Ingestible electronic technologies for advanced monitoring of the gastro-intestinal tract

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***Abstract* — The gastro-intestinal (GI) tract is a very important part of the human digestive system but remains largely inaccessible for unobtrusive monitoring. Ingestible electronic devices are a very interesting concept to address this need. This paper discusses the current state of ingestible electronic devices and explores the potential they hold to provide unprecedented insight by measuring several aspects of the complex bio-chemical processes that happen in the GI tract in real-time. This will require novel sensor technology capable of measuring relevant markers with adequate specificity and accuracy. In order to be able to scale this functionality down to a form factor of an easily digestible pill, ultra-low-power wireless interface electronics are needed. This paper discussed some of the challenges related to sensing, wireless communication and powering where innovation is needed to enable the next generation of ingestible electronic devices.**

***Index Terms*—Ingestible, gastro-intestinal, electro-chemical sensing, wireless powering, CMOS integrated circuits**

I. Introduction

TECHNOLOGICAL advancements have always been one of the important key drivers for innovation in healthcare. The evolution of devices for wearable and remote healthcare over the last 2 decades is just one clear example. Fueled by innovations in sensor technology, material technology and micro- and nanoelectronics, certain medical monitoring and treatments previously only possible in a hospital environment are now readily available at the point of need as wireless wearable devices (see Fig. 1). Cardiovascular health assessment is one the largest application of wearable devices, with the number of other applications growing rapidly. For example, monitoring of diabetic patients has completely changed by the introduction of continuous glucose monitors and biosensors are being developed for detection of biomarkers in sweat and saliva. Wearable sensors increasingly enable monitoring of sleep quality, mental health, pulmonary disorders, and can support women fertility tracking and monitoring of fetal heart rate and movement [1].

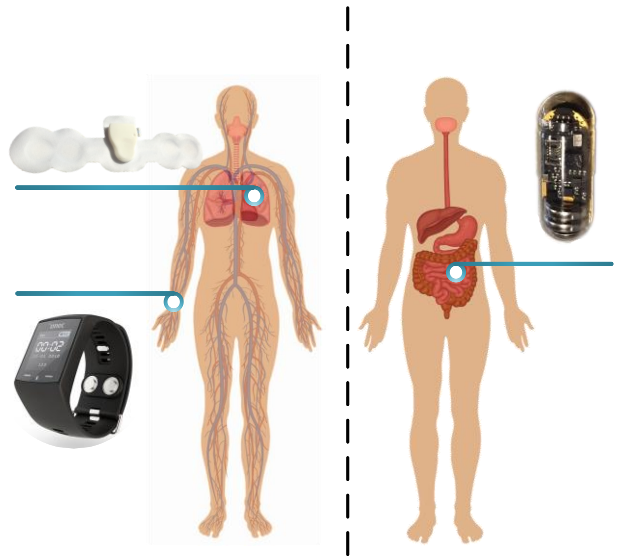

Fig. 1. Most wearable devices like health patches and wristbands allow to measure parameters related to the cardiovascular or pulmonary system while ingestible devices can target the GI tract.

Existing wearables have limited abilities to measure the gastrointestinal (GI) tract, which is where ingestible electronic devices come into the picture (Fig. 1). The GI tract, part of the digestive system, is crucial in health and plays a central role in many diseases. Although it is difficult to assess total GI disease burden in the general population, it is certain that gastrointestinal symptoms can have a substantial impact on an individual's quality of life and can highly disrupt daily life activities and employment [2]. Chronic digestive disorders contribute, in addition, substantially to health care costs [2]. The impact and prevalence of GI diseases is only expected to grow due to poor nutritional choices, increasing levels of obesity, an aging society and high levels of alcohol consumption. Recent research has hypothesized that the influence of the GI tract is not limited to digestive and metabolic disorders[3], but could also influence brain functioning, through the microbiota-gut-brain axis [4] or play a

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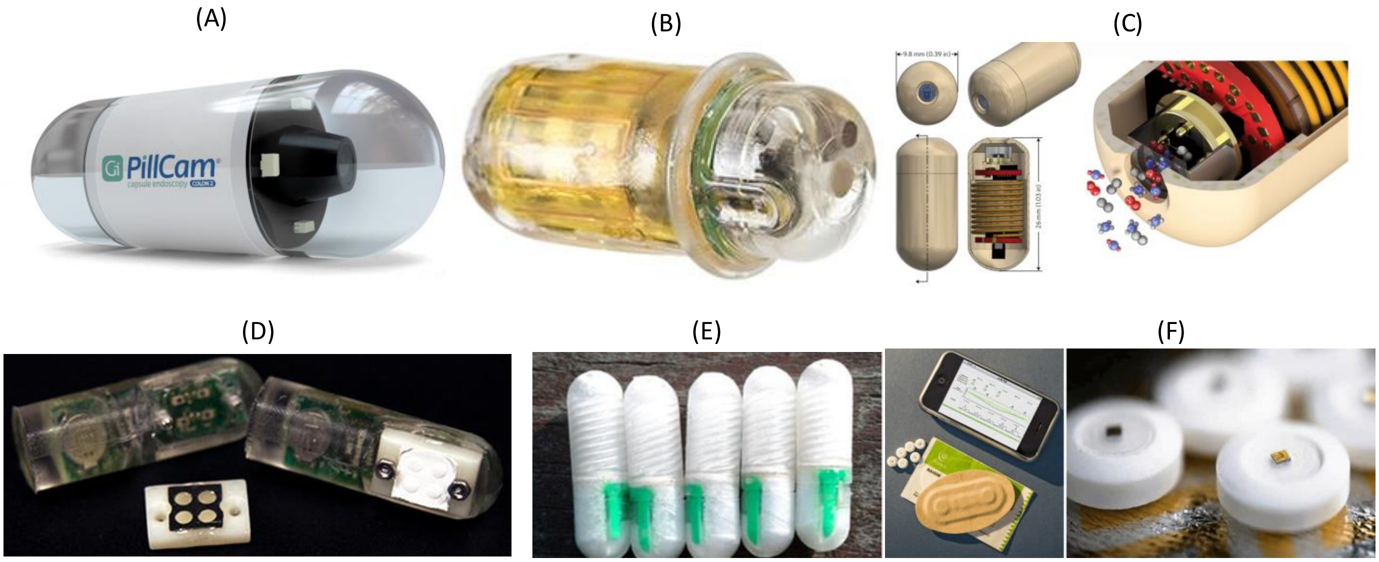

Fig. 2. A non-exhaustive view of modern ingestibles devices. (A) Medtronic PillCam: Capsule endoscopy (B) Medtronic SmartPill motility sensor (C) Ingestible gas sensor [12] (D) Ingestible sensor for gut health based on genetically modified bacteria [14] (E) Osmotic pump sampling pill [15] (F) Proteus Discover - ingestible electronic pills for therapy adherence [16].

role in lung [5] and cardiovascular diseases [6]. Scientists have only started to unravel the complex interactions between genetic, environmental, immune, microbial, nutrition and other factors influencing the GI tract.

Current practices and methods to investigate the exact workings of our metabolic system and diagnose maladies and disorders include offline analysis of blood, stool samples, biopsies, endoscopic inspection, radiographic, and symptom-based diagnostics. While these have their place and merit, they all have their drawbacks and no tools exist that can measure the complex intricacies of an individual's metabolic system in a continuous manner. In an effort to address these challenges, research groups around the world are pioneering advanced ingestible technology that could allow unique and unprecedented insights into the human metabolic system [7][8].

In this paper, we will give an overview of the functionalities of existing ingestible devices and describe future device potential. While the intent of this paper is not to provide an exhaustive overview, we will discuss some more recent advanced research devices and sketch the directions the field is moving to. We will dive deeper into some of the remaining technical challenges, specifically in the domain of miniaturized electronics where significant innovation is needed.

II. Current State of Ingestible Electronic Devices

The idea of ingestible devices is not new. In fact, clinical researchers were already exploring ingestible pH, temperature and pressure sensors more than 60 years ago [9]. In the decades following, interest remained but was hindered by available technology. The advancements in the late nineties and early 2000s in cheap, reliable and small (CMOS) imagers and RF wireless communication, heralded a wave of ingestible camera-pills. PillCam (Medtronic) (Fig. 2a) was one of the first FDA-approved commercially available devices. Nowadays multiple commercial players offer wireless endoscopic pill-shaped ingestible cameras. They offer the ability to visually inspect the intestine replacing uncomfortable, often painful endoscopic procedures. A thorough review of capsule endoscopy can be found in [10].

Camera-pills are mostly limited to optical recording and lack more advanced/multi-modal sensing capabilities. While visual inspection obviously has tremendous merits, approximately half of the gastrointestinal disorders (so-called functional gastrointestinal disorders) have no observable abnormalities. Furthermore, imaging is not suitable for a full assessment of gut health nor to assess nutritional status. In order to achieve this, new technologies are needed for multi-modal electrophysiological and electro-chemical sensing. Recent years have seen more proliferation in ingestible devices with a stronger focus on other sensing modalities than optical. By embedding a pH, temperature and pressure sensor (Fig. 2b), gastric emptying and colon transit times can be estimated [11] providing insight into gut motility. Researchers also explored miniaturization of gas sensors and embedding them in an ingestible device [12]. This ingestible device (Fig. 2c) can measure a number of gas concentrations, which the authors can link to certain fermentation processes.

Reliable bio-chemical sensing in a volume-constrained and low-power manner is extremely tricky and still largely unsolved for more complex analytes. An interesting approach to tackle this issue, is to leverage the power of nature itself. In [14], the authors developed environmentally resilient biosensor bacteria to perform the bio-chemical sensing. These bacteria were engineered to express bioluminescence when binding to target biomolecules. The electronic ingestible device (Fig. 2.d) in this case consisted of a very low-power luminescence detector.

While multiple groups across the world are working on reliable miniaturized bio-chemical sensing, the challenges on achieving adequate sensitivity and specificity in the human GI tract are enormous. As such, some approaches focus on devices that can take multiple liquid samples along the GI tract, for example [15] – Fig. 2e. The more complex devices can take multiple samples on demand (i.e. at specific locations of interest along the GI tract). These devices are recovered when they are expelled from the human body so samples can be analyzed in a lab. While this approach poses some obvious practical challenges, it is nevertheless extremely valuable in biomarker research and discovery as well as for specific diagnostics.

Another example of an FDA-approved ingestible device, is Proteus discover [16] (Fig. 2f), developed to address the problem of medication compliance. It is a miniature chip that together with 2 metal sheets can be embedded inside a pharmaceutical drug. When the drug is ingested and reaches the stomach, the metals are exposed to the stomach acid. This essentially creates an electro-chemical half-cell generating enough energy for the device to transmit a signal which is received by a wearable device. As such it allows an effective means to measure if a patient has taken a specific medication.

Creating ingestible devices is a multi-disciplinary challenge as far as the research, development, and validation of these devices is concerned. For the sake of brevity, we will focus in the remainder of this paper primarily on the electronic challenges on sensing, powering and communication. The challenges in other domains, not specifically addressed in this paper, like encapsulation, localization, auto-locomotion, drug delivery, prolonged residence, biocompatibility or clinical research however are an integral part of bringing ingestibles to market.

III. Sensing Opportunities and Challenges

The digestive system is a very intricate system with various complex physiological process taking place along the GI tract. One can think of many different sensors and sensing modalities that could be used to monitor these processes, including peristaltic movement and electrophysiology of the enteric nervous system, pH and simple ions (i.e. H^+, K^+, Cl^- and Na^+) and electrolytes, all the way to very complex and challenging analytes including neurotransmitters, hormones and bacteria [7]. Advances in materials science, chemistry, optics and the progress with micro- and nanoelectronics make the miniaturization of relevant sensing technology feasible. The combined requirement of a miniaturized sensor (while maintaining a fast, sensitive and specific response) with ultra-low power consumption poses numerous challenges. A common electrochemical sensor often embedded in ingestibles is a pH sensor exploiting ion-selective field-effect transistors (ISFETs). These devices operate similarly to MOSFETs and are nowadays considered the most convenient solution for fast, miniaturized pH sensing. Their sensitivity to H^+ is governed by the surface potential of the dielectric layer which exchange hydrogen ions with the surrounding electrolyte.

Next to pH, dietary minerals like sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), chloride ($Cl^–$), hydrogen phosphate ($HPO_4^{2–}$), and hydrogen carbonate ($HCO_3^–$), are useful markers to assess the electrolyte balance of the GI tract. These can be measured with ion selective electrodes (ISE) [17]. Nitric oxide has an important role in gastrointestinal diseases and influences motility and mucosal function of GI tract [18]. Local measurement of oxidative stress could help in detecting changes of the chemical composition of the gut [19]. While amperometric detection of these molecules is at present feasible in benchtop solutions, achieving adequate sensitivity, specificity and sensor longevity in an ingestible pill form factor has been unproven. A multi-array ingestible platform that incorporates biomolecules like enzymes and antibodies could revolutionize the field of medical diagnostic and help prevention and treatment of many GI tract-related diseases like Crohn's disease, obesity, diabetes, irritable bowel syndrome, Parkinson's disease and even provide access to the complex gut microbiome (Fig. 3). It is important to note that both potentiometric and amperometric sensors require a stable reference electrode. This requirement adds further challenges in terms of size constrains but is a key aspect for reliable results.

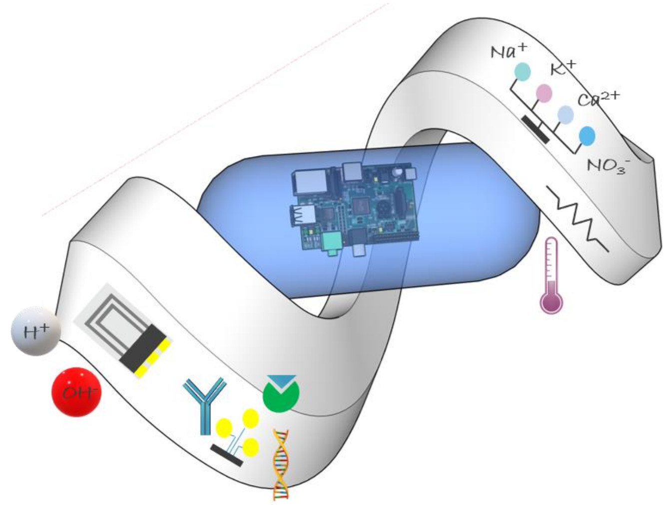

Fig. 3. Schematic overview of different sensors (pH, ions, temperature and biomarkers) envisioned for an ingestible electronic pill.

Next to analysis of the GI fluid, also gas sensing is being considered [12]. Hydrogen, carbon dioxide, nitrogen, and oxygen are the main intestinal gases and due to their correlation with fermentative activity of gut microbiome, could help the definition of dietary regimes of patients. This technology is based on gas sensing via different heat modulation elements, which exploit the gas properties of chemisorption/physisorption on surfaces at different temperatures [12].

While the initial ingestible sensors measured mostly pH, temperature and pressure, the above-mentioned examples are technological attempts toward specific diagnostics based on bio-chemical sensing principles. The research on sensing principles and accompanying electronics is still in early stages. Optimal sensors developed and validated at the laboratory scale have to face the complexity of the GI environment which is abundant in bio-particles like proteins, carbohydrates and fat triggering biofouling processes. Some of the fouling processes, which are part of the natural body defense system, occur in time frames of minutes to hours. This poses numerous obstacles to the implementation of ingestible electronics which can result in signal attenuation, reduction of sensitivity, non-specific recognition and even trigger a severe and harmful immune response. A judicious choice of materials and molecules is not sufficient to prevent the inactivation of the sensor surface and therefore surfaces exposed to complex body fluids must be engineered with an effective antifouling strategy [13]. Many strategies can be pursued like morphological changes of surface properties or proper functionalization with antifouling molecules. These aim to camouflage the device or to discourage fouling events at its first stage. A promising approach is represented by biocompatible membranes or micro-valve systems which can guarantee the permeation of analytes while excluding the active surface of the sensor from being in contact with GI fluids.

Of course, sensors themselves require suitable interface electronics. To achieve extremely low-power, high sensitivity and a small form factor, the sensors must be co-developed with suitable interface circuits. The chip design community is indeed looking at extremely low-power electro-chemical sensor interface ICs [20-24]. In [23], Huang et al. report an IC which measures on-chip sensor electrodes for protein, glucose, pH and temperature using a reconfigurable multi-sensor interface. Apart from the sensing front-end, it also includes a 402MHz wireless transmitter, an energy harvesting interface and digital processing, all together only consuming 942uW. In [24], Wang et al. focused on long battery life by achieving ultra-low power consumption of 5.5nW. Within this power budget, they manage to operate a potentiometric analog front-end, a 2.4GHz wireless transmitter, timing generation circuitry and a DC-DC converter.

IV. Communication Opportunities and Challenges

The various sensor data needs to be communicated to the outside world. As such ingestible devices require a suitable wireless communication which poses its own challenges towards further miniaturization. The most common method for wireless communication is modulating electromagnetic (EM) waves. The link quality is to a large extent determined by the antenna efficiency and the channel absorption in the frequency band used. Small antennas typically have poor radiation efficiency and are more sensitive to the surrounding environment. To increase the antenna efficiency while minimizing its size, one option is to use higher carrier frequencies. However, the EM absorption by human tissue also increases with frequency [25]. This is even more severe for ingestible applications where the tissue depth can be >15cm. Current ingestible electronics often make use of the Medical Implant Communication Service (MICS). This 402-405MHz band is a licensed band for diagnostic and therapeutic medical implants and body-worn medical devices and provides good tradeoffs in tissue absorption and antenna radiation efficiency [26]. Compared to ISM bands like 2.4GHz or 900MHz, the MICS band has much less interference. Lower frequency bands such as Near Field Communication (NFC) have comparatively much lower body absorption but typically have very limited range, low data rates and rely on good alignment between transmitter and receiver.

While advancements in CMOS have allowed most active circuitry of any wireless communication system to be integrated on a chip, a number of critical components, essential for wireless communication, are still mostly discrete and therefore bulkier components. The largest ones are typically the crystal and antenna impedance matching network. To meet the stringent volume constraints, [27] demonstrates a specifically designed fully integrated RF communication chip codesigned with an antenna (Fig. 4). This is mainly achieved with 2 important features:

Integrated antenna impedance matching: For optimal link efficiency, the RF circuit input impedance should be well matched to the antenna impedance, which is usually achieved

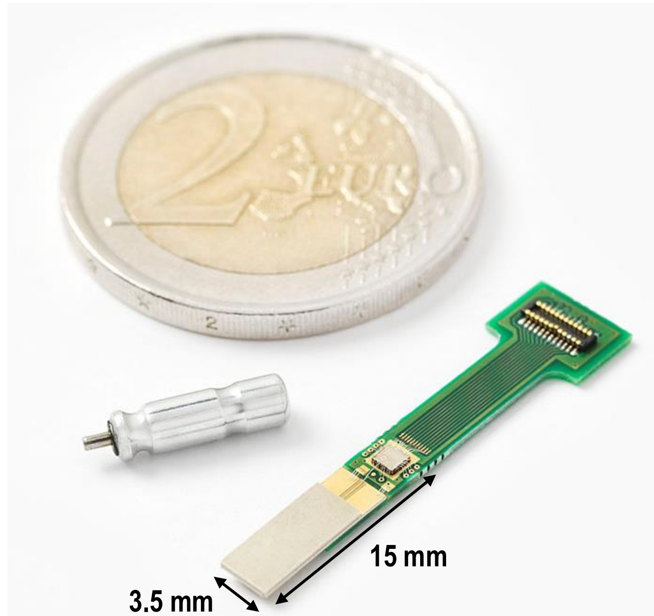

Fig. 4. An ultra-miniature wireless radio for ingestible applications [27].

with an external antenna impedance network. For ingestible solutions with physically small antennas however, the exact location along the GI tract and its local properties (i.e. empty or full stomach), body movement and the tissue properties of the surrounding environment of the antenna significantly influence its impedance [28]. A Tunable Matching Network (TMN) and a matching detector are preferred to manage the antenna impedance variation adaptively in real-time [29]. [27] proposes hence an on-chip TX/RX shared TMN. The chip continuously monitors the TX output signal strength, which is indicative of antenna impedance mismatch, with a power detector [30]. This approach is relatively simple but suffers from poor out-of-band interference rejection. A loop-back impedance detection [27] recycling RX hardware is free from the interference issue and provides good matching detection results without additional hardware. The on-chip capacitor bank of the TMN is automatically adjusted to find the optimum impedance matching point.

Integrated frequency reference: an accurate timing reference provided by a crystal is one of the indispensable external components in conventional wireless communication systems. However, just like the impedance matching network, it is a fairly bulky component. Film Bulk Acoustic Resonators (FBARs) [31] are an alternative to quartz crystals but require a special integration process. Another approach is a protocol-based timing calibration presented in [32]. However, it is undesirable for the MICS standard, which strictly regulates carrier stability (±100ppm) for compliance with the standard. An implant initiation protocol [27] with a phase-tracking RX topology [33] provides periodic frequency calibration. After initial frequency calibration with a look-up-table and on-chip temperature sensor, the phase-tracking RX extracts the carrier frequency from the received signal. The first millimeter-scale crystal-free MICS-compatible radio [27] shows the possibility of wireless communication for the ingestible application. As shown in Fig. 4, the total volume is 1 ×3.5×15mm^3, including a 1×3.5×3.8mm^3 PCB and a miniature antenna.

V. Powering Opportunities and Challenges

Ingestible devices require a suitable power source. Most existing ingestible devices are currently battery-powered, and the batteries take up roughly 30%-40% of the volume of the device. There is a clear trade-off between battery volume and energy density. While SMD solid-state batteries can achieve very small form factors, they have fairly poor energy densities. For example, [34] has a capacity of 0.14mAh in a volume of just 16mm^3 resulting in 26mWh/cm^3 energy density. Typical button cells, which are much larger, can achieve energy densities of >450mWh/cm^3. Energy density may increase in future by exploiting 3D-microbattery electrode technologies [35]. However, thermal dissipation will be one of the biggest challenges with the increase of volumetric energy density.

An interesting alternative consists in using the chemicals normally present in the body to build a battery which would never deplete. This is the concept behind (bio)fuel cells. For example, [36] presented an in-vitro power density of 3.7mW/cm^2. However, fuel cells are affected by very limited lifetime (on the order of few hours) when inserted in the body [37], making them today less attractive.

Considering that present solutions for storing or generating energy chemically are not satisfactory yet, transferring wirelessly energy from the outside of the body to the inside seems a viable alternative (see Fig. 5). Many stringent constrains affecting ingestibles do not apply for a power transmitter placed outside the body. Since its size can be much larger without significant discomfort, a much bigger battery can be used. Extensive research has been conducted in developing wireless powering techniques using electromagnetic and mechanical means of energy transfer.

Transferring thermal energy is in principle also possible: the implant would include a ThermoElectric Generator (TEG), which converts a local temperature gradient into electrical power. However, creating temperature gradients inside the body is not only difficult, but also dangerous, small temperature increases of only a few degrees can lead to necrosis[38]. Additionally, the temperature gradient needed to generate µW levels of power is sizeable: for generating 1µW of power more than 1ºC/mm is needed [39].

There are 3 main forms of electromagnetic wireless power transfer: inductive, radiofrequency and optical. Inductive wireless powering is the most commonly used for powering implants because the magnetic permeability of the body is almost equal to the one of air. Because of that, the path losses in the human tissues are almost insignificant: as low as 6.6x10^{-3}dB/mm at 21MHz [40]. Another important advantage of inductive powering techniques, is the relatively large power density safety limit, up to 100mW/mm^2 [41]. In addition, since energy is not transferred via wave propagation, no energy is lost because of reflections by the skin and between tissues with different properties. However, inductive powering suffers from strong sensitivity to misalignment between the power transmitting coil outside the body and the implanted receiving coil. This limits its adoption to cases in which the location of the implant is known in advance.

Wireless powering using mid-field or far-field radio frequency electromagnetic waves on the other hand is less sensitive to misalignment, in principle allowing to power

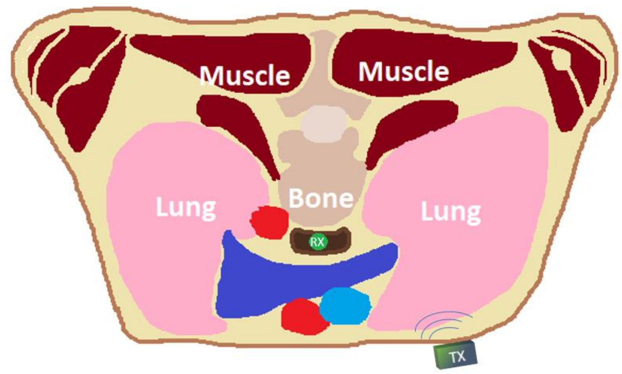

Fig. 5. Implanted device inserted in the middle of the human torso and powered by an external wearable power transmitter.

implants with unknown position. However, radiofrequency power transmission suffers from significant path losses in human tissue, as high as 0.2dB/mm at 2.4GHz [42]. Additionally, safety limits are 1000 times lower down to 0.1 mW/mm^2 [41]. Also, since the energy transfer happens via wave propagation, significant reflection occurs already at the interface between air and skin, with a reflection coefficient up to 72% at 2.4GHz [42]. Finally, since the body is not a homogeneous medium, multi-path reflections will occur also inside the body, reducing further the effectiveness of this technique.

Electromagnetic waves in the optical spectrum are also characterized by low sensitivity to misalignment between the power source and implant. The safety exposure limit of the human body to optical energy is very high: up to 300mW/mm^2 between 550nm and 750nm wavelength [43][44]. However, the path loss in human tissue is very high: more than 17dB/mm between 300nm and 1µm wavelength [45]. Notice that even though infrared radiation is characterized by the lowest path loss in the optical spectrum, its use is limited by the risk of tissue heat-up, causing cellular damage. Similarly, as with radiofrequencies, also the optical spectrum is affected by multi-path reflections.

Wireless power transfer can also occur via mechanical means, in particular ultrasound pressure waves. Given that the body is mostly composed of water, the propagation of sound waves is very effective and path losses are as low as 0.054dB/mm [46]. The safety power limits are reasonable, in the order of 7.2mW/mm^2 [47]. The worst problem affecting ultrasound power transfer is the reflection coefficient between air and skin, which is as high as 99.9%. In order to mitigate this loss, good acoustic coupling must be ensured in the whole path from transmitter to receiver. This implies the use of acoustic gels and the receiver, i.e. the ingestible pill, must remain in close contact with the tissue in order to receive power. Even then, good acoustic coupling cannot be guaranteed throughout the body, for example due to the presence of bone tissue.

In summary, energy storage limitations in terms of volumetric density and the low lifetime of fuel drives the development of alternative techniques such as wireless powering to power permanent implants. However, each technique is affected by a prominent weaknesses which limit its applicability. Research is ongoing aiming to overcome the disadvantages of each of these power transfer techniques. The use of multiple power transmitters seems beneficial in all wireless powering techniques: multiple transmitting coils can reduce the misalignment sensitivity [48], while beamforming can be used to focus electromagnetic [49] and ultrasound [50] waves.

VI. Conclusion

Ingestibles provide direct access to the GI tract and could as such enable unprecedented insight. In this paper we addressed some of the challenges this community faces on sensing technology focusing primarily on bio-chemical sensing and challenges related to ultra-low-power miniature wireless interface electronics. Looking at what the technological advancements have meant for wearables in the last 2 decades, it is clear that one of the areas where we might see a similar explosive growth, is ingestible devices focused on demystifying our gastrointestinal inner workings.

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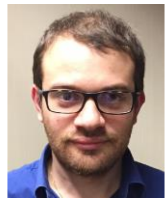

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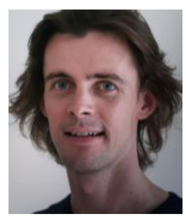

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