Trends in Biotechnology

CellPress

Special Focus on Materials

Review

Materials Advances for Next-Generation Ingestible Electronic Medical Devices

Christopher J. Bettinger[1,2,*]

Electronic medical implants have collectively transformed the diagnosis and treatment of many diseases, but have many inherent limitations. Electronic implants require invasive surgeries, operate in challenging microenvironments, and are susceptible to bacterial infection and persistent inflammation. Novel materials and nonconventional device fabrication strategies may revolutionize the way electronic devices are integrated with the body. Ingestible electronic devices offer many advantages compared with implantable counterparts that may improve the diagnosis and treatment of pathologies ranging from gastrointestinal infections to diabetes. This review summarizes current technologies and highlights recent materials advances. Specific focus is dedicated to next-generation materials for packaging, circuit design, and on-board power supplies that are benign, nontoxic, and even biodegradable. Future challenges and opportunities are also highlighted.

Trends

Microelectronic device miniaturization. There is a continuous trend in the miniaturization and reduced power consumption of many electronic components including transistors and logic elements, optoelectronics, and biosensors.

Bioresorbable electronics. Imparting novel properties of transience and biodegradability to functional electronics has the potential to reduce the intrinsic risk of many types of ingestible electronic devices.

Biologically derived energy storage materials. Naturally occurring endogenous compounds can serve as nontoxic electrochemical energy storage materials when combined with benign minerals and aqueous electrolytes. This materials framework could serve as on-board energy storage systems to power next-generation ingestible electronic devices.

The Promise of Next-Generation Electronic Medical Devices

Emerging healthcare strategies of the 21st century will be informed by datasets that are generated from continuous physiological monitoring of the human body. Comprehensive biosensor networks and modalities for therapeutic intervention can be established by connecting wearable electronics, implantable devices, and other sensing hardware to create a mobile health technology ecosystem [1,2]. Wearable electronics are advantageous because they are minimally invasive while implantable devices can measure biomarkers and monitor *in vivo* physiology with increased specificity. Implantable electronic devices also offer efficient channels for therapeutic delivery as evidenced by the clinical success of pacemakers, cochlear implants, continuous glucose monitors, and deep brain stimulators [3,4]. Next-generation implantable devices may include brain–machine interfaces, neurostimulators for 'electroceuticals' [5], and smart-controlled release systems [6]. Rapid advances in implantable electronic devices are enabled in part by miniaturized low-power microelectronics, improved packaging, and increased battery performance. Unfortunately, implantable medical devices are highly invasive and subject to manufacturing challenges and economic constraints. Chronic implants evoke complex biological responses that impact device performance [7,8] and increase the risk of complications such as fibrosis and infection [9]. Novel materials that may address these technical challenges are subject to strict regulatory standards because of the nature of the implant.

Alternative channels for biosensing and therapeutic intervention utilize semi-invasive modalities such as electronic contact lenses and ingestible electronics [10,11]. This complementary class of medical devices could feed additional data into biosensor networks and provide new avenues

[1]Department of Materials Science and Engineering, Carnegie Mellon University, Pittsburgh, PA 15213, USA
[2]Department of Biomedical Engineering, Carnegie Mellon University, Pittsburgh, PA 15213, USA

*Correspondence:
cbetting@andrew.cmu.edu
(C.J. Bettinger).

for therapeutic delivery. Semi-invasive electronic devices harness the advantages of electronic implants (e.g., active electronics, on-board sensors, actuators, telemetry) while obviating many of the challenges. Ingestible electronics, in particular, could transform many aspects of monitoring and treating diseases because of the wide range of biomarkers and therapeutic targets in the gut. Although the prospect of ingestible electronics is intriguing, many challenges remain. Progress in ingestible electronics may benefit from recent advances in materials including flexible electronics, biologically derived energy storage materials, and biomaterials-based circuits. This review summarizes recent advances in ingestible electronics and highlights several recent clinical successes. Anticipated challenges and future opportunities in next-generation devices are also outlined with a focus on the need for novel materials. Specific focus is granted to new materials for energy storage, flexible electronic components, and biodegradable circuitry for potential use in edible electronic devices.

Current Technologies for Ingestible Electronics

One of the first applications of ingestible electronic devices was *in vivo* measuring of physiological biomarkers in ambulatory human subjects. Continuous monitoring of core body temperature, oxygen tension, and gastrointestinal (GI) pH provides valuable insight into real-time human performance [12] (Figure 1). Early devices leveraged silicon-based microelectronics for *in vivo* sensing and communication. Advances in microelectronic fabrication have enabled miniaturization and increased the sophistication of devices. Form factors with smaller dimensions increase the probability of free gastric transit while limiting the risk of device retention [13–15]. For example, the Discover by Proteus is a personalized digital medicine system that consists of a small ingestible sensor and an external transceiver to monitor patient compliance when taking oral medications (Proteus Digital Health, Redwood City, CA, USA) [16]. The ingestible component consists of a millimetric scale device ($W \times L \times t = 1 \times 1 \times 0.3\ mm^3$) that contains an integrated circuit (IC) powered by an Mg–Cu electrochemical couple. The IC contains nonvolatile memory and a circuit to modulate the current of a dipole within the sensor. The sensor modulates the current in the dipole to produce data that is then transmitted to the external receiver via an electric field. The device contains structures to increase the amplitude of the E-field and an adhesive to affix the device on oral tablets. The device remains dormant until the electrochemical cell is formed upon contact with gastric fluid (Figure 1B). The device transmits data with 99.1% positive detection accuracy despite significant variations in externally

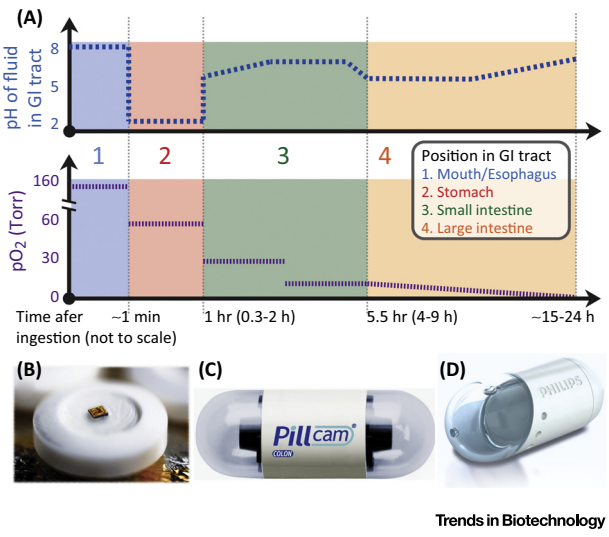

Figure 1. Gastrointestinal Tract Physiology and Recent Examples of Ingestible Electronics. (A) Spatially-dependent physiological parameters within the gastrointestinal (GI) tract. Gastric transit times approximate values for foodstuffs and strongly depend on the size and geometry of the device along with the physiological state. The transit times for the stomach and small intestine represent median (min–max) times for a device ($D \times L = 6\ mm \times 15\ mm$) [66]. The transit time for the large intestine represents a range that is estimated from that of nondisintegrable tablets in the fasted state. Representative examples of ingestible medical devices including the (B) ingestible component of the Discover by Proteus Digital Health (affixed to pill, $W \times L = 2\ mm \times 2\ mm$), (C) PillCam by Given Imaging ($D \times L = 11\ mm \times 26\ mm$), (D) IntelliCap by Philips ($D \times L = 11\ mm \times 26\ mm$). Images reproduced with permission.

recorded signals that vary with device orientation, stomach contents, and the composition and geometry of the torso. The device also poses minimal risk since silicon-based electronics are composed of nontoxic materials and can be fabricated using CMOS-compatible manufacturing. Furthermore, the risk of electromagnetic interference with tissue is managed by limiting discharge currents (0.1 mA for 4 min), minimizing signal voltages (<1 mV), and using communication frequencies (10–30 kHz) that do not interfere with physiological processes (10–100 Hz). This device achieved a CE mark in Europe and FDA approval in the USA as a Class II device through a *de novo* classification [17].

Another application for ingestible electronics is wireless capsule endoscopy [18]. Imaging the upper GI tract using ingestible devices is valuable because early detection of many diseases is possible even though this region is difficult to access using traditional endoscopy. A typical wireless capsule endoscope contains a camera, an LED array for illumination, on-board logic for data processing, a transmitter, and a power supply. These components are packaged in water impermeable polymer capsules with cylindrical form factors ($D = 10$ mm; $L = 25$ mm) (Figure 1C). Devices are powered for 8–12 h using on-board batteries composed of nontoxic materials (e.g., Ag_2O) or through telemetry [19]. Data transfer is achieved through radio frequency (RF) transmission or propagation of electrical signals directly through the tissue. Ingestible devices can also use on-board sensors for programmable-controlled release. One example is the IntelliCap (Philips, Eindhoven, The Netherlands) (Figure 1D), which is a device that contains a battery, an IC, pH sensor, temperature sensor, RF wireless transceiver, fluid pump, and drug reservoir. The IntelliCap offers spatiotemporal control of drug delivery in the GI tract by using pH measurements to determine device location. This device can transmit physiological information or drug delivery data in real time to external receivers. The IntelliCap is used primarily in pharmaceutical research as a tool to measure pharmacokinetics on novel drug candidates [20]. The current state of the art in capsule endoscopy using off-the-shelf materials and components has been summarized in detail elsewhere [21]. Other emerging applications for ingestible electronics include biosensors fabricated from edible materials that detect microbial populations in food or on tooth enamel [22]. This class of biosensors can be fabricated using biopolymer substrates and passive sensing elements. Optical sensors utilize laminated thin films of gold microstructures with a reflection signature that is altered in the presence of adherent bacteria or upon spoilage. RF-based sensors can detect the adsorption of single bacteria where the impedance increases through changes in resistance.

Materials Challenges for Existing Ingestible Device Technology

There are many anticipated risk elements for ingestible electronic devices. How can patient compliance be maintained for devices that may be difficult to self-administer? What is the long-term impact of electronic communication through the body? What is the environmental impact of devices that may accumulate in wastewater treatment facilities? Many of these questions have been answered in part by successful clinical testing of devices such as the PillCam and the Proteus Discover. One of the most significant risk elements is device retention within the GI tract [23]. The risk associated with device retention stems from the physical properties of the device and the disease state of the GI tract. The dimensions of many complex ingestible devices are comparable to inner diameter of the lumen within the GI tract. Most devices have a rigid polymeric coating to protect the electronic components. Encapsulation materials often render the device rigid, incompressible, and nondegradable/nondisintegrable. Ingestible devices for wireless capsule endoscopy adopt a form factor that is cylindrical with dimensions of $D \times L = 10 \pm 3$ mm $\times$ 25 ± 5 mm that results in a 1.4% chance of retention [23]. The incidence of retention can be as high as 2.6% in patients with enteropathies such as Crohn's disease and bleeding [15]. Retained devices are surgically extracted in 58.7% of these cases [15]. Capsules can be retained for up to 4 years in the GI tract, which increases the risk of perforation of the lumen or device failure. While the retention risk is tolerable for one-time use devices such as wireless

capsule endoscopy, the chances of retaining at least one device is >50% for 45 independent events. Large nondegradable capsules are therefore poorly suited for applications that require repeated administration such as periodic biosensing or dose schedules that required repeated device ingestion. The ingestible component of the Proteus Discover system reduces the risk of chronic retention by using millimetric dimensions and hydrolytically labile Si/SiO_2 [24]. The potential impact of ingestible electronics could be expanded if more sophisticated devices (similar in complexity to wireless endoscopy) could exhibit reduced risk of complications associated with retention while preserving clinically relevant functions such as *in vivo* imaging and diagnostics.

Fabricating ingestible electronic devices from materials with mechanical properties that promote gastric transit and chemical signatures that facilitate biodegradation could expand the scope of applications for ingestible electronic devices. Potential applications include biosensing and delivery of high-molecular weight compounds such as insulin, protein-based therapeutics, antibodies, or vaccines. These prospective applications require an expanded materials toolbox.

The Present and Future Materials Toolbox for Ingestible Electronics

Materials selection for ingestible medical devices can be informed from other nonmedical applications including nutritional supplements and food additives. Minerals may serve as valuable materials for device components and energy storage materials (Table 1). The

Table 1. Select Minerals and Other Inorganics that are Both Used as Materials for Ingestible Devices and Have a Significant Recommended Dietary Intake

Minerals	Daily Intake[a]	Function in Edible Electronic Device[b]	Selected Refs
Boron	<20 mg	Component of anodes in aqueous primary cells	[67]
Calcium	1000 mg	Component for secondary alkaline batteries	[68]
Copper	2 mg	Copper hexacyanoferrate battery electrodes	[69]
Iron (Fe_3O_4)	15 mg	Anodes in aqueous supercapacitors	[70]
Magnesium	350 mg	Anode in primary cell; anode in semifuel cell system with sea water electrolyte	[33,71–73]
Manganese (MnO_2)	5 mg	Cathode in aqueous supercapacitor; cathode in aqueous Li cells	[74,75]
Molybdenum (MoO_3)	75 g	Anodes in aqueous supercapacitors	[76]
Nickel	<1 mg	Nickel hexacyanoferrate electrodes for aqueous Na^+/K^+ batteries	[77]
Phosphorus	1000 mg	Component is phosphate-based cathodes for Na^+ batteries	[78]
Potassium	3500 mg	Ion in various aqueous electrochemical systems	[79,80]
Silicon (SiO_2)	n/a[c]	Hydrolytically labile active layers in high-performance silicon devices	[24,81]
Sodium	2400 mg	Ion in various aqueous electrochemical systems	[32,82,83]
Vanadium	<1.8 mg	Ion in aqueous flow cell batteries	[84,85]
Zinc (Zn and ZnO)	15 mg	Anode in aqueous polymer batteries; active layer in thin-film transistors	[51,86–88]

[a]Daily intake estimated from the US Recommended Dietary Allowance (RDA).
[b]Battery electrode materials limited to aqueous electrolytes.
[c]n/a, not applicable.

Table 2. Representative Examples of Small Molecule Organics and Polymers That Have Been Used in Edible Electronic Devices

Small Molecule Organics and Polymers	Function in Edible Electronic Device	Selected Refs
Gellan gum	Flexible substrate material	[26,89]
Sodium alginate	Flexible substrate material; proton conductor	[90,91]
Chitin	Flexible substrate material; proton conductor	[92]
Silk fibroin	Flexible substrate, dielectric material, waveguide material	[93]
Poly(β-hydroxy polyester)	Flexible substrate, dielectric material	[46]
Pectin	Flexible substrate material	[90]
Reflectin	Proton conductor	[94]
Poly(vinyl alcohol)	High-k dielectric	[46]
Albumin	High-k dielectric	[95,96]
Sucrose	High-k dielectric	[97]
Gelatin	Dielectric material	[98]
Indigo	Active layer in thin-film transistors	[31,53]
β-Carotene	Active layer in thin-film transistors	[52]
Melanin	Anode in aqueous Na^+ batteries; cathode in Na^+/Mg^{2+} batteries	[32,33]

recommended dietary allowance (RDA) informs the range of acceptable doses for many inorganic materials including magnesium, zinc, copper, molybdenum, manganese, iron, and selenium [25]. Other bioinert noble metals may also be safely consumed including gold, platinum, and even silver (350 μg_{Ag}/day for a 70-kg person). Many of these materials can serve as electrode materials in batteries or components in devices such as antennae, logic elements, and biosensors.

Many synthetic organic polymers that are used as food additives may be repurposed for many applications in edible electronics. Emulsifiers and protective coatings include polyethylene glycol (PEG), gellan gum, and cellulose [26,27]. These materials commonly serve as bulk materials or temporary coatings for ingestible devices. Biopolymers isolated from foodstuffs can also serve as materials for dielectric layers and substrate materials (Table 2). Materials that are generally recognized as safe (GRAS) by the FDA can be used in devices without premarket approval, which can expedite clinical trials for many ingestible devices [28]. Furthermore, there are many naturally occurring biologically derived compounds that exhibit unique electronic functionality including conjugated small molecules, proteins, nucleic acids, saccharides, and pigments [29–33]. Naturally occurring small molecules and biopolymers produce a materials toolbox for designing logic elements that operate stably within the GI tract while minimizing the risk of toxicity or adverse events.

Biomaterials for Ultracompliant Electronics

The ideal form factor of ingestible electronic devices would facilitate gastric transit and minimize the risk of retention in the GI tract. Rigid nondisintegrable tablets with a largest dimension of 11 mm transit the stomach freely since the diameter of the resting pyloric sphincter in 12.8 ± 7 mm [34]. This anatomical consideration provides an upper bound on the device dimension that has been considered in the design of many ingestible device geometries. Constraints on device dimension could eventually limit the prospective functionality of next-generation systems. For example, it may be beneficial to include on-board energy storage systems that permit increased

operating times for ingested devices. Devices with piezoelectric components or large antennae (>11 mm) may permit efficient energy and data transfer between ingested devices and epidermal transmitters.

Large device dimensions may be needed to contain antenna for communication, on-board batteries to power electronics, and reservoirs to store and deliver therapeutics. Devices with nominal sizes that are larger than the characteristic inner diameter of the lumen in the GI tract can be fabricated using mechanically compliant materials. Recent advances in flexible batteries and antennae may be leveraged for ingestible medical devices [35,36]. Flexible and stretchable devices fabricated using elastomers could be packaged into temporary shapes to facilitate passage through the small intestine before adopting larger form factors. Devices could also be fabricated from compressible materials such as hydrogels. Biologically derived ionomers such as heparin can be synthesized into hydrogel templates for conducting polymers. The resulting biohybrid composite is ultracompliant ($G' \sim 1$ kPa), redox active, and electronically conductive [37]. More recent demonstrations can integrate electronic structures directly with adhesive hydrogels through transfer printing [38]. Compressible electronic devices could facilitate transit through anatomical constrictions through the GI tract. Mechanically compliant electronic components and packaging could also reduce the risk of lumen perforation in cases of device retention. Both recent and future advances in flexible electronics can be leveraged to expand the design space for ingestible electronic devices.

Edible Materials for Powering Ingestible Electronics

Perhaps one of the most crucial challenges in ingestible electronics is designing on-board energy storage systems that offer adequate performance while minimizing risk to the patient. Electrochemical storage materials are typically designed to optimize charge storage capacity (both gravimetric and volumetric), cycle life, and cost. Ingestible batteries should be informed by orthogonal considerations such as reduced toxicity and attenuated immunogenicity. Batteries for ingestible electronics could use gastric fluid as an electrolyte and electrodes composed of benign materials including minerals (Table 1), activated carbon, or redox active biopolymers. Melanin pigments represent an intriguing option as a benign electrode material in batteries that use aqueous electrolytes. Melanin pigments are redox active and reversibly bind many cations with promiscuous affinity. Melanin pigments can serve as both anode and cathode materials depending upon the initial oxidation state. Melanin anodes (600-mg active material) coupled with manganese oxide cathodes can supply 5 mW of power for up to 20 h [32], while preoxidized melanin cathodes (600-mg active material) coupled with sodium–titanium phosphate anodes can supply 18 mW of power for up to 16 h (Y.J. Kim et al., unpublished). Melanin cathodes that use aqueous Mg^{2+} electrolytes are also rechargeable (Figure 2A). These batteries satisfy the power requirements of many existing medical devices including sensors and drug delivery pumps [39]. The required volume of active electrode material is compatible with standardized form factors commonly used in wireless capsule endoscopy. Additionally, melanin electrodes may disintegrate and biodegrade within the GI tract to reduce the risk of long-term complications associated with device retention [29].

Electrochemical couples can also serve as an on-board power source for ingestible electronics. This simple and robust strategy utilizes nontoxic metallic contacts to generate transient currents. The electrochemical cell in the ingestible component of the Proteus Discover system utilizes thin-film Mg anodes (8 μm thick; 0.0079 mg) and Cu cathodes (7 μm thick; 0.0071 mg), which produce open circuit potentials of 1.85 V at 0.1 mA for ~4 min. The electrodes use amounts of Mg and Cu that are well below the maximum allowable daily limit. Ingestible primary batteries can be produced using Mg coupled with other cathode materials including Mo, W, and Fe [40]. The operating voltages of Mg–Mo, Mg–W, and Mg–Fe are 0.75 V, 0.65 V, and 0.45 V, respectively.

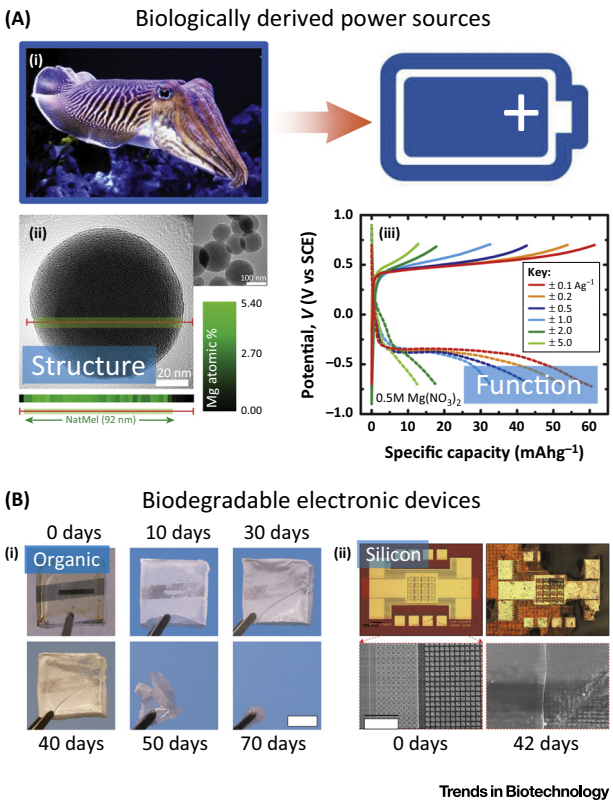

Figure 2. Biologically Derived Materials and Biodegradable Components for Ingestible Electronics. (A) Preoxidized natural melanin pigments serve as a suitable cathode material for aqueous Mg^{2+} batteries. (A, ii) Melanin nanoparticles can be packaged into cathodes that can be (A, iii) discharged and (re)charged using Mg^{2+} with a voltage hysteresis of 0.83 V. Reproduced from Kim *et al.* [33]. Copyright WILEY-VCH Verlag GmbH&Co. KGaA, Weinheim. (B, i) Poly(L-lactide-*co*-glycolide) (PLGA) substrates can be combined with polyvinyl alcohol (PVA) dielectric layers and small molecule conjugated active layers to create organic thin-film transistor arrays that can disintegrate *in vitro*. Scale bars represent 5 mm. Reproduced from Bettinger and Bao [46]. Copyright WILEY-VCH Verlag GmbH&Co. KGaA, Weinheim. (B, ii) Silicon-based devices built at the 90-nm node on silk fibroin substrates can partially disintegrate in water after 42 days. Scale bars represent 10 μm. Reproduced from Yin *et al.* [50]. Copyright American Physical Society. Images reproduced with permission.

Glucose oxidase fuel cells represent another strategy for on-board power generation. This strategy was originally designed to power implantable devices but could also serve as a viable option for powering ingestible electronics [41]. Other types of external power transmission include ultrasonic energy coupled with piezoelectric harvesters [42] or mid-field E-field transmission [43]. These emerging strategies provide 1 μW to 1 mW depending on the device geometry. External power transmission can potentially reduce the intrinsic size of the device, but may require additional hardware such as external batteries, transmission coils, wearable devices, and tethers.

Biodegradable Materials for Electronic Device Components

Fabricating devices using biodegradable bulk materials and electronic components can obviate the risk of long-term device retention. There are many prominent examples of polymeric materials and dielectrics that are either water soluble or biodegradable through hydrolysis or enzymatic activity. Many synthetic polymers can be processed into thin films or used as resins in photolithography and 3D printing including poly(vinyl alcohol) (PVA), PEG, polyesters, polyanhydrides, and their derivatives. Natural biopolymers can also be leveraged as biodegradable dielectrics including proteins (e.g., silk fibroin, albumin), polysaccharides (e.g., gellan gum, pullulan), and DNA [44]. Biopolymers with high densities of aromatic and polar groups can serve as high-k dielectrics for logic devices [45]. These materials can be combined and processed into microstructures to create logic elements that could serve as the foundation for more complex devices. One such example is the fabrication of organic thin-film transistors on bioresorbable substrates [46]. Small molecule organic semiconductors combined with PVA dielectrics and bioinert metals can form transistors that exhibit figures of merit for device performance that are suitable for RF circuits and can disintegrate *in vitro* within approximately 2 months of incubation in simulated body fluid (Figure 2B,i).

There are several prominent examples of biodegradable materials with unique intrinsic optoelectronic properties including semiconducting behavior and switching. Silicon is perhaps the most important material in the microelectronics industry. The native oxide layer of silicon thin films hydrolyzes into silicic acid under physiological conditions [47]. Silicic acid is a benign compound that is found in the ocean and can function as a nutritional supplement [48]. The disintegration rate of silicon devices can be accelerated by creating microstructures composed of ultrathin silicon membranes [49]. This principle has been utilized in the fabrication of complex integrated circuits at the 90-nm node [50]. Other inorganic materials may be used in logic elements including transition metal oxides (e.g., ZnO) [51]. Organic semiconductor materials may also be used as biodegradable active layers in logic elements. Recent work suggests that nontoxic small conjugated molecules such as indigo and β-carotene can serve as active layers with charge carrier mobilities of ~1 and 10^{-3} cm^2 V^{-1} s^{-1}, respectively [52,53]. Despite the relatively low stability and reduced performance of organic semiconductors compared with silicon, carbon-based microelectronic devices may be suitable for ingestible electronics because of the temporary nature of the device and modest performance requirements. For example, device functions such as sensing routines and RF communications could utilize circuits that contain organic transistors. Biologically derived materials may be used in optical components. Deep HOMO levels of DNA render it as an effective hole-blocking layer in laminated OLED structures. Silk fibroin is an attractive material for optical waveguides in biophotonics owing to its index of refraction (n = 1.54 @ λ = 633 nm) and facile doping.

Finally, there are numerous benign biodegradable metals including Zn, Mg, Fe, Cu, and Zn–Ca alloys. The toxicity and biodegradation kinetics of these metals have been studied in the context of bioabsorbable implants such as temporary orthopedic devices and stents [54]. One technical challenge for macroscopic devices is that rapid hydrogen evolution can form gaseous pockets near the implant site. This potential challenge has been addressed by engineering new alloys based on Mg–Zn–Ca [55]. The risk of excessive hydrogen evolution is minimized for ingestible electronics since these materials will be used in thin-film devices such as biodegradable antennae or interconnects. One unique challenge in using biodegradable metals for ingestible electronic devices is that the physical properties of the material shift as the material oxidizes and dissolves. Unpredictable corrosion events could alter the performance of RF coils during power transmission or data transfer. Bioinert noble metals could be used for crucial device components. Metals such as Au, Pt, Pd, and Ag are nontoxic, benign, and are commonly ingested in food products. Although these compounds have the possibility to accumulate in the GI tract, the overall risk is limited because of the small quantities used in thin-film structures and temporary exposure.

Potential Applications of Ingestible Electronics

There are many types of biomarkers and therapeutic targets in the GI tract that are available for sensing and modulation. The ability to measure and perturb these targets will increase as ingestible devices utilize novel materials for energy storage and harvesting, next-generation electronic materials that are flexible, stretchable, or biodegradable, and new biosensing modalities with increased sensitivity and selectivity. The potential scope of capabilities of ingestible electronic devices will expand with increasing primary knowledge related to immunity, the gut microbiome, metabolism, and the interplay between these complex systems. Many debilitating diseases are associated with bacterial infections within the GI tract including *Clostridium difficile* infection (CDI). CDI is among the highest hospital-acquired infection in the Western hemisphere [56]. Early detection of CDI could prevent large outbreaks, but current methods of diagnosing are inaccurate and take several days to perform. An ingestible biosensor that is capable of early detection of CDI and other infections within the GI tract could accelerate the timelines for diagnosis. Inflammatory disorders such as Crohn's disease and irritable bowel syndrome (IBS) are other examples of debilitating diseases that manifest in the GI tract [57,58]. Early and rapid

detection of these diseases using minimally invasive biosensors afforded by ingestible electronic devices could increase the treatment options for early treatment.

The gut microbiome plays an integral role in human health by regulating metabolism and inflammation [59]. Causal relationships link microbiome composition with metabolic and immune pathologies. Imbalanced (dysbiotic) gut compositions are implicated in many pathologies including type 1 and type 2 diabetes mellitus [60], obesity [61], cancer [62], atherosclerosis [63], and inflammatory bowel disease (IBD) [64]. Early detection of dysbiotic microbiota populations could enable prophylactic eubiotic restoration. One of the many challenges facing eubiotic restoration is the vast spatiotemporal heterogeneity in the composition of the gut microbiome and the complex genetic and biochemical environments within the GI tract. Current methods to determine gut microbiome composition rely on analyzing genetic information from bacteria in the feces. This limited sample may provide biased or inaccurate information regarding the gut microbiome composition within the organ of interest. Ingestible sensors could enable real-time monitoring of microbiome composition.

Edible electronics may also serve as a tool for therapeutic intervention. Ingestible-controlled release devices with on-board sensors can measure physiological parameters within the GI tract and the rate of colonic absorption of model drug compounds (IntelliCap) [65]. This device deploys a payload from a single reservoir. Next-generation devices may adopt a 'pharmacy-on-a-chip' model in which multiple reservoirs can be released at arbitrary timelines [6]. These devices could be further miniaturized and optimized for ingestible formats. Controlled release systems could enable the delivery of high-value compounds with increased bioavailability such as protein-based therapeutics, antibodies, vaccines, prebiotics, or probiotics.

Concluding Remarks and Future Perspectives

Ingestible electronics as medical devices could transform the diagnosis and treatment of many diseases associated with the GI tract. Increased interest in edible electronic devices stems from the confluence of emerging technological innovations coupled with recent scientific discoveries. A blueprint for regulatory approval and cost-effective manufacturing practices has been established by several commercially successful devices including wireless capsule endoscopes, integrated biosensor-controlled release devices, and ingestible event markers. Identifying a specific indication that can be diagnosed or treated more efficiently using the unique capabilities of ingestible devices could accelerate regulatory approval and clinical translation. The potential impact of ingestible electronics will expand as more materials are added to the design toolbox. Next-generation devices, batteries, and sensing elements that operate stably in the GI tract and are composed of materials that are biodegradable, mechanically compliant, and nontoxic could expand the scope of potential clinical impact of edible electronics. Materials that permit frequent ingestion of devices and minimize the risk of retention are especially valuable.

The overall impact of ingestible electronic medical devices may expand with technological advances in other disciplines. For example, the rapid growth of wearable electronic devices is commonly viewed as a standalone technology space for minimally invasive recording of biomarkers in real time. Wearable electronics may be a complementary and crucial support technology to expand the capabilities of ingestible electronics. External wearable devices may facilitate data transfer and power transmission. Soft robotics is another field that may support advances in edible electronics. Millimetric scale devices that freely locomote within the GI tract may also expand the range of applications and therapeutic potential of ingestible electronics. The specific applications of prospective devices must be identified through collaborative partnerships between both engineers and clinicians. Taken together, edible electronic devices may play a pivotal role in the early detection and treatment of pathologies within the GI tract and beyond.

Outstanding Questions

How will regulatory guidelines previously established for implantable devices map to ingestible devices? How will regulatory guidelines for foods and vitamins apply to materials that are used as structural and functional components of ingestible medical devices that provide either sophisticated diagnostic or therapeutic functions?

What device packaging strategies, materials, and form factors can facilitate gastric transit and limit toxicity while still providing robust operation within the GI tract *in vivo*? What are appropriate timescales for *in vivo* operational lifetime versus residence time within the GI tract? What is an acceptable range of timescales given the potentially broad scope of applications for prospective devices?

To what extent are the parameters for systems engineering known? How can low-power electronics, communication elements, on-board power supplies, and other components be designed for broad use as an ingestible electronic medical device? What unique circumstances or constraints must be considered when devices are intended to operate stably within the GI tract?

Acknowledgments

Funding was provided by the following organizations: the American Chemical Society Petroleum Research Fund (ACS PRF #51980-DNI7); Defense Advanced Research Projects Agency (D14AP00040); Pittsburgh Innovation Works. C.J.B. would like to acknowledge the work of many other laboratories whose contributions could not be included owing to formatting restrictions.

References

1. Hayes, D.F. *et al.* (2014) Personalized medicine: risk prediction, targeted therapies and mobile health technology. *BMC Med.* 12, 37
2. Topol, E.J. *et al.* (2015) Digital medical tools and sensors. *JAMA* 313, 353–354
3. Wilson, B.S. *et al.* (1991) Better speech recognition with cochlear implants. *Nature* 352, 236–238
4. Gough, D.A. *et al.* (2010) Function of an implanted tissue glucose sensor for more than 1 year in animals. *Sci. Transl. Med.* 2, 42ra53
5. Famm, K. *et al.* (2013) Drug discovery: a jump-start for electroceuticals. *Nature* 496, 159–161
6. Farra, R. *et al.* (2012) First-in-human testing of a wirelessly controlled drug delivery microchip. *Sci. Transl. Med.* 4, 122ra21
7. Koschwanez, H.E. and Reichert, W.M. (2007) In vitro, in vivo and post explanation testing of glucose-detecting biosensors: current methods and recommendations. *Biomaterials* 28, 3687–3703
8. Park, H. and Park, K. (1996) Biocompatibility issues of implantable drug delivery systems. *Pharm. Res.* 13, 1770–1776
9. An, Y.H. and Friedman, R.J. (1998) Concise review of mechanisms of bacterial adhesion to biomaterial surfaces. *J. Biomed. Mater. Res.* 43, 338–348
10. Badugu, R. *et al.* (2003) A glucose sensing contact lens: a non-invasive technique for continuous physiological glucose monitoring. *J. Fluoresc.* 13, 371–374
11. Liao, Y-T. *et al.* (2012) A 3-CMOS glucose sensor for wireless contact-lens tear glucose monitoring. *IEEE J. Solid State Circ.* 47, 335–344
12. Byrne, C. and Lim, C.L. (2007) The ingestible telemetric body core temperature sensor: a review of validity and exercise applications. *Br. J. Sports Med.* 41, 126–133
13. Baichi, M.M. *et al.* (2006) What we have learned from 5 cases of permanent capsule retention. *Gastrointest. Endosc.* 64, 283–287
14. Davis, S.S. *et al.* (1986) Transit of pharmaceutical dosage forms through the small intestine. *Gut* 27, 886–892
15. Liao, Z. *et al.* (2010) Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest. Endosc.* 71, 280–286
16. Hafezi, H. *et al.* (2015) An ingestible sensor for measuring medication adherence. *IEEE Trans. Biomed. Eng.* 62, 99–109
17. Proteus Digital Health Inc. (2013) *510(k) Summary – Proteus Patch Including Ingestible Sensor,* Proteus Digital Health, Inc
18. Iddan, G. *et al.* (2000) Wireless capsule endoscopy. *Nature* 405, 417
19. Yuce, M.R. and Dissanayake, T. (2012) Easy-to-swallow wireless telemetry. *IEEE Microw. Mag.* 13, 90–101
20. Van der Schaar, P.J. *et al.* (2013) A novel ingestible electronic drug delivery and monitoring device. *Gastrointest. Endosc.* 78, 520–528
21. Munoz, F. *et al.* (2014) A review of drug delivery systems for capsule endoscopy. *Adv. Drug Deliv. Rev.* 71, 77–85
22. Mannoor, M.S. *et al.* (2012) Graphene-based wireless bacteria detection on tooth enamel. *Nat. Commun.* 3, 763
23. Li, F. *et al.* (2008) Retention of the capsule endoscope: a single-center experience of 1000 capsule endoscopy procedures. *Gastrointest. Endosc.* 68, 174–180
24. Brinker, C.J. (1988) Hydrolysis and condensation of silicates: effects on structure. *J. Non-Cryst. Solids* 100, 31–50
25. Lukaski, H.C. (1995) Micronutrients (magnesium, zinc, and copper): are mineral supplements needed for athletes? *Int. J. Sport Nutr.* 5 (Suppl.), S74–S83
26. Ferris, C.J. and Panhuis, M. (2009) Conducting bio-materials based on gellan gum hydrogels. *Soft Matter* 5, 3430–3437
27. Kamper, S.L. and Fennema, O. (1984) Water vapor permeability of edible bilayer films. *J. Food Sci.* 49, 1478–1481
28. Burdock, G.A. and Carabin, I.G. (2004) Generally recognized as safe (GRAS): history and description. *Toxicol. Lett.* 150, 3–18
29. Bettinger, C.J. *et al.* (2009) Biocompatibility of biodegradable semiconducting melanin films for nerve tissue engineering. *Biomaterials* 30, 3050–3057
30. Gomez, E.F. *et al.* (2014) Exploring the potential of nucleic acid bases in organic light emitting diodes. *Adv. Mater.* Published online December 12, 2014. http://dx.doi.org/10.1002/adma.201403532
31. Irimia-Vladu, M. (2013) 'Green' electronics: biodegradable and biocompatible materials and devices for sustainable future. *Chem. Soc. Rev.* 43, 588–610
32. Kim, Y.J. *et al.* (2013) Biologically derived melanin electrodes in aqueous sodium–ion energy storage devices. *Proc. Natl. Acad. Sci. U.S.A.* 110, 20912–20917
33. Kim, Y.J. *et al.* (2014) Catechol-mediated reversible binding of multivalent cations in eumelanin half-cells. *Adv. Mater.* 26, 6572–6579
34. Coupe, A.J. *et al.* (1991) Correlation of the gastric emptying of nondisintegrating tablets with gastrointestinal motility. *Pharm. Res.* 8, 1281–1285
35. Inui, T. *et al.* (2015) A miniaturized flexible antenna printed on a high dielectric constant nanopaper composite. *Adv. Mater.* 27, 1112–1116
36. Kaltenbrunner, M. *et al.* (2010) Arrays of ultracompliant electrochemical dry gel cells for stretchable electronics. *Adv. Mater.* 22, 2065–2067
37. Ding, H. *et al.* (2014) Biologically derived soft conducting hydrogels using heparin-doped polymer networks. *ACS Nano* 8, 4348–4357
38. Wu, H. *et al.* (2015) Transfer printing of metallic microstructures on adhesion-promoting hydrogel substrates. *Adv. Mater.* 27, 3398–3404
39. Nisar, A. *et al.* (2008) MEMS-based micropumps in drug delivery and biomedical applications. *Sens. Actuat. B: Chem.* 130, 917–942
40. Yin, L. *et al.* (2014) Materials, designs, and operational characteristics for fully biodegradable primary batteries. *Adv. Mater.* 26, 3879–3884
41. Cracknell, J.A. *et al.* (2008) Enzymes as working or inspirational electrocatalysts for fuel cells and electrolysis. *Chem. Rev.* 108, 2439–2461
42. Ozeri, S. and Shmilovitz, D. (2010) Ultrasonic transcutaneous energy transfer for powering implanted devices. *Ultrasonics* 50, 556–566
43. Yakovlev, A. *et al.* (2012) Implantable biomedical devices: wireless powering and communication. *IEEE Commun. Mag.* 50, 152–159
44. Cuervo, A. *et al.* (2014) Direct measurement of the dielectric polarization properties of DNA. *Proc. Natl. Acad. Sci. U.S.A.* 111, E3624–E3630
45. Gaspar, D. *et al.* (2014) Nanocrystalline cellulose applied simultaneously as the gate dielectric and the substrate in flexible field effect transistors. *Nanotechnology* 25, 094008
46. Bettinger, C.J. and Bao, Z. (2010) Organic thin-film transistors fabricated on resorbable biomaterial substrates. *Adv. Mater.* 22, 651–655
47. Bogush, G.H. and Zukoski, C.F., IV (1991) Studies of the kinetics of the precipitation of uniform silica particles through the hydrolysis and condensation of silicon alkoxides. *J. Colloid Interf. Sci.* 142, 1–18
48. Wickett, R.R. *et al.* (2007) Effect of oral intake of choline-stabilized orthosilicic acid on hair tensile strength and morphology in women with fine hair. *Arch. Dermatol. Res.* 299, 499–505

49. Hwang, S-W. *et al.* (2014) Dissolution chemistry and biocompatibility of single-crystalline silicon nanomembranes and associated materials for transient electronics. *ACS Nano* 8, 5843–5851
50. Yin, L. *et al.* (2015) Materials and fabrication sequences for water soluble silicon integrated circuits at the 90 nm node. *Appl. Phys. Lett.* 106, 014105
51. Pal, B.N. *et al.* (2008) Solution-deposited zinc oxide and zinc oxide/pentacene bilayer transistors: high mobility n-channel, ambipolar, and nonvolatile devices. *Adv. Funct. Mater.* 18, 1832–1839
52. Burch, R.R. *et al.* (2004) Electrical properties of polyunsaturated natural products: field effect mobility of carotenoid polyenes. *Synth. Met.* 146, 43–46
53. Głowacki, E.D. *et al.* (2013) 25th anniversary article: Progress in chemistry and applications of functional indigos for organic electronics. *Adv. Mater.* 25, 6783–6800
54. Witte, F. (2010) The history of biodegradable magnesium implants: a review. *Acta Biomater.* 6, 1680–1692
55. Zberg, B. *et al.* (2009) MgZnCa glasses without clinically observable hydrogen evolution for biodegradable implants. *Nat. Mater.* 8, 887–891
56. Kelly, C.P. and LaMont, J.T. (1998) *Clostridium difficile* infection. *Annu. Rev. Med.* 49, 375–390
57. Mattila, E. *et al.* (2012) Fecal transplantation, through colonoscopy, is effective therapy for recurrent *Clostridium difficile* infection. *Gastroenterology* 142, 490–496
58. Van Nood, E. *et al.* (2009) Struggling with recurrent *Clostridium difficile* infections: is donor faeces the solution? *Euro Surveill.* 14, 19316
59. Honda, K. and Littman, D.R. (2012) The microbiome in infectious disease and inflammation. *Annu. Rev. Immunol.* 30, 759–795
60. Musso, G. *et al.* (2011) Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes. *Annu. Rev. Med.* 62, 361–380
61. Qin, J. *et al.* (2012) A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 490, 55–60
62. Schwabe, R.F. and Jobin, C. (2013) The microbiome and cancer. *Nat. Rev. Cancer* 13, 800–812
63. Turnbaugh, P.J. *et al.* (2009) A core gut microbiome in obese and lean twins. *Nature* 457, 480–484
64. Frank, D.N. *et al.* (2007) Molecular–phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc. Natl. Acad. Sci. U.S.A.* 104, 13780–13785
65. Koziolek, M. *et al.* (2014) Investigation of pH and temperature profiles in the GI tract of fasted human subjects using the IntelliCap® system. *J. Pharm. Sci.* 104, 2855–2863
66. Worsøe, J. *et al.* (2011) Gastric transit and small intestinal transit time and motility assessed by a magnet tracking system. *BMC Gastroenterol.* 11, 145
67. Yang, H.X. *et al.* (2004) Metal borides: competitive high capacity anode materials for aqueous primary batteries. *Electrochem. Solid-State Lett.* 7, A212–A215
68. Yu, J. *et al.* (2001) A study of calcium zincate as negative electrode materials for secondary batteries. *J. Power Sources* 103, 93–97
69. Wessells, C.D. *et al.* (2011) Copper hexacyanoferrate battery electrodes with long cycle life and high power. *Nat. Commun.* 2, 550
70. Qu, Q. *et al.* (2011) 2D Sandwich-like sheets of iron oxide grown on graphene as high energy anode material for supercapacitors. *Adv. Mater.* 23, 5574–5580
71. Medeiros, M.G. and Dow, E.G. (1999) Magnesium-solution phase catholyte seawater electrochemical system. *J. Power Sources* 80, 78–82
72. Winther-Jensen, B. *et al.* (2008) Control of magnesium interfacial reactions in aqueous electrolytes towards a biocompatible battery. *Electrochim. Acta* 53, 5881–5884
73. Kong, Y. *et al.* (2012) A battery composed of a polypyrrole cathode and a magnesium alloy anode — toward a bioelectric battery. *Synth. Met.* 162, 584–589
74. Hong, M.S. *et al.* (2002) Use of KCl aqueous electrolyte for 2 V manganese oxide/activated carbon hybrid capacitor. *Electrochem. Solid-State Lett.* 5, A227–A230
75. Manickam, M. *et al.* (2004) Lithium insertion into manganese dioxide electrode in MnO2/Zn aqueous battery: part I. A preliminary study. *J. Power Sources* 130, 254–259
76. Tang, W. *et al.* (2011) Aqueous supercapacitors of high energy density based on MoO3 nanoplates as anode material. *Chem. Commun.* 47, 10058–10060
77. Wessells, C.D. *et al.* (2011) Nickel hexacyanoferrate nanoparticle electrodes for aqueous sodium and potassium ion batteries. *Nano Lett.* 11, 5421–5425
78. Palomares, V. *et al.* (2012) Na-ion batteries, recent advances and present challenges to become low cost energy storage systems. *Energy Environ. Sci.* 5, 5884–5901
79. Kanoh, H. *et al.* (1997) Electrochemical intercalation of alkali-metal ions into birnessite-type manganese oxide in aqueous solution. *Langmuir* 13, 6845–6849
80. Eftekhari, A. (2004) Potassium secondary cell based on Prussian blue cathode. *J. Power Sources* 126, 221–228
81. Hwang, S.-W. *et al.* (2012) A physically transient form of silicon electronics. *Science* 337, 1640–1644
82. Whitacre, J.F. *et al.* (2010) Na4Mn9O18 as a positive electrode material for an aqueous electrolyte sodium-ion energy storage device. *Electrochem. Commun.* 12, 463–466
83. Ellis, B.L. and Nazar, L.F. (2012) Sodium and sodium-ion energy storage batteries. *Curr. Opin. Solid State Mater. Sci.* 16, 168–177
84. Skyllas–Kazacos, M. and Grossmith, F. (1987) Efficient vanadium redox flow cell. *J. Electrochem. Soc.* 134, 2950–2953
85. Li, L. *et al.* (2011) A stable vanadium redox-flow battery with high energy density for large-scale energy storage. *Adv. Energy Mater.* 1, 394–400
86. Macdiarmid, A.G. *et al.* (1985) Electrochemical characteristics of "polyaniline" cathodes and anodes in aqueous Electrolytes. *Mol. Cryst. Liq. Cryst.* 121, 187–190
87. Grgur, B.N. *et al.* (2008) Polypyrrole as possible electrode materials for the aqueous-based rechargeable zinc batteries. *Electrochim. Acta* 53, 4627–4632
88. Sun, B. and Sirringhaus, H. (2005) Solution-processed zinc oxide field-effect transistors based on self-assembly of colloidal nanorods. *Nano Lett.* 5, 2408–2413
89. Higgins, T.M. *et al.* (2011) Gellan gum doped polypyrrole neural prosthetic electrode coatings. *Soft Matter* 7, 4690–4695
90. Galus, S. and Lenart, A. (2013) Development and characterization of composite edible films based on sodium alginate and pectin. *J. Food Eng.* 115, 459–465
91. Liu, Y.H. *et al.* (2014) Proton conducting sodium alginate electrolyte laterally coupled low-voltage oxide-based transistors. *Appl. Phys. Lett.* 104, 133504
92. Zhong, C. *et al.* (2011) A polysaccharide bioprotonic field-effect transistor. *Nat. Commun.* 2, 476
93. Parker, S.T. *et al.* (2009) Biocompatible silk printed optical waveguides. *Adv. Mater.* 21, 2411–2415
94. Ordinario, D.D. *et al.* (2014) Bulk protonic conductivity in a cephalopod structural protein. *Nat. Chem.* 6, 596–602
95. Chang, J.-W. *et al.* (2011) Chicken albumen dielectrics in organic field-effect transistors. *Adv. Mater.* 23, 4077–4081
96. Ma, M. *et al.* (2014) Organic field-effect transistors with a low driving voltage using albumin as the dielectric layer. *RSC Adv.* 4, 58720–58723
97. Irimia-Vladu, M. *et al.* (2010) Edible electronics: biocompatible and biodegradable materials for organic field-effect transistors. *Adv. Funct. Mater.* 20, 4017
98. Mao, L.-K. *et al.* (2013) Pentacene organic thin-film transistors with solution-based gelatin dielectric. *Org. Electron.* 14, 1170–1176