [32], [48], [72]-[75]	Drug delivery capsule [87], [88]	Athletes' muscle performance trackers [89]	
Retina stimulators [76], [77]	pH sensing of the esophagus [16]	Shoulder subluxation rehabilitation [90]	
Cochlear implants [16], [78]	Pressure/temperature sensing of the	Knee osteoarthritis rehabilitation [90]	
Parkinson's stimulators [79]	gastrointestinal tract [16]	Hand contraction treatment [92]	
Brain computer interfaces for prosthetic limbs [80]	Gastric stimulators [9]	Ulcers treatment [93]	
Chronic pain stimulators [81]		Hemicranias treatment [94]	
Glucose monitors [16]		Urinary incontinence treatment [95]	
Drug infusion systems [16]			
Identity verification chips [16]			

images, fluorescence-based ingestible capsules have also been reported [84]. These systems typically include three submodules, namely optical imaging, electronics control and image acquisition, and information processing and transmission.

2) Ingestible Sensors: Ingestible capsules are often used to sense physiological parameters inside the body as a means to diagnose a number of conditions. For example, an ingestiblesensor scheme developed by Proteus Digital Health has already been FDA approved, and is being rolled out for heartfailure related drugs [85]. In another case [14], a sensor was presented for detecting the ingestion of a pharmaceutical tablet or capsule (see Fig. 5(b)). Clinical trials in 412 subjects demonstrated 99.1% detection accuracy and 0% false positives. The system further allowed direct correlation between drug ingestion, health-related behaviors (e.g., physical activity), and critical metrics of physiological response (e.g., heart rate, sleep quality, and blood pressure). More recently, custom-made ingestible capsules were demonstrated that can measure the concentration of different gases during digestion in the gut [86]. It is noted that changes in production of certain gases in the human gut have been linked to gastrointestinal disorders including painful constipation, irritable bowl syndrome, and colon cancer.

3) Drug Delivery Capsules: This class of applications refers to electronic pills that are used to precisely deliver a certain drug along the gastrointestinal tract. In one case, a micropositioning mechanism was reported that can be easily integrated into a capsule, and deliver 1 ml of targeted medication [87]. The micropositioning mechanism allows a needle to be positioned within a 22.5° segment of a cylindrical capsule and be extendible by up to 1.5mm outside the capsule body. In another case, a smart pill was designed to release powdered medication just before reaching the ileocecal valve, where the small and large intestine meet (see Fig. 5(c)) [88]. Once activated through a magnetic proximity fuse, the capsule opens up and releases its powdered payload.

A number of future applications are envisioned for ingestible devices. Examples include: personalized drug delivery capsules to treat digestive disorders and diseases, higher-bandwidth data transmission to enable better diagnosis, ingestible sensors that are taken along with regular pills to

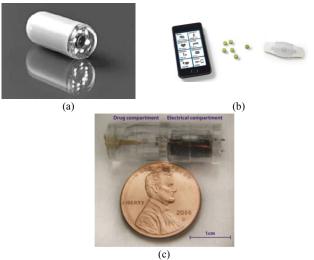


Fig. 5. Example ingestible devices reported to date: (a) Given Imaging capsules for visualizing the gastrointestinal tract [82], (b) ingestible capsule to monitor medication adherence [14], and (c) ingestible capsule for targeted drug delivery [88].

affirm that a patient has taken the correct dosage, electronic capsules that monitor physiological reactions to the dose, capsules that activate and sense in specific parts of the gastrointestinal tract and digestive system, devices that can track electrical activity at the gastrointestinal tract while also measuring transit times, and smart capsules that release specialized drug profiles at specific target locations or when they detect a certain sensing event.

C. Injectable Medical Devices

Given their minimally invasive nature and smart capabilities, injectables are seen by many as the next generation of medical devices. Example applications for wireless injectable medical devices reported to date are summarized in Table III. Specifically, the term 'injectable' may refer to two classes of devices, as outlined below:

1) Micro-sensors injected into the human body by means of a needle. Very recently, Profusa demonstrated an injectable sensor, namely the Lumee Oxygen sensor, that can monitor oxygen levels in the surrounding tissues (see Fig. 6(a)) [89]. The sensor has the thickness of a few human hairs and the

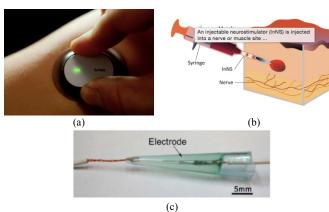


Fig. 6. Example injectable devices reported to date: (a) injectable Lumee Oxygen sensor [89], (b) ingestible micro-stimulator [15], and (c) electrode formed via sequential material injections [91].

length of a piece of long-grain rice, and is made of hydrogel permeated with fluorescent dye that is sensitive to oxygen. To read the device, light is shined on the skin, and an optical reader is picking up the emissions. Notably, the brightness of the fluorescence diminishes as oxygen binds to chemical receptors in the dye. Envisioned applications include, but are not limited to, monitoring of peripheral artery disease, and tracking of athletes' muscle performance.

- 2) Micro-stimulators injected into the human body by means of a needle. Injectable stimulators are currently explored as a less invasive and unobtrusive alternative to the implantable stimulators discussed above [15]. A typical injectable neurostimulator includes stimulating electrodes, an antenna for biotelemetry and power harvesting, and electronics used to control the stimulation (see Fig. 6(b)). In fact, preliminary results using injectable stimulators to treat post-stroke shoulder subluxation and knee osteoarthritis have already demonstrated very promising results [90]. In fact, *in-vivo* tests where subjects self-administered stimulation for 6 or 12 weeks demonstrated reduction in shoulder subluxation by $55\% \pm 54\%$ and decrease in pain by $78\% \pm 18\%$.
- 3) Three-dimensional (3-D) medical electronics that are directly built inside the human body through sequential injections. A recently developed technology demonstrates that 3-D fabrication of medical devices can be directly performed at the target biological tissues using sequential injections. Materials to be injected for realizing such flexible and miniaturized electronics entail biocompatible packaging materials and liquid metal inks. As a proof-of-concept, a variety of ElectroCardioGram (ECG) and stimulator electrodes have already been sequentially built at the target tissues, and validated both in-vitro and in-vivo (see Fig. 6(c)) [91]. Impedance measurements indicated that the formed electrodes had an overall electrical resistance of 16kOhm.

Injectable medical devices are expected to significantly grow over the next few years. Challenges to be addressed in the future are mostly related to powering and fabrication of injectable antennas/electronics within a tiny footprint. Once these challenges are resolved, a number of future applications are envisioned for injectable devices including treatment of hand contraction [92], ulcers [93], hemicranias [94], seizures, urinary incontinence [95], sleep apnea, etc.

IV. CONCLUSION

A review was presented for in-body wireless medical devices (implantables, ingestibles, injectables), addressing the state-of-the-art technology, and discussing opportunities. Overall, design of in-body devices is highly challenging, and needs to concurrently address concerns related to operation frequency selection, antenna design, powering, and biocompatibility. Currently, extensive research efforts are pursued to address such technological concerns, along with developing novel sensing methods, materials, and, eventually, new clinical applications for in-body devices. Overall, in-body devices are opening up new opportunities for medical prevention, prognosis, and treatment that quickly outweigh any design challenges and/or concerns on their invasive nature.

In the future, unobtrusive in-body devices are envisioned to collect a multitude of physiologic data from the early years of each individual. Babies, children, and young healthy people would employ such unobtrusive devices to monitor heart rate, physical activity, nutritional status, calories burned, sleep duration, organ function, breathing rate, etc. Eventually, in the case of medical need, healthcare data collected over the years would enable personalized and, thus, much more efficient and cost-effective intervention. This big-data approach aims to enable a shift from reactive and symptom-based medicine to a proactive healthcare model. Applications are numerous, ranging from elderly monitoring to monitoring individuals in developing countries or individuals in the military, space, and sports arenas.

REFERENCES

- C. Pang et al., "Recent advances in flexible sensors for wearable and implantable devices," J. Appl. Polym. Sci., vol. 130, pp. 1429-1441, Nov. 2013.
- [2] G. Gurain et al., "Miniature microwave biosensors," *IEEE Microw. Mag.*, vol. 16, pp. 71-86, May 2015.
- [3] Y.-L. Zheng et al., "Unobtrusive sensing for wearable devices for health informatics," *IEEE Trans. Biomed. Eng.*, vol. 61, pp. 1538-1554, May 2014
- [4] B.G. Celler et al., "Home telemonitoring of vital signs Technical challenges and future directions," *IEEE J. Biomed. Health Inf.*, vol. 19, pp. 82-91, Jan. 2015.
- [5] B. He et al., "Grand challenges in interfacing engineering with life sciences and medicine," *IEEE Trans. Biomed. Eng.*, vol. 60, pp. 589-598, Mar. 2013.
- [6] Nikita K.S. (ed), Handbook of Biomedical Telemetry, Wiley-IEEE, 2014.
- [7] K.D. Stephan et al., "Social implications of technology: the past, the present, and the future," *Proc. IEEE*, vol. 100, pp. 1752-1781, 2012.
- [8] U. Kawoos et al., "Too much pressure," *IEEE Microw. Mag.*, vol. 16, pp. 39-53, Mar. 2015.
- [9] S. Rao et al., "Body electric," *IEEE Microw. Mag.*, vol. 16, pp. 54-64, Mar. 2015.
- [10] M. Yuce et al., "Easy-to-swallow wireless telemetry," *IEEE Microw. Mag.*, vol. 13, pp. 90-101, Oct. 2012.
- [11] E.Y. Chow et al., "Implantable RF medical devices," *IEEE Microw. Mag.*, vol. 14, pp. 64-73, Jun. 2013.
- [12] A. Kiourti et al., "A wireless fully-passive neural recording device for unobtrusive neuropotential monitoring," *IEEE Trans. Biomed. Eng.*, vol. 63, pp. 131-137, Jan. 2016.
- [13] M.K. Goenka et al., "Capsule endoscopy: present status and future expectation," World J. Gastroenterol., vol. 20, pp. 10024-10037, Aug. 2014
- [14] H. Hafezi et al., "An ingestible sensor for measuring medication adherence," *IEEE Trans. Biomed. Eng.*, vol. 62, pp. 99-109, Jan. 2015.

- [15] X. Li et al., "The injectable neurostimulator: an emerging therapeutic device," *Trends in Biotechn.*, vol. 33, pp. 388-394, Jul. 2015.
- [16] A. Kiourti et al., "Implantable and ingestible medical devices with wireless telemetry functionalities: a review of current status and challenges," Wiley Bioelectrom., vol. 35, pp. 1-15, 2014.
- [17] A. Kiourti et al., "Miniature implantable antennas for biomedical telemetry: from simulation to realization," *IEEE Trans. Biomed. Eng.*, vol. 59, pp. 3140-3147, Nov. 2012.
- [18] A. Kiourti et al., "A review of implantable patch antennas for biomedical telemetry: challenges and solutions," *IEEE Antennas Wireless Propag. Mag.*, vol. 54, pp. 210-227, Jun. 2012.
- [19] F.J. Huang et al., "Rectenna application of miniaturized implantable antenna design for triple-band biotelemetry communication," *IEEE Trans. Antennas Propag.*, vol. 59, pp. 2646-2653, Jul. 2011.
- [20] J. Ha et al., "Compact zeroth-order resonance antenna for implantable biomedical service applications," *Electron. Lett.*, vol. 47, pp. 1267-1269, Nov. 2011
- [21] C. Liu et al., "Compact dual-band antenna for implantable devices," IEEE Antennas Wireless Propag. Lett., vol. 11, pp. 1508-1511, 2012.
- [22] L.J. Xu et al., "Dual-band implantable antenna with open-end slots on ground," *IEEE Antennas Wireless Propag. Lett.*, vol. 11, pp. 1564-1567, 2013.
- [23] T. Karacolak et al., "In-vivo verification of implantable antennas using rats as model animals," *IEEE Antennas Wireless Propag. Lett.*, vol. 9, pp. 334-337, 2010.
- [24] C. Liu, "A hybrid patch/slot implantable antenna for biotelemetry," *IEEE Antennas Wireless Propag. Lett.*, vol. 11, pp. 1646-1649, 2013.
- [25] A. Kiourti et al., "Miniature scalp-implantable antennas for telemetry in the MICS and ISM bands: design, safety considerations and link budget analysis," *IEEE Trans. Antennas Propag.*, vol. 60, pp. 3568-3575, Aug. 2012.
- [26] W.C. Liu et al., "Miniaturized implantable broadband antenna for biotelemetry communication," *Microw. Opt. Technol. Lett.*, vol. 50, pp. 2407-2409, 2008.
- [27] L.J. Xu et al., "Miniaturized dual-band antenna for implantable wireless communications," *IEEE Antennas Wireless Propag. Lett.*, vol. 13, pp. 1160-1163, 2014.
- [28] R.S. Alrawashdeh et al., "Broadband flexible implantable loop antenna with complementary split ring resonators," *IEEE Antennas Wireless Propag. Lett.*, vol. 14, pp. 1506-1509, 2015.
- [29] J. Gemio et al., "Human body effects on implantable antennas for ISM bands applications: models comparison and propagation losses study," J. Prog. Electrom. Res., vol. 110, pp. 437-452, 2010.
- [30] M.S. Islam et al., "Converting a wireless biotelemetry system to an implantable system through antenna redesign," *IEEE Trans. Microw. Theory Techn.*, vol. 62, pp. 1890-1897, Sept. 2014.
- [31] C.-K. Wu et al., "Design of novel S-shaped quad-band antenna for MedRadio/WMTS/ISM implantable biotelemetry, applications," *Int. J. Antennas Propag.*, vol. 2012, pp.1-12, 2012.
 [32] H. Bahrami et al., "Biological channel modeling and implantable UWB
- [32] H. Bahrami et al., "Biological channel modeling and implantable UWB antenna design for neural recording systems," *IEEE Trans. Biomed. Eng.*, vol. 62, pp. 88-98, Jan. 2015.
- [33] C.H. Kang et al., "A novel folded UWB antenna for wireless body area network," *IEEE Trans. Antennas Propag.*, vol. 60, pp. 1139-1142, Feb. 2012
- [34] L.S. Xu et al., "Effects of dielectric values of human body on specific absorption rate following 430, 800, and 1200 MHz RF exposure to ingestible wireless device," *IEEE Trans. Inf. Technol. Biomed.*, vo. 14, pp. 52-59, Jan. 2010.
- [35] S.H. Lee et al., "A wideband spiral antenna for ingestible capsule endoscope systems: experimental results in a human phantom and a pig," *IEEE Trans. Biomed. Eng.*, vol. 58, pp. 1734-1741, Jun. 2011.
- [36] S.H. Lee et al., "Wideband thick-arm spiral antenna for ingestible capsules," Microw. Opt. Technol. Lett., vol. 53, pp. 529-532, 2011.
- [37] H. Rajagopalan et al., "Wireless medical telemetry characterization for ingestible capsule antenna designs," *IEEE Antennas Wireless Propag. Lett.*, vol. 11, pp. 1679-1682, 2013.
- [38] W. Seo et al., "A meandered inverted-f capsule antenna for an ingestible medical communication system," *Microw. Opt. Technol. Lett.*, vol. 54, pp. 1761-1765, Jul. 2012.
- [39] C. Liu et al., "Circularly polarized helical antenna for ISM-band ingestible capsule endoscope systems," *IEEE Trans. Antennas Propag.*, vol. 62, pp. 6027-6039, Dec. 2014.

- [40] H. Huang et al., "Properties and applications of electrically small folded ellipsoidal helix antenna," *IEEE Antennas Wireless Propag. Lett.*, vol. 11, pp. 678-681, 2012.
- [41] P. Wouters et al., "A low power multi-sensor interface for injectable microprocessor-based animal monitoring system," Sensors and Actuat., vol. 41, pp. 198-206, 1994.
- [42] C. De Balthasar et al., "Design of antennas to power injectable microstimulators: a systematic approach," in *Proc. 9th Annu. Conf. Int. FES Soc.*, Sept. 2004.
- [43] J.H. Schulman, "The feasible FES system: battery powered BION stimulator," *Proc. IEEE*, vol. 96, pp. 1226-1239, Jul. 2008.
- [44] E. Johannessen et al., "Toward an injectable continuous osmotic glucose sensor," J. Diab. Scien. Technol., vol. 4, pp.882-892, Jul. 2010.
- [45] B.C. Towe et al., "A microwave powered injectable neural stimulator," in *Proc. Eng. Med. Biol. Soc.*, 2012.
- [46] P. Li et al., "A wireless power interface for rechargeable battery operated medical implants," *IEEE Trans. Circ. Syst.*, vol. 54, pp. 912-916, Oct. 2007.
- [47] C. Sauer et al., "Power harvesting and telemetry in CMOS for implanted devices," *IEEE Trans. Circ. Syst.*, vol. 52., pp. 2605-2613, Dec. 2005.
- [48] E. Moradi et al., "Measurement of wireless link for brain-machine interface systems using human-head equivalent liquid," *IEEE Antennas Wireless Propag. Lett.*, vol. 12, pp. 1307-1310, 2013.
- [49] S. Ozeri et al., "Ultrasonic transcutaneous energy transfer for powering implanted devices," *Elsevier Ultrason.*, vol. 50, pp. 556-566, 2010.
- [50] M.A. Karami et al., "Powering pacemakers from heartbeat vibrations using linear and nonlinear energy harvesters," *Appl. Phys. Lett.*, vol. 100, 2012.
- [51] A. Cadei et al., "Kinetic and thermal energy harvesters for implantable medical devices and biomedical autonomous sensors," *Meas. Scien. Technol.*, vol. 25, Nov. 2013.
- [52] B.J. Bowers et al., "Spherical, rolling magnet generators for passive energy harvesting from human motion," *J. Micromech. Microeng.*, vol. 19, Aug. 2009.
- [53] S. Cosnier et al., "Towards glucose biofuel cells implanted in human body for powering artificial organs: Review," *Electroch. Commun.*, vol. 38, pp. 19-23, Jan. 2014.
- [54] H.N. Schwerdt et al., "Wireless fully passive multichannel recording of neuropotentials using photo-activated RF backscattering methods," *IEEE Trans. Microw. Theory Techn.*, vol. 63, pp. 2965-2970, Sept. 2015.
- [55] S.A. Shabalovskaya et al., "Surface, corrosion and biocompatibility aspects of Nitinol as an implant material," *Biomed. Mat. Eng.*, vol. 12, pp. 69-109, 2002.
- [56] P. Soontornpipit et al., "Miniaturized biocompatible microstrip antenna using genetic algorithm," *IEEE Trans. Antennas Propag.*, vol. 53, pp. 1939, 1945, Jun. 2005.
- [57] A. Ramesh et al., "Towards in vivo biosensors for low-cost protein sensing," *Electron. Lett.*, vol. 49, pp. 450-451, Mar. 2013.
- [58] C.J. Plummer et al., "The use of permanent pacemakers in the detection of cardiac arrhythmias," *Europace*, vol. 3, pp. 229-232, 2001.
- [59] D. Reynolds et al., "A leadlesscardiac transcatheter pacing system," New Engl. J. Med., vol. 374, pp. 533-541, Feb. 2016.
- [60] R. Warty et al., "Characterization of implantable antennas for intracranial pressure monitoring: reflection and transmission through a scalp phantom," *IEEE Trans. Microw. Theory Techn.*, vol. 56, pp. 2366-2376, Oct. 2008.
- [61] U. Kawoos et al., "In-vivo trans-scalp evaluation of an intracranial pressure implant at 2.4 GHz," *IEEE Trans. Microw. Theory Techn.*, vol. 56, pp. 2356-2365, Oct. 2008.
- [62] X. Meng et al., "Dynamic study of wireless intracranial pressure monitoring of rotational head injury in swine model," *Electron. Lett.*, vol. 48, pp. 363-364, Mar. 2012.
- [63] M.W.A. Khan et al., "Remotely powered piezoresistive pressure sensor: toward wireless monitoring of intracranial pressure," *IEEE Microw. Wireless Compon. Lett.*, vol. 26, pp. 549-551, 2016.
- [64] M.H. Behfar et al., "Biotelemetric wieless intracranial pressure monitoring: an in vitro study," *Int. J. Antennas Propag.*, vol. 2015, 2015.
- [65] L. Yu et al., "Chronically implanted pressure sensors: challenges and state of the field," Sensors, vol. 14, pp. 20620-20644, 2014.
- [66] E.Y. Chow et al., "Fully wireless implantable cardiovascular pressure monitor integrated with a medical stent," *IEEE Trans. Biomed. Eng.*, vol. 57, pp. 1487-1496, 2010.

- [67] O.H. Murphy et al., "Continuous in vivo blood pressure measurements using a fully implantable wireless SAW sensor," *Biomed. Microdev.*, vol. 15,, pp. 737-749, 2013.
- [68] M. Theodor et al., "Subcutaneous blood pressure monitoring with an implantable optical sensor," *Biomed. Microdev.*, vol. 15, pp. 811-820, 2013.
- [69] S.H. Ellozy et al., "First experience in human beings with a permanently implantable intrasac pressure transducer for monitoring endovascular repair of abdominal aortic aneurysms," *J. Vasc. Surg.*, vol. 40, pp. 405-412, 2004.
- [70] Adamson, P.B. et al. "Champion trial rationale and design: the long term safety and clinical efficacy of a wireless pulmonary artery pressure measurement system," J. Card. Fail., vol. 17, pp. 3-10, 2011.
- [71] G. Karageorgos et al., "Self-powered impantable electromagnetic device for cardiovascular system monitoring through arterial wall deformation," in *Proc. 6th Int. Conf. Wireless Mob. Commun. Healthc.*, Nov. 2016.
- [72] M. Yin et al., "Wireless neurosensor for full-spectrum electrophysiology recordings during free behavior," *Neuron.*, vol. 84, pp. 1-13, 2014.
- [73] H.N. Schwerdt et al., "A fully passive wireless microsystem for recording of neuropotentials using RF backscattering methods," J. Microelectromech. Syst., vol. 20, pp. 1119–1130, 2011.
- [74] C. Lee et al., "A high-sensitivity fully-passive neurosensing system for wireless brain signal monitoring," *IEEE Trans. Microw. Theory Techn.*, vol. 63, pp. 2060–2068, 2015.
- [75] C. Lee et al., "Miniaturized fully-passive brain implant for wireless acquisition of very low-level neural signals," *IEEE Antennas Wireless Propag. Lett.*, 2016.
- [76] D.B. Shire et al., "Development and implantation of a minimally invasive wireless subretinal neurostimulator," *IEEE Trans. Biomed. Eng.*, vol. 56, pp. 2502-2511, Oct. 2009.
- [77] J. Weiland et al., "Retinal prosthesis," *IEEE Trans. Biomed. Eng.*, vol. 61, pp. 1412-1424, May 2014.
- [78] L.M. Watson et al., "Children's communication mode five years after cochlear implantation: changes over time according to age at implant," *Cochl. Impl. Int.*, vol. 7, pp. 77-91, Nov. 2013.
- [79] A.L. Benabid et al., "Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease," in *Elsevier Neurol.*, vol. 8, pp. 67-81, Jan. 2009.
- [80] F. Lotte et al., "Regularizing common spatial patterns to improve BCI designs: unified theory and new algorithms," *IEEE Trans. Biomed. Eng.*, vol. 58, pp. 355-362, Feb. 2011.
- [81] H.-W. Chiu et al., "Pain control on demand based on pulsed Radio-Frequency stimulation of the dorsal root ganglion using a batteryless implantable CMOS SoC," *IEEE Trans. Biomed. Circ. Syst.*, vol. 4, pp. 350-359, Dec. 2010.
- [82] D. Panescu, "An imaging pill for gastrointestinal endoscopy," *IEEE Eng. Med. Biol. Mag.*, vol. 24, pp.12-14, Aug. 2005.
- [83] J. Thone, et al., "Design of a 2 Mbps FSK near-field transmitter for wireless capsule endoscopy," Sens. Actuators A, Phys., vol. 156, pp. 43-48, Nov. 2009.
- [84] M. Kfouri et al., "Towards a miniaturised wireless fluorescence-based diagnostic imaging system," *IEEE J. Select. Topics Quantum Electron.*, vol. 14, pp. 226-234, Jan./Feb. 2008.
- [85] G. Zorpette, "Putting electronics in people," IEEE Spectr., Mar. 2014.
- [86] K. Kalantar-zadeh et al., "Intestinal gas capsules: a proof-of-concept demonstration," *Gastroent.*, vol. 150, p. 27, Jan. 2016.
- [87] S.P. Woods et al., "Wireless capsule endoscope for targeted drug delivery: mechanics and design considerations," *IEEE Trans. Biomed. Eng.*, vol. 60, pp. 945-953, Apr. 2013.
- [88] W. Yu et al., "A smart capsule with GI-tract-location-specific payload release," *IEEE Trans. Biomed. Eng.*, vol. 62, pp. 2289-2295, Sept. 2015.
- [89] http://profusa.com/lumee/
- [90] A.C. Dupont et al., "First clinical experience with BION implants for therapeutic electrical stimulation," *Neuromod.*, vol. 7, pp. 38-47, 2004.
- [91] C. Jin et al., "Injectable 3-D fabrication of medical electronics at the target biological tissues," *Scientif. Rep.*, vol. 3, 2013.
- [92] L.L. Baker et al., "Preliminary experience with implanted microstimulators for management of post-stroke impairments," J. Neurol. Phys. Ther., vol. 30, pp. 209-222, 2006.
- [93] M.J. Kane et al., "BION microstimulators: a case study in the engineering of an electronic implantable medical device," *Med. Eng. Phys.*, vol. 33, pp. 7-16, 2011.
- [94] B. Burns et al., "Treatment of hemicranias continua by occipitalnerve stimulation with a bion device: long-term follow-up of a crossover study," *Lancet Neurol.*, vol. 7, pp. 1001-1012, 2008.

[95] J. Groen et al., "Chronic pudendal nerve neuromodulation in women with idiopathic refractory detrusor overactivity incontinence: results of a pilot study with a novel minimally invasive implantable ministimulator," *Neurol. Urodyn.*, vol. 24, pp. 226-230, 2005.



Asimina Kiourti (S'10–M'14) received the Diploma degree in electrical and computer engineering from the University of Patras, Greece, in 2008, the M.Sc. degree in technologies for broadband communications from University College London, U.K., in 2009, and the Ph.D. degree in electrical and computer engineering from the National Technical University of Athens, Greece, in 2013.

She is currently an Assistant Professor of Electrical and Computer Engineering at The Ohio State

University, Columbus, OH, USA. She has authored or coauthored more than 90 journal and conference papers and seven book chapters. Her research interests include medical sensing, antennas for medical applications, RF circuits, bioelectromagnetics, and flexible textile-based electronics.

Dr. Kiourti is Associate Editor for the IEEE Transactions on Antennas and Propagation. She has received several awards and scholarships, including the IEEE Engineering in Medicine and Biology Society (EMB-S) Young Investigator Award for 2014, the IEEE Microwave Theory and Techniques Society (MTT-S) Graduate Fellowship for Medical Applications for 2012, and the IEEE Antennas and Propagation Society (AP-S) Doctoral Research Award for 2011.



Konstantina S. Nikita (M'96-SM'00) received the Diploma in Electrical Engineering and the Ph.D. degree from the National Technical University of Athens (NTUA), as well as the M.D. degree from the Medical School, University of Athens.

From 1990 to 1996, she worked as a Researcher at the Institute of Communication and Computer Systems. In 1996, she joined the School of Electrical and Computer Engineering, NTUA, as an Assistant

Professor, and since 2005 she serves as a Professor at the same School. She is an Adjunct Professor of Biomedical Engineering and Medicine, Keck School of Medicine and Viterbi School of Engineering, University of Southern California. She has authored or co-authored 165 papers in refereed international journals, 41 chapters in books, and over 300 papers in international conference proceedings. She is editor of seven books in English, and author of two books in Greek. She holds two patents. She has been the technical manager of several European and National R&D projects. She has been honorary chair/ chair of the program/organizing committee of several international conferences and she has served as keynote/invited speaker at international conferences, symposia and workshops organized by NATO, WHO, ICNIRP, IEEE, URSI, etc. She has been the advisor of 26 completed Ph.D. theses, several of which have received various awards. Her current research interests include biomedical telemetry, biomedical signal and image processing and analysis, simulation of physiological systems, and biomedical informatics.

Dr Nikita is Associate Editor of the IEEE Transactions on Biomedical Engineering, the IEEE Journal of Biomedical and Health Informatics, the IEEE Transactions on Antennas and Propagation, the Bioelectromagnetics, and the Journal of Medical and Biological Engineering and Computing. She has received various honors/awards, among which, the Bodossakis Foundation Academic Prize (2003) for exceptional achievements in "Theory and Applications of Information Technology in Medicine". She has been a member of the Board of Directors of the Atomic Energy Commission and of the Hellenic National Academic Recognition and Information Center, as well as a member of the Hellenic National Council of Research and Technology. She has also served as the Deputy Head of the School of Electrical and Computer Engineering of the NTUA. She is a member of the Hellenic National Ethics Committee, a Founding Fellow of the European Association of Medical and Biological Engineering and Science (EAMBES), a Fellow of the American Institute for Medical and Biological Engineering (AIMBE), a member of the Technical Chamber of Greece and of the Athens Medical Association. She is also the founding chair and ambassador of the IEEE-EMBS, Greece chapter and vice chair of the IEEE Greece Section.