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## Wireless, Battery-free Platforms for Collection of Biosignals

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### Abstract

Recent progress in biosensors have quantitatively expanded current capabilities in exploratory research tools, diagnostics and therapeutics. This rapid pace in sensor development has been accentuated by vast improvements in data analysis methods in the form of machine learning and artificial intelligence that, together, promise fantastic opportunities in chronic sensing of biosignals to enable preventative screening, automated diagnosis, and tools for personalized treatment strategies. At the same time, the importance of widely accessible personal monitoring has become evident by recent events such as the COVID-19 pandemic. Progress in fully integrated and chronic sensing solutions is therefore increasingly important. Chronic operation, however, is not truly possible with tethered approaches or bulky, battery-powered systems that require frequent user interaction. A solution for this integration challenge is offered by wireless and battery-free platforms that enable continuous collection of biosignals. This review summarizes current approaches to realize such device architectures and discusses their building blocks. Specifically, power supplies, wireless communication methods and compatible sensing modalities in the context of most prevalent implementations in target organ systems. Additionally, we highlight examples of current embodiments that quantitatively expand sensing capabilities because of their use of wireless and battery-free architectures.

### 1. Introduction

Rapid progress of highly integrated sensing technologies enabled by advances in electronics (Keyes, 1988; Popovici et al., 2013; Rasouli and Phee, 2010) materials (Joung, 2013; Khan et al., 2016; Lacour et al., 2005; L. Wang et al., 2019) and sensors (Bonato, 2005; K. et al., 2004; Ray et al., 2019) form the basis of symbiosis between biology and digital technologies. Sensors and sensing systems that enable continuous and precise collection of high-fidelity biological signals are key technologies to realize the next generation of digital medicine. Such systems require sophisticated hardware with substantial power requirements and consequently wired interfaces that tether subjects to a specific location, which complicates recovery, limits applicable use cases, and negatively impacts signal fidelity through induction of motion artifacts (Hamilton et al., 2000; Hartmut Gehring et al., 2002). Further, tethers limit operation during daily activity thereby lowering quality of life, especially in the case of diagnosis and therapy of chronic illnesses (Bade et al., 2018; Bize et al., 2007; Rejeski and Mihalko, 2001). The ability to monitor biosignals continuously,

however, coupled with modern data analysis tools such as artificial intelligence (AI) (Chen and Asch, 2017; Ravì et al., 2017; Zhu et al., 2020), is predicted to yield significantly improved diagnostic and therapeutic capabilities (Obermeyer and Emanuel, 2016). To realize such advanced systems, there is a substantial need to increase seamless recording capabilities that operate autonomously and without user interaction to enable continuous data streams for diagnosis, fundamental research and therapeutics (Richard, 2015).

A direct requirement for chronic sensing is wireless operation (Dieffenderfer et al., 2015; Gaddam et al., 2008; Lynch and Loh, 2006; Patel et al., 2012; Zubiete et al., 2011). Current wireless sensing platforms in both wearable and implantable form factors rely largely on battery-powered designs to eliminate the need for tethered connections while providing capabilities in wearable sensing (Baig et al., 2017; Patel et al., 2012), neuroscience discovery (Farahmand et al., 2012), and organ specific biosignal recording (Kiourti et al., 2014; Ledet et al., 2012; Oliver et al., 2009). Although more suitable than their tethered counterparts, these systems fall short in yielding continuous, high-fidelity signals due to the bulk associated with batteries, which impacts system modulus and therefore conformality to the target organ system, resulting in reduced interface quality (Heikenfeld et al., 2018). Batteries inherently reduce functional lifetime and require subject interaction during charging events, which leads to loss of compliance, reduction in overall recording time and in the case of fundamental research studies, negatively impacts experimental outcomes (Q. Huang et al., 2016; Seneviratne et al., 2017; W. Xu et al., 2019).

A solution to this problem is offered by a new class of wireless and battery-free sensing systems in both wearable and implantable form factor with broad applications in medicine and research, encompassing a wide range of sensing modalities (Ferguson and Redish, 2011; Khan et al., 2020). These devices are characterized by their use of soft mechanics for conformal application to their target organ system and wireless, battery-free operation capabilities that reduce bulk while enabling continuous function without the need for user intervention. Beyond their use in human-centered applications (Ray et al., 2019), these systems have been introduced into animal-model research as investigative tools for development of novel sensing platforms (Burton et al., 2020; Hao Zhang et al., 2019) and closed-loop systems (Liu et al., 2020; Mickle et al., 2019), where physiological constraints prohibit the use of traditionally powered devices and enable insight into fundamental working principles of biological processes and underlying physiologies. Implementation of wireless, battery-free sensing systems require careful consideration of use-case, application, and sensing requirements to yield device form factors that allow for intimate integration with target organ systems to extract performance benefits over conventional approaches. Figure 1 summarizes key components that comprise these wireless and battery-free sensing systems, typical metrics for each component are provided in Supplementary Table 1 This review discusses key building blocks for these systems, namely wireless power transfer, data communication, current compatible sensing modalities and use cases for sending for these modalities in the context of their application in organ systems. It also highlights strategies for impactful combination of the components into wireless, battery-free sensors and sensor systems and provides a snapshot of current capabilities, while examining rationale behind design choices and highlighting current barriers and opportunities.

## 2. Implementation of wireless, battery-free sensing systems

Key aspects in the creation of wireless, battery-free sensing include the strategy for power supply and technology for wireless communication. The availability of power often drives design choices of the wireless sensor system, dictates system capabilities, and is considered the bottleneck for most applications. In this section, we will explore currently available power casting and harvesting techniques, their operation principles, general advantages and challenges towards the use in the creation of fully integrated sensor systems. We will also identify links to wireless communication capabilities, options for sensing modalities and discuss practical combinations.

### 2.1. Power casting and harvesting techniques

Wireless power transfer (WPT) schemes lay the foundation for system-level integration of wireless, battery-free wearable and implantable sensing platforms and their capabilities largely determine system (communication bandwidth, sensing modality, operational range, form factor etc.) and sensor performance (resolution, sampling rate, accuracy, specificity, etc.) (Ahire and Gond, 2017; Hui et al., 2013; Radousky and Liang, 2012; Xie et al., 2013). Generally, wireless, battery-free sensing systems are powered by two categories of power sources (Amar et al., 2015): 1. externally directed energy that can be harvested by using radio frequency (RF) antennas (X. Tian et al., 2019), magnetic resonant coils (Bandodkar et al., 2019b; Lin et al., 2020), photovoltaic cells (S. Lee et al., 2018) or ultrasonic transducers (Hinchet et al., 2019; Seo et al., 2016) that we call power casting techniques in this review; 2. internal energy provided by the subject that can be converted to useful electrical power by piezo/tribo/thermoelectric power converters or bio-fuels (Bullen et al., 2006; Dagdeviren et al., 2017; S. Park et al., 2018; Settaluri et al., 2012; He Zhang et al., 2019) that we call energy harvesting techniques in this review. Operation mechanisms, representative device embodiments and implementations, that expand the use case over conventional tethered or battery-powered systems, are summarized in Figure 2 and Figure 3. In the following section, we will provide an overview of the notable progress of WPT methods and explore considerations when choosing a power supply strategy and highlight examples of their implementations.

**2.1.1 Power casting techniques**—Utilization of RF energy casting by an external source specifically designed to power wireless battery-free sensors in the nonradiative near-field regime (between 0 and  $\lambda$  from the transmitter) has demonstrated power transfer for stable operation over distances of up to 60 cm (Yu et al., 2019). Typically, frequencies in the range of 0.1 – 200 MHz (Barman et al., 2015; Ramrakhyani et al., 2011; Stoecklin et al., 2016) are utilized because of low tissue absorption ( $< 20$  mW/kg) (Elder and Cahill, 1984; Gutruf and Rogers, 2018). Figure 2A (upper schematic) illustrates the operational principle of near-field magnetic resonant coupling (MRC) that relies on the impedance matched and tuned primary and secondary antennas with and without passive resonating elements that can be used to increase operating distance and harvesting efficiency (Imura and Hori, 2017). Here, the secondary coil antenna captures the magnetic field induced by the primary coil antenna that generates alternating current (AC) which is subsequently rectified to direct current (DC) and voltage regulated to drive the electronic circuits and sensing components

(Barman et al., 2015; Hui et al., 2013). A power level of up to 500 mW can be obtained with MRC (Yu et al., 2019). This power transfer scheme is compatible with established radio-frequency identification (RFID) or near-field communication (NFC) (13.56 MHz) technologies that allows for simultaneous wireless communication through load modulation techniques (Lazaro et al., 2018), which enables sensor systems with small form factor and multimodal sensing capabilities (Chung et al., 2019; Han et al., 2018). The non-radiative nature of MRC confines its use to a distance less than the diameter of the transmitting coil antenna (Barman et al., 2015), limiting the utility of this powering scheme in applications such as body-wide sensor networks where sensor nodes are located throughout the body with distances up to a meter and various relative orientations (Cao et al., 2009). Recently, wearable near-field enabled clothing has been demonstrated by embroidering conductive thread on conventional textiles (Jiang et al., 2020; Lin et al., 2020) to form connected planar inductor patterns that function as relays between physically separated locations and enable wireless powering and data connectivity well-beyond the range of normal NFC (Figure 1A, lower schematic) (Lin et al., 2020), thereby highlighting a potential pathway to extend current limitations in power transfer for this technology.

In the context of implantable sensors, MRC is particular advantageous because of the relatively low specific absorption rate by tissues (Cecil et al., 2010; Elder and Cahill, 1984; Gutruf and Rogers, 2018) and high robustness against changes in dielectric environment resulting in stable device operation across various complex arenas such as those containing aquatic environments (Burton et al., 2020). In addition, MRC allows for a high level of design flexibility of the geometry of the receiving coil antenna, therefore the device layout can be adapted for complex anatomical structures (Samineni et al., 2017). In recent years, numerous wireless, battery-free implantable sensors have been demonstrated using MRC, that can operate in freely moving subjects in established test arenas for neuroscience discovery without addition of any externalized hardware to the subject. (Burton et al., 2020; Kang et al., 2016; Mickle et al., 2019; Hao Zhang et al., 2019) Figure 2B depicts a representative example where a subdermally implantable photometric device monitors the  $\text{Ca}^{2+}$  dynamics with cell specificity in the brains of freely-behaving mice (Burton et al., 2020).

The operation mechanism of far field RF radiation power casting is shown in Figure 2C (upper schematic), where radiative electromagnetic (EM) energy is transmitted into the surrounding space and reaches distances in the far field region ( $\gg 2\lambda$ , where  $\lambda$  is 0.1 – 1m) (X. Huang et al., 2016; Merli et al., 2011), leading to an operational range (0.1 – 3 m) large enough to cover body area networks (Cao et al., 2009). However, the high frequency (up to 2.5 GHz (X. Tian et al., 2019)) RF energy used here shows relatively high tissue absorption (SAR  $\sim$  0.1 - 6.15 W/kg) (Ho et al., 2015; X. Huang et al., 2016; Montgomery et al., 2015; Poon et al., 2010) resulting in heating effects and safety concerns, limiting their utility in implantable sensing devices. In addition, due to the directionality of EM wave propagation evoked by anisotropy of antennas, the power transfer efficiency strongly depends on spatial alignment of both the transmitting and receiving antennas (X. Huang et al., 2016; Park et al., 2015) and is prone to interference by surrounding dielectric materials with high electric susceptibility or conductive materials (Dobkin, 2012). As a result, hot spots and dead zones of EM energy density may appear, leading to concentrated tissue absorption or insufficient

power transfer, respectively. A recent report of metamaterial textiles provides a viable solution to these transmission challenges where clothing is structured by patterns of conductive textiles that support surface-plasmon-like mode and confines the RF waves propagation close to the body surface (Figure 2C, lower schematic), yielding wearable multi-nodal sensor network with high energy efficiency wireless communication (Figure 2D, lower image) (X. Tian et al., 2019). Photovoltaic (PV) effect can be harnessed to convert light in the near infrared (NIR, e.g. 780 - 850 nm (Lu et al., 2018b; Moon et al., 2017)) and visible (~ 400 – 750 nm (Obaid and Lu, 2019)) regions into electrical power for wireless sensors, as depicted schematically in Figure 2E (upper schematic) (Jinno et al., 2017; S. Park et al., 2018). Energy can be either harvested from environmental light (S. Park et al., 2018) (e.g. sunlight, for wearable applications) or, more commonly, cast by dedicated light sources (J. Kim et al., 2020; S. Lee et al., 2018; Lim et al., 2020) (e.g. LED or laser, for implantable applications). Inorganic PV cells based on Si or III-V semiconductors have the advantages of good stability, mature technologies, as well as compatibility with standard microfabrication processes (Chen et al., 2018; Kim et al., 2012, 2010), the latter enabling ultraminiaturized devices that incorporate application specific integrated circuits (ASICs) for high-performance, low-power-consuming, on-board data processing, as well as monolithic integration of optical communication modules (Figure 2E, lower diagram) (S. Lee et al., 2018). The implementation of PV devices for deep-tissue implants is limited due to the absorption and scattering of light by biological tissues (Bevilacqua et al., 1999; Yaroslavsky et al., 2002). For example, with the incident light energy kept below the threshold of tissue damage (250 – 300 mW/mm<sup>2</sup> for 20 minutes of continuous exposure, corresponding to a heating of 5 °C in the illuminated brain tissue (Podgorski and Ranganathan, 2016)), the operation depth is estimated to be less than ~ 3 mm even for ultra-low power ASIC microscale neural recorder that consumes only ~ 1 μW (S. Lee et al., 2018). Intrinsically flexible materials such as organic PV are suitable for wearable applications that undergo substantial mechanical manipulation and strain (Jinno et al., 2017). In a recent study, ultra-flexible organic PV cells were used to drive organic electrochemical transistors (OECT) attached on the finger or the surface of heart to record cardiac signals, highlighting the potential for self-powered wearable and implantable sensors (Figure 2F) (S. Park et al., 2018).

Another viable technology for WPT, although limited to implantable sensors, is ultrasonic (US) power casting (Figure 2G, upper schematic) (Basaeri et al., 2016) where an externalized ultrasonic transducer is placed in direct contact with the skin to generate US waves (wavelength ~ 0.1 – 1.5 mm (Nelson et al., 2009)) that propagate through tissues. Traditionally, a piezoelectric crystal is used to convert the mechanical vibrations into electrical energy to power the implant (Rosa and Yang, 2016; Seo et al., 2016). An alternative approach based on triboelectric effect has recently been proposed utilizing the US waves to induce micrometer-scale displacement of a polymer thin membrane to generate electrical energy through contact electrification (Figure 2G, lower half) (Hinchet et al., 2019). This technology is however only suitable for driving implants that consume < 100 μW due to its low efficiency (optimal efficiency ~ 0.03% at a distance of 5 mm) (Hinchet et al., 2019). US has the ability to penetrate deeper (> 10 cm (Kim et al., 2015)) into tissue compared to MRC, unless impeded by tissues with high absorption coefficient such as bone

(Izadifar et al., 2017). Figure 2H presents an example of such a ultrasound-powered mm-scale sensing device that records electrophysiological signals such as electromyogram (EMG) and electroneurogram (ENG) in anesthetized rats (Seo et al., 2016).

However, a requirement of this technology is the need for direct skin contact for the power casting device with impedance matching agents. This limits its applicability in freely behaving subjects or wearable devices as motion may induce impedance changes at the skin interface. Other challenges of using US transduction to drive wireless sensors include sensitivity to misalignment (Denisov and Yeatman, 2010) as well as potential cavitation effects (Nelson et al., 2009).

**2.1.1 Energy harvesting techniques**—In recent years, biological energy sources have attracted increasing attention as means to realize self-powered sensing systems (Huang et al., 2019; J. Wang et al., 2019). A potentially suitable power source for wearable and implantable sensing application are biofuel cells (BFC) that convert the chemical energy stored in biofluids such as sweat (Gao et al., 2016) and saliva (Mink et al., 2014) (for wearable devices), blood (Chen et al., 2019) and gastric fluid (Nadeau et al., 2017) (for implantable or ingestible devices) to power by oxidization of substances such as glucose or lactate, producing power typically ranging from 0.2 to 100  $\mu\text{W}/\text{cm}^2$  (Gonzalez-Solino and Lorenzo, 2018; Yu et al., 2020). Other technologies include piezo-/tribo-electric devices that generate a peak power of less than 1 mW from skeletal motion (Hwang et al., 2015) and a few tens of  $\mu\text{W}$  from visceral peristalsis (Dagdeviren et al., 2014; Yao et al., 2018) with an average power factor of  $> 10$  lower than peak power (Song et al., 2020), which is currently insufficient to support continuous system-level functions of fully integrated sensing devices. Temperature difference between the human body and the environment can be utilized to generate electric power via thermoelectric conversion. Recent advances in scalable fabrication and soft mechanics design have enabled compliant thermoelectric generators with form factors tailored for wearable applications (Nan et al., 2018; Wen et al., 2020). Current embodiments feature a modest power density (Nan et al., 2018; Settaluri et al., 2012),  $< 30 \mu\text{W}/\text{cm}^2$ , with typical skin-environment thermal gradient ( $\sim 10 \text{ K}$ ), which, at sufficient sizes and good thermal coupling to the skin, can power devices with low energy requirements (Leonov et al., 2008).

Most recently, innovations in material engineering and device design have resulted in encouraging progress in perspiration-enabled electrochemical biofuel cells (BFCs) (Bandodkar et al., 2020; Talkhooncheh et al., 2020; Yu et al., 2020) for wearable sensing devices. Figure 3A illustrates the layered makeup of a flexible and self-contained electronic skin powered by nanoengineered BFCs that yield power density of  $\sim 3.5 \text{ mW}/\text{cm}^2$ , sufficient for driving a monolithically integrated system that contains multiplexed metabolic sensors, signal conditioning components, and a Bluetooth system-on-chip (BLE SoC) module (Figure 3B) (Yu et al., 2020). An alternative strategy to exploit perspiration for electrical power generation is displayed in Figure 3C where a thin-film Mg-Ag/AgCl primary battery is activated once the cellulose membrane separator absorbs sufficient sweat and creates electrolytic conditions to close the circuit (Bandodkar et al., 2020), yielding a single-use sweat activated cell (SAC) with a power density of  $\sim 1.5 \text{ mW}/\text{cm}^2$  and stable operation for  $\sim$



5 hours when driving a flexible wireless heart-rate sensor (Figure 3D). (Amar et al., 2015; Zebda et al., 2018)

In summary, power casting schemes such as MRC (Burton et al., 2020; Y. Zhang et al., 2019) and RF transmission (Sample et al., 2008; X. Tian et al., 2019) are advantageous for supporting system-level functionalities for wireless and battery-free sensing technologies due to their technological maturity, high and continuous power availability (Amar et al., 2015; Huang et al., 2019). Biological power sources that harvest mechanical, thermal and biochemical sources in general suffer from inconsistent nature of energy delivery that hinder integration of continuously operating digital systems (Li et al., 2020; Zebda et al., 2018). Encouraging developments in this field are biofuel-based systems that are powered by sweat that can sustain multimodal devices with digital communication with prevalent protocols (Bandodkar et al., 2020; Yu et al., 2020).

## 2.2 Wireless communication schemes

An integral component of wireless, battery-free sensors is the wireless communication that provides pathways for transmitting sensor signals and/or control commands. Wireless communication technologies that have been used for wearable and implantable sensing devices include simplex communication such as optical modulation (Burton et al., 2020; S. Lee et al., 2018; Zhang et al., 2019), ultrasonic (Seo et al., 2016) or RF backscatter (Vasisht et al., 2018), and passive resonance shifting (Boutry et al., 2019), as well as duplex communication such as near-field communication (NFC) (Bandodkar et al., 2019b; Chung et al., 2019; Krishnan et al., 2018; Yu et al., 2019; Zulqarnain et al., 2020) and Bluetooth Low Energy (BLE) (Mickle et al., 2019; Yu et al., 2020). Factors that determine the choice of communication methods include power budget, data rate, operation distance, hardware system complexity and form factor, as well as technological maturity. For example, infrared (IR) modulation can be used for data uplink of miniaturized subdermal sensors due to its small footprint ( $\sim 0.5 \text{ mm}^2$ ) and well-established protocols (Burton et al., 2020; Zhang et al., 2019). RF backscatter is the preferred choice for body networks of passive sensors due to its extremely low power consumption and relatively long operation distance (in the range of meters) (Jameel et al., 2019) however is not easily translated due to the lack of widely-accessible hardware. BLE features duplex communication with high data rate (up to 200 kbps) and established infrastructures (Tosi et al., 2017), thus is often used where high-speed data communication (uplink) and control command transfer (downlink) are required (Mickle et al., 2019), nonetheless the relatively high power consumption ( $> 5 \text{ mW}$ ) (Tosi et al., 2017) limits the choice of power sources. Detailed discussion of the wireless communication technologies commonly used for wearable and implantable devices is extensively covered by review articles focusing on the topic (Cao et al., 2009; Liang and Yuan, 2016; Zatout, 2012).

## 2.3 Sensing Modalities

Wireless, battery-free systems leverage sensing modalities which utilize favorable mechanical properties and resulting intimate integration with sensing targets that result in high fidelity data streams outperforming their tethered counterparts. Unlocking this fundamental advantage requires system engineering with limited power and footprint in mind, restricting the choice of sensing modalities based on operation location and

application scenario. Given this dependency, it is most appropriate to review sensing modalities in conjunction with their respective target organ system and use case, outlined in section 3.

## 2.4 System architectures for wireless and battery-free sensors

In recent years, battery-free sensing systems have emerged as wearable or implantable tools to measure a wide range of biophysical, biochemical and physiological signals. We provide a comprehensive survey (Supplementary Information, Table S1) of the current research landscape which counts 49 papers of wireless, battery-free sensors and sensor systems. The dataset is compiled of work spanning the years of 2008 to 2021 and is comprised of sensors that provide digital data streams. Not included in this survey are passive sensors that rely on LC circuits (Niu et al., 2019), which are much simpler constructs that are very useful sensors for short time periods and simple applications, though have limited utility in chronic sensing applications. Figure 4 displays a visual compilation of the reported system architectures as a 3D scatter plot covering power source, communication method and sensing modality. Larger data points imply higher prevalence of corresponding system architectures and color indicates wearable or implantable system form factor.

The visualization reveals that near field powering as well as near field-based communication methods are the primary choice to enable single and multi-modal sensors. This is evident by statistical analysis which reveals that 70% of wearable sensors and 73% of implantable sensors utilize MRC. Data communication methods show a similar trend for wearable sensors of which 67% use NFC communication and 21% use backscatter. The exception, however, are implantable sensors which do not have a dominant communication technology of choice, here backscatter (18%) and NFC (15%) are the most popular, however a larger variety of communication methods is prevalent.

The popularity of near field power transfer and communication follows from a high compatibility with on-body applications (discussed in section 2.1) and also the availability of commercially available fully-integrated ICs that combine energy harvesting, communication and in some cases computation (Lazaro et al., 2018) in a compact package that can be seamlessly combined with existing sensing modalities (Bandodkar et al., 2019b). The miniaturized form factor also enables systems that feature high mechanical compliance, which is beneficial for sensing performance (Chung et al., 2019; Heo et al., 2018; Jeong et al., 2017; Jia et al., 2019). MRC is also often coupled with BT when higher data rates and longer communication distance are required (Mickle et al., 2019). The exception is implantable devices, where no dominant architecture has emerged. This is largely due to challenging electromagnetic conditions where communication methods suffer from attenuation in the surrounding tissues (Elder and Cahill, 1984).

## 3. Embodiments

Wireless, battery-free sensor systems require the combination of efficient energy harvesting and reliable data communication schemes that are tailored specifically towards the application to achieve best system performance. Often optimized solutions are application driven and engineered towards the sensing application and unique challenges arise from the



locations of the sensing target and the broader application scenario. To discuss system architectures, sensor performance and unique advantages derived from wireless, battery-free operation, this section is organized by target organ.

### 3.1 Central and peripheral nervous system

Interfaces with the central and peripheral nervous system become increasingly important tools to treat and diagnose neurodegenerative diseases (Cagnan et al., 2019), control prosthetics (Krasoulis et al., 2017), supplement rehabilitation (Osuagwu et al., 2016) and provide tools for the neuroscience community to decipher the working principle of the brain (Seymour et al., 2017). These sensing and stimulation techniques, broadly defined as neuromodulation, currently use tethered and head mounted devices that are prone to infection (Biran et al., 2007), limit subject mobility (Armstrong et al., 2013), and restrict investigations to single subject study and 2D environments (Bin et al., 2017). Battery-powered systems suffer from limited operation times, bulky form factors, and weight that impacts subject mobility (Harrison et al., 2011). For exploratory research both tethered and battery-operated devices may impact animal behaviors and require operator interactions that impose experimental biases (Lu et al., 2018a). Wireless, battery-free operation of these neuromodulation systems allow for small, lightweight devices that intimately interface with the central and peripheral nervous system to enable high-fidelity recording in experimental paradigms that extend to 3D ethologically relevant environments, multisubject investigations, and flying subjects (Burton et al., 2020; Chestek et al., 2009; Harrison et al., 2011, 2009; Shon et al., 2017; Thomas et al., 2012). These demonstrations expand the toolset for exploratory neuroscience and enable capabilities that match or outperform their tethered or battery-powered counterparts without effecting subject behaviors.

**3.1.1 Cell specific neuronal activity sensing**—Recording activity of specific neuronal populations is an important tool to decipher the central and peripheral nervous system (Cui et al., 2013; Falkner et al., 2016; Gunaydin et al., 2014). This is commonly accomplished through direct electrical readout of cell activity in the electrode vicinity, which typically requires high channel count arrays to capture activity of neuronal ensembles to gain mechanistic insight (Legatt et al., 1980). To capture cell type specific activity, photometric approaches can use viral vectors to deliver genetically encoded calcium indicators (GECIs) to select neuronal populations to observe  $\text{Ca}^{2+}$  dynamics, a proxy for recording neuronal activity (Zhao et al., 2011). Common photometric approaches require tethers (Armstrong et al., 2013; Murayama et al., 2007) or battery-powered devices (Khizarak et al., 2018; Kim et al., 2013; Lu et al., 2018a) that have a large impact on subject behavior and mobility while limiting experimental paradigms (Dombeck et al., 2010; Lu et al., 2018a; Miyamoto and Murayama, 2016). Wireless battery-free sensor systems offer a unique opportunity to expand current sensing capabilities by shrinking system size to enable subdermal implantation. This has been demonstrated in recent work on wireless photometers as shown in Figure 5A (Burton et al., 2020). The device utilizes MRC power transfer methods (13.56 MHz, discussed in section 2.1) in a thin (1.2 mm), highly miniaturized (10.5 × 7 mm), and light-weight (45mg) device capable of harvesting >17 mW in a 25.5 cm × 25.5 cm cage, allowing for stable operation with a peak power consumption 10.37 mW (Burton et al., 2020). This low power consumption for optoelectronic sensing schemes is attributed to

advanced digital power management of the analog to digital converters (ADC), comparators, and timers to minimize power consumption temporarily to 119  $\mu$ W, yielding lower average power needs (Burton et al., 2020; Lu et al., 2018a). The injectable photometric sensor probes are comprised of a blue (468 nm) micro-scale inorganic light emitting diode ( $\mu$ -LED) and a micro-scale inorganic photodetector ( $\mu$ -IPD) laminated with a narrow-band optical filter to reject blue light and selectively pass fluorescence signal from the Ca<sup>2+</sup> (523 nm), as shown in Figure 5A. A micro-controller ( $\mu$ C) enables precise timing of GECI excitation and digitally samples the photodetector to record fluorescence. IR data uplink is utilized to send sensor results to an external receiver as shown in Figure 5B. Low power data communication ( $\sim$ 3 mW) is realized through IR communication (discussed in section 2.2) (Burton et al., 2020; Tsimbalo et al., 2015). In this application IR communication was chosen because of low component count and minimal footprint on the device, that enables a form factor for subdermal implantation. This photometric device can record the fluorescence of 12.5  $\mu$ M Oregon Green 488 BAPTA-2, serving as a benchtop analog dye of GECIs, with the ability to detect calcium concentrations between 0.0625 and 32  $\mu$ M (Figure 5C), covering the physiological ranges of intracellular calcium in mammalian neurons during rest and activation (Burton et al., 2020; Grienberger and Konnerth, 2012) and outperforms recently reported battery-powered devices with similar sensor architectures (Lu et al., 2018a). The device represents a significant advance over current photometric systems because of its fully implantable form factor that expands recording capabilities to multiple subjects in three dimensional experimental paradigms and underwater experiments, such as the Morris water maze, which is difficult or impossible to realize with current tethered and battery-powered systems (Burton et al., 2020). The nonmagnetic component choice further enables compatibility with noninvasive imaging modalities. The advantage gained by wireless, battery-free architecture also extends to future devices. Because of the use of scalable fabrication and off the shelf electronic components, function can be readily adapted to new fluorescent indicators sensitive to voltage, proteins, metal ions, and pH (Adam et al., 2019; T.-W. Chen et al., 2013; Greenwald et al., 2018; Martynov et al., 2018). Implementation of multimodality sensing systems is also possible, combining stimulation with sensing modalities to expand neuromodulation capabilities to create the next generation of exploratory tools to decipher the central and peripheral nervous systems.

**3.1.2 Multimodal electrophysiological recording**—Capturing electrical activity of neuronal populations is important for species where genetic modification is not available. Creating technology to expand animal model diversity is especially important to draw universal mechanistic and circuit level insight on the function of the nervous system (White, 2016). An example of this technology is recent work involving insects to capture spinal and motor neural activation to gain insight into communication pathways that control specific muscle groups, for example, experiments that track small subjects while monitoring prey drive or escape behaviors (Fotowat et al., 2011; Harrison et al., 2011; Olberg et al., 2000). Current methods of analyzing neural and muscular activity in small insects are heavy and too bulky to record effectively in freely flying insects (Harrison et al., 2011). Wireless and battery-free device architectures can significantly advance current capabilities. For application in insects, a high degree of miniaturization is required, which can be accomplished with the use of ASICs that combine both energy harvesting, communication,

signal amplification, digitalization and processing to yield a very compact device form factor (6.8 mm × 4.6 mm) and low mass (38 mg), as shown in Figure 5D, compared to that of battery-powered versions of similar systems (13.0 mm × 9.5 mm, 790 mg) (Harrison et al., 2011; Thomas et al., 2012). Two light-weight gold wires (50 μm) form a dipole antenna that extends down the length of the dragonfly and provides up to 6 mW from far-field wireless power transfer (915 Mhz) from a central power casting system inside a flight arena for insects (discussed in section 2.1). The device consumes 1.23 mW of power, allowing for continuous operation up to ~1.91 m (Thomas et al., 2012). In this application far field energy harvesting is an advantageous technological choice because subjects are small and therefore do not have significant impact on electromagnetic environment and tissue absorption is less significant, resulting in long operational range capabilities. This system is capable of recording 10 extracellular neural and 4 EMG channels using hook shaped wires to establish an electrical interface with the spinal cord or muscle. Data is transmitted at 5 Mbps using back scatter communication (discussed in section 2.2) with energy consumption of 4 picojoules per bit (Liu et al., 2019), resulting in suitable performance to cover the bandwidth requirements that are imposed by 14 channel recordings with sufficient sampling rate to capture neural activity spikes. Figure 5 E shows a microscopic image of the ASIC die (2.36mm × 1.88 mm, 250 μm thick) that includes the functionality described above. Figure 5F shows device performance over multiple channels of the device. The system is capable of recording at 11-bit resolution with a sampling rate of 250 Hz–10 kHz for spinal recording and 5 Hz–700 Hz for EMG recording, sufficient for comprehensive recordings of the central and peripheral nervous systems of insects. The demonstration of such a device highlights the benefits of system integration in an ASIC that contributes to the miniaturization and reduction in power consumption via the elimination of peripherals that are required for broadly applicable and programmable IC's. The device also demonstrates that sensing capabilities can be expanded towards new species, increasing the animal model pool to insects. However, it should be noted that this is a highly optimized sensing solution that requires the subject to be very small in size and addition of sensing modalities will require a redesign of the ASIC, which is typically lengthy and costly.

**3.1.3 High density 100 channel electrophysiological recording**—High density neural recordings are important tools for deciphering the working principle of the brain and offer an avenue towards tailored therapeutics, such as seizure detection, and have been an active area of research for the last decade (Miccoli et al., 2019; Obien et al., 2015; Viventi et al., 2011). This form of neural interface is also translatable to human applications and devices of this type are actively translated towards diagnostic, therapeutic and brain machine interface applications. A popular sensing format of this device class are microelectrode array (MEA) that allow for high density recordings and enable investigation into neurological diseases, brain injuries, and effects of pharmaceuticals through precise spatial mapping of action potential propagation over time (Cheng et al., 2019; Ferrea et al., 2012; Ghane-Motlagh and Sawan, 2013). A typical bottleneck for these devices is the high power consumption that is required due to the higher channel count, thus limiting current technologies to tethered connections or large battery packs (Chestek et al., 2009) that often require bulky connectors and ports (Suner et al., 2005) to supply power to the device and allow transmission of high-fidelity recorded signals. Both of these approaches are acceptable

for exploratory neuroscience with large animal models that are under constant supervision and care, however, are not a form factor that is likely to be adopted for the operation in patients with active lifestyles. Wireless, battery-free sensing approaches offer a path towards fully implanted systems via integration of both energy harvesting components, communication and low power analog frontend for MEA neural interfaces as shown in the bottom right of Figure 5G. Recently, devices that enable direct neural recording capability of up to 100 channels in an implantable wireless form factor (8 mm × 7.6 mm) (Cheng et al., 2012; Harrison et al., 2009, 2007; Sharma et al., 2011; Thurgood et al., 2009; Watkins et al., 2006) as shown in the center of Figure 5G, allow for chronic recording of neural signals with short distance telemetry. Integration of both energy harvesting and communication yields miniaturized form factors. Wireless power transfer using near field MRC (discussed in section 2.1) with a frequency of 2.64 MHz, reducing tissue absorption (Ziaie et al., 1997) and delivering up to 30 mW of power at distances of up to 2 cm from the primary antenna (Cheng et al., 2012; Harrison et al., 2008, 2007).

The 100 channel MEA is micro-machined silicon and features platinum electrodes, projecting 1.5 mm deep with an 80 µm electrode separation (Nordhausen et al., 1996) (in the inset of Figure 5G) and is used to penetrate the target area of the brain. The recorded signals are wirelessly transmitted using backscatter communication (discussed in section 2.2) at 433 Mhz with a data rate of 330 kb/s (Chestek et al., 2009) and a separate antenna dedicated to this frequency, see functional diagram Figure 5H. The higher frequency is utilized to support the high data rate requirement. Additionally, these devices can be programmed to select which channels are digitized and turn off select amplifiers that are not providing useful neural signals, thus lowering overall power consumption. These devices are capable of receiving commands to set voltage threshold for spike detection of local field potentials using comparators, reducing overall communication bandwidth and power consumption to transmit neurological signal wirelessly (Cheng et al., 2012; Harrison et al., 2008, 2007). The sensor can record neural potentials with 100 channels to measure local field potentials and detect activity spikes with potentials of 50-500 µV and has a discrete spike detection mode where only spike amplitude and time of the event are transmitted to realize low power operation (Cheng et al., 2012; Harrison et al., 2008, 2007). In-vivo experiment shows validation of device operation with 30 superimposed signals from the auditory cortex of a cat as shown in Figure 5I. Demonstration of such high channel count operation with wireless, battery-free device architectures highlight that systems operating with full subdermal implantation are possible in the near future for large animal models and humans, greatly expanding the potential of neural interfaces towards the realization of digital medicine and electroceutical intervention for chronic and neurodegenerative disease (Vesuna et al., 2020). Recent interest of commercial companies such as Neuralink, Amuza and Intan Technologies highlights the potential of this technological approach and forecasts impact on diagnostics, therapeutics and potentially performance enhancing applications (Grand et al., 2013; Musk, 2019; Petkos et al., 2019).

### 3.2 Cardiovascular system

Understanding and treating cardiovascular diseases often requires high-fidelity and chronic data acquisition for accurate diagnosis to delineate subtle changes in physiology that

indicate onset or current status of disease (Hillebrand et al., 2013; Muller et al., 1989; Wilmot et al., 2012). Current practices in cardiac monitoring and diagnostics either require tethered connections in clinical settings or large wearable devices that are not suitable for long-term recordings (Hong et al., 2019; Walsh 3rd et al., 2014). Recent works in battery-free, wireless cardiac sensing devices have moved towards eliminating the need for tethered connections and battery-powered supplies. This provides solutions to currently cumbersome systems that yield improvements of signal fidelity (Alberto et al., 2020; Besnoff et al., 2013; Chung et al., 2019; Kim et al., 2017; Kim et al., 2016; H. Zhang et al., 2019) while broadening the scope of diagnostic and monitoring capabilities to detect chronic changes in physiology (Ray et al., 2019). In this section, we review sensing modalities used in cardiovascular applications, namely optical and electrical schemes, to measure oxygen saturation, biopotentials, and flow dynamics. We also explore both wearable and implantable systems implementing these functionalities and discuss how these devices advance the state of cardiac sensing capabilities.

**3.2.1 Optical**—Optical sensing approaches are useful tools in cardiovascular medicine and utilized in many applications such as photoplethysmography (PPG) (Allen, 2007) and pulse oximeters (Tremper, 1989), which use a narrowband light sources and photodetectors to probe target tissue with light and extract heart rate and blood oxygenation information via absorption variation induced by the oxygenation state of hemoglobin (Jubran, 2015, 1999; Liu et al., 2016). Conventional methods of pulse oximetry are unsuitable for long-term recording due to susceptibility to motion artifacts associated with increased mass of power supplies and electronics (DeMeulenaere, 2007; Sinex, 1999; Yan and Zhang, 2008). Changes of relative orientation of the light source and detector induced by the weight of the sensor system assembly and underlying vasculature causes net changes in signal, interrupting continuous acquisition (Barker, 2002; Hayes and Smith, 2001). Because of high power requirements (~10 mW) of optoelectronic components paired with a Nyquist frequency of 0.5 Hz with most systems operating closer to or above 5 Hz (Choi and Shin, 2017) (See SI Table 2), the lifetime of battery-powered devices is limited, and form factors are not sufficiently small for implantation or long-term, continuous use in wearable application scenarios. Wireless and battery-free devices have been demonstrated as viable solutions to these shortcomings.

An example of this device class is a highly miniaturized wearable pulse oximeter (Jeonghyun Kim et al., 2017) which utilizes MRC (discussed in section 2.1) and NFC (discussed in section 2.2) to provide indefinite and motion artifact-free blood oxygenation information. The device, shown in Figure 6A, uses a  $\mu\text{C}$  and a bare-die NFC IC to facilitate power management, device function, and data communication. NFC is chosen for this use case due to its technological maturity and availability in modern smartphones with sufficient power availability (up to 20 mW for devices of this size) (Lazaro et al., 2020).

A red and infrared LED are located 2 mm away from the photodetector in the same plane to achieve an optimized optical path through the tissue. The components are optically separated using a black, elastomeric encapsulation. This allows for a soft, intimate optical interface with the fingernail, epidermis and other body parts, a key aspect in increasing signal fidelity that is not possible with current battery-powered systems due to their inherent rigidity.

Onboard amplification and digitalization render a compact device with ultra-small footprint and flexible mechanics that enables the use on a variety of body locations, increasing utility in comparison to tethered and battery-powered solutions. The diverse functionality of the system is shown in Figure 6B, where the device can be attached and function with high-fidelity on topologically complex regions such as the fingernail or earlobe. Figure 6C shows the enhanced fidelity of data collection during motion when compared to commercially available devices. In this experiment, devices undergo induced motion as indicated with grey shading. The inertia of commercial device experiences large motion artifacts, rendering the data acquired during that time unusable. The wireless and battery-free system, due to its favorable mechanics and miniaturization, can collect high-fidelity signals without any effect from motion, enabling continuous data collection without signal loss. SpO<sub>2</sub> values collected from the wireless, battery-free system falls within a standard deviation of 1.5%, which is significantly improved compared to current state of the art systems that offer a 2-3% tolerance on SpO<sub>2</sub> estimations. All currently demonstrated battery-free devices for this application operate using MRC and NFC, because of power availability needed for operation of the optoelectronics, small footprint to provide favorable mechanical properties, and robust data communication pathway coupled with widely available network infrastructure such as smart phones (Opperman and Hancke, 2011; Sidén et al., 2011). Current technology is still limited in operation range due to power requirements of the system and the use of MRC. With the improvement of power transfer techniques and development of low power methodologies for pulse oximetry, the functional range can be increased.

In addition to wearable systems, wireless and battery-free oximetry devices have been demonstrated for the use in localized implantable oxygenation measurements for use in animal model research, which allows for investigation into a variety of medically relevant parameters such as neural activity (Zhang et al., 2019) and tumor microenvironments (Hopf and Rollins, 2007). Devices such as those shown in Figure 6D provide the capability to gain valuable insights in a freely moving *in vivo* and ethnologically relevant environments, which would otherwise require the subject to be under anesthesia or immobilized, prohibiting longitudinal mechanistic and diagnostic insight (Reichelt et al., 2008; Theodor et al., 2014). This device features a near-field coupling coil for MRC power transfer and IR communication, a system architecture used in photometric recordings described in section 2.1 and 2.2. The device is designed to measure localized oxygenation (Zhang et al., 2019a). This detection method is enabled by microfabrication of the sensing probes with inorganic microscale LEDs and photodetectors that use an outline of less than 300  $\mu\text{m}$ , enabling direct injection into the target organ for probing into the region of interest and minimizing tissue damage in comparison to full device implantation in the target region (sensor probe makeup shown in inset Figure 6D). Operation of the device is demonstrated in Figure 6E, where the oximetry probe has been placed into the tissue region proximal to the femoral artery of an anesthetized rat. The fidelity of measurement is detailed in Figure 6G. In this experiment, the local oxygen saturation near the femoral artery was measured while the subject was exposed to varying levels of oxygen. In this work the devices were also used in freely moving subjects to probe oxygenation levels in the rodent brain during exposure to hypoxic environments. The improved fidelity of wireless, battery-free systems allows for real-time data acquisition of local oxygenation plasticity of target organ, which is not possible with



conventional devices. These new class of implantable oximetry devices highlight the possibility to enable investigation into cardiac and local oxygen perfusion dynamics in freely moving subjects, expanding possible experimental paradigms. The approach also has potential to be used as a therapeutic device to monitor surgery recovery and personalize pharmacological therapies.

**3.2.1 Electrophysiological and Electromagnetic**—Electrical recording of cardiovascular biosignals can be acquired using electrophysiological sensing that records small voltage signals that arise from the depolarization of cardiomyocytes, a technique often used in noninvasive devices with more recent developments implementing electromagnetic sensing schemes that can record blood flow dynamics *in vivo* for advanced diagnostics (Liebl et al., 2019; Parthasarathy et al., 2016). These signals require high-fidelity recording systems and continuous monitoring to extract diagnostic information, particularly for diseases which may present sporadically such as intermittent arrhythmia. The most commonly used sensing system are electrocardiograms (ECGs) that extract heart rate and give insight into functional events, such as the QRS complex (Becker, 2006; Meek and Morris, 2002). In the case of noninvasive recording methods, impedance with the skin plays a critical role in extracting high-fidelity signals (Heikenfeld et al., 2018). Currently for most clinically relevant applications this is accomplished with hydrogel electrodes that offer low impedance (Shay et al., 2018) and reduce motion artifacts. This, however, results in a limited lifetime (McAdams, 2006; Searle and Kirkup, 2000) leading to implementation of bulky systems with interchangeable electrode schemes that are not suitable for continuous long-term recording, prohibiting their use for early onset detection of disease (Walsh 3rd et al., 2014). This issue is exacerbated in fragile patient populations such as neonates, as currently employed wet electrode systems utilize adhesives that result in skin injuries, leaving lifelong scars (Cartlidge et al., 1990; Lund, 2014). Wireless, battery-free sensing systems in combination with advanced electrode technology can overcome many of the challenges and have been widely investigated for use in electrophysiological monitoring (Besnoff et al., 2013; Chung et al., 2019; Jeong et al., 2019; Mandal et al., 2010; Zulqarnain et al., 2020). These devices feature miniaturized electronics with soft, conformal mechanics that enable the use of epidermal dry electrodes that offer low impedance to the skin without the use of adhesives (Chen et al., 2014; Chlaihawi et al., 2018; Li et al., 2018; L. Tian et al., 2019) enabling detection of discrete changes in cardiac potentials with operating conditions (200 Hz sampling and >15mW power consumption) on par with conventional wired methods (see SI Table 2). Figure 7A shows a demonstration of such a device that features a binodal dry electrode system, MRC and NFC communication (see section 2.1 and 2.2) with epidermal-like mechanics for the use in neonatal intensive care. MRC and NFC were selected to enable simultaneous power harvesting and data communication using a single antenna resulting in minimal peripheral component requirements that allow for soft mechanics required for high-fidelity operation. The operation scenario is defined, the NICU bed of the premature infant, which is a small operational space that can be equipped with a dedicated antenna system to power the device and receive data continuously without direct contact to the patient. To overcome typical data rate limitations of NFC, the device handles processing and analysis on the sensor side, reducing bandwidth requirements. Other similar wearable system have been developed that enable operation at longer distances of 1 m, through the use of far field

energy harvesting systems and Bluetooth communication protocols (Alberto et al., 2020; Besnoff et al., 2013). Figure 7B shows an infant patient with an attached ECG system to wirelessly record ECG signals. The system incorporates ultra-thin circuits that are structured with serpentine patterns to enable epidermal mechanics (Zhang et al., 2013). The contact relies solely on Van der Waals forces to minimize stresses at the epidermal interface and eliminate the need for adhesives. System mechanics and resulting sensing performance enable immediate and secondary benefits to health outcome such as increased child-parents bonding, which has been shown to be an important factor in neonatal development (Pineda et al., 2018). The use of nonmagnetic components allows for compatibility with common medical imaging techniques, such as MRI and X-ray, without significant image distortion, a favorable characteristic for long-term use in a hospital setting such as the NICU. Figure 7C shows heart rate data extracted from the device in comparison to the wired, gold standard data. The fidelity of this system matches the signal quality of the gold standard, with little variation in the QRS complex despite the use of a binodal system over conventional three electrode systems. Conceptually this class of device utilizes scalable monolithic fabrication, allowing for easy expansion of sensing modalities. The devices shown here are also capable of recording local skin temperature and photoplethysmography (Chung et al., 2019). The successful implementation of systems that leverage wireless, battery-free system architectures to enable epidermal mechanics to conform to the epidermis highlights an important avenue towards systems that record chronically and also impact sensing modalities that rely on acquisition of electronic signals from other organs such as muscles and related applications in electromyography (Liu et al., 2018) and more recently in electroencephalography (see section 3.1.3).

*In vivo* blood flow dynamics monitoring, is an important metric to assess cardiovascular health, however, sensing flow accurately is difficult because arterial specificity is needed, which cannot easily be achieved with noninvasive devices (Gradman, 2012; M. et al., 2018; Tarbell et al., 2014; Yoram and R., 2006). Diseases such as atherosclerosis (Texon et al., 1965), deep vein thrombosis (Fortuny et al., 2015), and aortic valve disease (Hope et al., 2011) are examples that feature disruptions in blood flow dynamics with serious impacts on health. Implementation of diagnostic and preventative chronic sensing solutions would dramatically increase patient outcomes. For example, patients with aortic valve disease have an increased risk of cardiovascular complications with higher rates of mortality and morbidity (Goland et al., 2007; Tjang et al., 2007) due to dysfunction of artificial heart valves and subsequent thrombosis or pannus formation (Ma et al., 2015). Early discovery of flow obstruction and mechanical failures associated with heart valves can prompt effective intervention, which is vital for improving outcomes for these patients (Abraham and Perl, 2017). Because patients undergo surgery as part of their treatment, there is an opportunity to implement sensing devices invasively without additional risk, wireless and battery-free devices are essential in this application scenario (Cong et al., 2009) because they do not require secondary surgery for replacement of batteries that can pose additional health risks to the patient (Jones et al., 2001). An example of such a device is an implant to monitor blood flow *in vivo* is shown in Figure 7D (Vennemann et al., 2020). The device is capable of detecting variation of flow rate through the ascending aorta. The device operates using both MRC and NFC as a means of power harvesting and data transfer. As with many implantable

systems discussed in section 2.1 and 2.2, MRC is used in this case due to its ability to propagate deeper into the body, while providing enough power to sustain digital electronic device operation and NFC is used as communication method because of minimal data rate requirements and small footprint required for implementation. An overview of device function is demonstrated in Figure 7E. This system exploits Faraday's law and provides a constant magnetic field using passive magnets to produce a lateral magnetic field cross sectional to the artery. Electrodes embedded on the arterial walls detect the induced voltage by the flow of conductive liquid (blood), which is proportional to the fluid velocity. Results of this *in vitro* study are displayed in Figure 7F. Sensing fidelity enables the visualization of peak systolic flow and flow when the valve is closed. Implemented *in vivo*, this system can give insight into cardiac cycle variability and subtle, transient changes of flow, which can indicate the onset of heart valve failure. Recent advances in implantable cardiovascular devices benefit substantially from wireless power transfer and communication capabilities and enable sensing systems that collect information for peripheral blood flow (Yeshwant and Ghaffari, 2019) and changes in blood pressure (DeHennis and Wise, 2006; Murphy et al., 2013; Park et al., 2016) expanding current exploratory research tools and diagnostic capabilities substantially. Rapid development of these sensors suggests development of body networked systems in the near future that utilize wearable and implantable devices to provide a holistic insight into cardiac health. Challenges to enable these architectures are communication protocols with very little signal delay to resolve cardiac dynamics.

### 3.3 Endocrine and Metabolic System

A more recent application of wireless and battery-free sensor platforms has been their use in electrochemical investigation, specifically analysis of biomarkers of the endocrine and metabolic system in sweat and interstitial fluid (Bandodkar et al., 2019c; Bandodkar and Wang, 2014; Kassal et al., 2018; Scholten and Meng, 2018; Zhao et al., 2019). Monitoring of these biochemical markers involved in metabolic diseases has vast relevance for many patient populations suffering from illnesses such as hypokalemia (Kardalas et al., 2018) and diabetes (Giesbertz and Daniel, 2016; Vashist, 2012). Gold standard methods of detection mostly rely on separated biomarker collection from the subject and subsequent, temporally shifted analysis in laboratory grade equipment, which has significant drawbacks due to sample degradation and significant limitations in sampling rate (Harker et al., 2006; LeGrys et al., 2007). A recent development for monitoring of diabetes, a pancreatic disease where the body fails to produce the amount of insulin to regulate sugar levels in the blood (Nathan et al, 1993), is the deployment of continuous glucose monitoring systems (GCMs) which represents an area of development with advances in device technology that enable patients with diabetes to monitor insulin levels continuously and ensure proper interventions (Rodbard, 2016). This is achieved via a insertion of a probe into the interstitial area of the body to continuously monitor glucose levels, and in some cases pump insulin in a closed-loop system (Bruen et al., 2017; Penforinis et al., 2011). Devices feature a bulky system that is clipped on a belt and features invasive methods of data collection that are unfavorable for many patients as they are generally painful and time consuming (Villena Gonzales et al., 2019). These devices represent the current state of the art in biosensing for endocrine and metabolic sensors. Progress in this area can affect the quality of life for a large patient population. For example, an estimated 415 million people living with diabetes worldwide

(Chatterjee et al., 2017). Investigation into sweat-based extraction of biomarkers as the means for noninvasive monitoring of markers such as glucose, potassium and chloride (Baker and Wolfe, 2020; Heikenfeld, 2016; Heikenfeld et al., 2018; Moyer et al., 2012) is therefore a very active research area.

**3.3.1 Wearable Endocrine and Metabolic Sensors**—Wireless, battery-free sensing approaches offer opportunities to enable the realization of devices with conformal epidermal mechanics and minimally invasive implants that require little to no patient interaction with the ability to monitor multiple metabolites continuously to overcome current technological challenges. An example of such a device is presented in Figure 8A. This platform is comprised of two components, namely a one-time use microfluidic chip for on skin sweat collection, known as epifluidics (Choi et al., 2018; Koh et al., 2016), and biochemical analysis electronics for interfacing with passive sensors embedded in the epifluidic platform. The system relies on MRC and NFC (discussed in section 2.1 and 2.3) for this device architecture due to compatibility with smartphone systems, allowing for simultaneous power transfer, data communication, and in this case automated image collection to read out colorimetric sensing elements present in the epifluidic channels. The sensor architecture in this device is, unlike the highly integrated systems discussed in the previous sections, intentionally modular to facilitate reusability of the wireless, battery-free electronics and the one-time use epifluidics sensor that is worn on the skin to capture sweat. Figure 8B shows the system in use on the skin and highlights the diverse sensing modalities that make use of colorimetric analysis that require photographic imaging of the device to determine changes color and shading to extract values for pH and chloride monitoring, as well as automated calculations of sweat rate and sweat volume. The epifluidic system also includes biofuel-based sensors are able to detect sweat-based metabolites such lactate and glucose (Choi et al., 2018; Reeder et al., 2019). Figure 8C highlights data collected using the wearable device and is compared to the standard method of lactate detection, nuclear magnetic resonance spectroscopy (NMR) (Harker et al., 2006). In this example, the biofuel cell system continuously measures the change in lactate production in the sweat over time. This continuous collection enables insight into discrete changes in concentration over time which stands in stark contrast to the NMR analysis that only provides temporally averaged values with possible degradation of the sample between capture and analysis. Devices such as the epidermal device featured in Figure 8A–C represent a rapidly growing research area that harnesses sweat to analyze biomarkers for continuous sensing of multiple biomarkers including glucose (Bandodkar et al., 2019b; Hourlier-Fargette et al., 2020; G. Xu et al., 2019a), lactate (Bandodkar et al., 2019b; Hourlier-Fargette et al., 2020), chloride (Bandodkar et al., 2020, 2019b), sweat pH (Bandodkar et al., 2019b; Mazzaracchio et al., 2021; Song et al., 2020; G. Xu et al., 2019a) and other physiologically relevant biomarkers (Bandodkar et al., 2020, 2019a; Cheng et al., 2021; Hourlier-Fargette et al., 2020; Kim et al., 2018; S. B. Kim et al., 2020; Song et al., 2020; G. Xu et al., 2019a, 2019b). Sensing systems of this device class use primarily MRC and NFC due to its robust infrastructure, and recent work featured in section 2.1 has utilized RF and other internal power harvesting techniques to eliminate the need of a power casting source (G. Xu et al., 2019a) leading the way towards fully autonomous embodiments with broad impact in health diagnostics and

preventative screening for individuals who are at risk for metabolic disease (Gao et al., 2016; Jia et al., 2013).

**3.3.2 Implantable Endocrine and Metabolic Sensors**—For the most accurate representation of physiologically relevant biochemical levels, it is beneficial to implement implantable systems, as they can collect biodata directly from the interstitial fluid for more accurate and real time information and do not suffer from epidermal interface erosion (Arora, 2013; Ming Li et al., 2007; Scholten and Meng, 2018). Implantable devices of this nature face harsher constraints on system design as form factor, power transfer, and sensing modality have to factor in patient comfort, system robustness, and invasiveness required for the implantation procedure. Current implantable systems for this application suffer from poor lifetime and biocompatibility (H. Lee et al., 2018) and generally require transdermal probes for operation (Corrie et al., 2015; Hage et al., 2010; Lucarelli et al., 2012), limiting patient function and increasing discomfort due to secondary procedures to recover sensors after use. Therefore, miniaturization of the implanted sensor architecture is often chosen as a design philosophy. A representative device this class of sensor system is shown in Figure 8D (Mujeeb-U-Rahman et al., 2019a). This system utilizes ultra-small CMOS-based wireless, battery-free glucose monitoring systems in a form factor ideal for minimally invasive implantation. For this device, a CMOS based system including sensing, power, and communication electronics serves as the platform of the solid-state sensor used to detect interstitial levels of glucose. This device functions using RF power transfer (see section 2.1) at a frequency of 900 MHz, which is suitable for subdermal implantation when combined with a powering and readout system in close proximity. Backscattering is used for communication because it can be implemented on one chip and enables low-power operation (5 mW) (Liu et al., 2019; Mujeeb-U-Rahman et al., 2019b). Additionally, the proximity to the biofluid results in a fast response time that is significantly improved over traditional transcutaneous devices (H. Lee et al., 2018). Figure 8E displays working principle, where the implant is powered by a wearable transmitter that casts power and communicates and functions as a gateway via Bluetooth to relay information for storage and analysis. Figure 8F shows the sensors response to varying concentrations of glucose in physiologically relevant ranges (Bruen et al., 2017). The device demonstrates significantly improved interstitial fluid lag when compared to other continuous glucose monitoring systems, with high sensitivity (40 mg/dl) during periods of hypoglycemia. This sensitivity is achieved with lifetimes of over 1 month of operation and high sampling rates of 1 kHz (See SI Table 2). Implantable systems of this form factor provide precise, effective means of delivering high-fidelity information without on-going risk of infection or interface failure that can avoid serious consequences for health outcomes (Ahmadi and Jullien, 2009; DeHennis et al., 2016; Kropff et al., 2017) Utilization of external, battery-free power sources enables long-term data collection from the system without the need for repeated insertion of probes or changing of batteries. More broadly, the approach of using an external wearable power source and readout electronics in combination with miniaturized implantable sensors has the potential to be highly impactful for chronic applications that require high fidelity signal acquisition over a long time. The access to interstitial fluid has the potential to expand sensing targets well beyond glucose monitoring towards fully integrated closed-loop disease management, which can have significant impact on diagnostic and therapeutic digital medicine capabilities.

**3.3.3 Ocular Endocrine and Metabolic Sensors**—The miniaturization achieved through implementation of wireless, battery-free strategies, coupled with progression of material science towards mechanically compliant systems has proliferated use towards unique target organ systems that are inaccessible or impractical targets with the current state of technology. One such example has been the development of smart contact lenses, which provide an avenue to sense intraocular pressure (G.-Z. Chen et al., 2014) and tear-based biomarkers (Ku et al., 2020; Liao et al., 2012; Zhang et al., 2011). This is significant because tear-based fluids contain a rich amount of biochemical information and can be accessed without invasive methods (Farandos et al., 2015). Recent attempts to use this sensing target with passive resonator designs which can be realized with few components, typically a capacitive or resistance-based sensor coupled with an antenna loop, however, chronic system stability of this class is usually poor (Chen et al., 2013; Kim et al., 2017). Recent innovations in this class of devices have expanded the functionality with active digital sensing components. The device featured in Figure 8G (Keum et al., 2020), shows such a system that incorporates a tear-based glucose sensing platform with flexible drug delivery that monitors tear glucose concentrations with active, on-demand pharmaceutical delivery. The device uses MRC power transfer at 443 MHz (see section 2.1) and low-power backscatter communication (see section 2.2). The system is fully integrated on a single die ASIC that houses an analog interface that can detect  $\mu\text{A}$  changes in current while simultaneously deploying drug delivery capabilities in a contact lens form factor (Shown in Figure 8H). This device implements real-time electrochemical detection of glucose concentration via using bioconjugated electrodes, specifically a platinum working electrode coated with Chitosan and polyvinyl alcohol hydrogels that contain glucose oxidase (GOx). Glucose is oxidized at the working electrode to produce a current representing the concentration of glucose. Sensing performance of  $1\mu\text{A}/15\text{mg dl}^{-1}$  is superior to conventional tear-based analysis systems that do not allow for continuous monitoring (La Belle et al., 2016; Lee et al., 2019). Control of drug delivery is modulated through a voltage-controlled dissolution of a gold membrane, allowing for release of pharmaceuticals. Figure 8I shows system function during an *in vivo* study involving diabetic small animal models that are treated with insulin. The system shows good agreement with blood glucose levels considering lag inherent in glucose presentation in tear fluid, which has been previously studied (Aihara et al., 2018; Sen and Sarin, 1980). This and other demonstrations (Gulsen and Chauhan, 2004; Joohee Kim et al., 2017; Kownacka et al., 2018; Ku et al., 2020; La Belle et al., 2016; Liao et al., 2012; Zhang et al., 2011) show that tear fluid as a sensing target and the eye as a location for noninvasive drug delivery are an opportunity to advance diagnostic and therapeutic capabilities and substantially improve the quality of life for a large patient population. The location of these sensors requires the use of wireless and battery-free system architectures because of the need for low profile layout that occupies minimal space to avoid irritation and clear vision. The success of this class of devices will largely depend on sensor stability and technological maturity of power casting and integrated receiving systems that enable continuous operation in the eye (Chiou et al., 2017).

### 3.4 Other Physiological Systems

Wireless, battery-free sensing systems can expand capabilities to a broad range of target organ systems. In this section, we capture most impactful sensing systems outside of



commonly targeted organ systems discussed in prior sections with demonstrations of devices that expand current sensing technologies. We discuss platforms that are made possible with implementation of this technology, and briefly describe approaches that go beyond the implementation of a sensor or a sensor system and demonstrate device which can operate in a closed loop.

**3.4.1 Integumentary**—The epidermis is the largest organ on the body and is susceptible to many injuries and diseases that are difficult to monitor with the current state of technology. Epidermal interfaces are traditionally plagued with interfacial challenges due to high impedance caused by high rates of epidermal turnover (Halprin, 1972). Wireless, battery-free sensing systems can provide a platform to address these challenges by enabling an intimate contact that results in lower impedance and lower motion artefacts, resulting in continuous recording capabilities such as the devices outlined in sections 3.1.1, 3.2.1, and 3.3.1. This high fidelity interface is not only limited to optical and electrical signals but can also be extended towards mechanical and thermal signatures (Kwak et al., 2020) that enable advanced applications in the detection of wound healing (Hattori et al., 2014), skin hydration (Krishnan et al., 2017), and blood perfusion (Webb et al., 2015). Figure 9A shows such a device used for thermal characterization of the skin in an ultra-small, conformal form factor. This system relies on MRC and NFC (see sections 2.1 and 2.2) to provide power to the thermal actuator/sensing unit while simultaneously utilizing thermography to capture changes in temperature to determine variations in thermal conductivity and heat capacity of the skin (Krishnan et al., 2018). Thermal actuation is a power intensive process, thus adequate power availability is essential for system function. For this use case, MRC is used as the power transfer method due to its high power-availability ( $\sim 20$  mW for this embodiment) (Lazaro et al., 2020). Communication is achieved with NFC, which is the preferred candidate for on skin applications (see section 2.2). The sensing principle relies on transfer of heat to the superficial epidermal layer using constant power thermal actuation and simultaneous monitoring of temperature to calculate the thermal conductivity of the underlying tissue. This scheme is only possible when thermal mass of the sensor/actuator combination is low and the thermal coupling to the target tissue is good, which can only be efficiently achieved with thin epidermal interfaces. At a low constant power (2 mW) the sensor/actuator combination can locally heat the underlying tissue below the threshold of sensation ( $\sim 6$  K) (Krishnan et al., 2018), providing sensor function with no user perception. The change in temperature, can then be used to compute thermal conductivity of the underlying tissue layers. This sensor configuration can achieve a resolution of  $0.02 \text{ W m}^{-1} \text{ K}^{-1}$ , which enables the insight into tissue health and properties such as hydration (Krishnan et al., 2017), wound healing (Hattori et al., 2014), and infection (Madhvapathy et al., 2018). Figure 9B shows a subject's arm, in which the device was used to probe tissue properties of a class II burn injury. This system is able to detect the subtle changes in thermal conductivity evoked by the severity of burn damage to the underlying epidermis, corresponding results are shown in figure 9C, that clearly show distinction in thermal properties between the probed tissue locations. In the same work the authors also report on the capability to detect other conditions such as ischemia (Regas and Ehrlich, 1992) and flow in shunted arteries and more recent work has used the technique as monitors for shunt flow in hydrocephalous patients (Krishnan et al., 2020). The work also shows the capability to track skin hydration

over several days, this is possible due to the dry epidermal interface that is stable despite epidermal turnover. These capabilities highlight the impact of this technology when coupled with wireless and battery-free devices to continuously assess skin health and highlight possible applications in chronic wound healing (Dargaville et al., 2013; Pasche et al., 2009), skin transplant health (Jain and Shakya, 2009) and skin irritation, conditions that effect a large patient populations.

**3.4.3 Urinary**—The ability to deliver power continuously to power digital electronics naturally suggests the usage of on-board computing on the device itself. The sensor systems that we review in the previous sections, however, only do this in a limited capacity to, for example, to reduce bandwidth requirement for communication links (section 2.2). An approach that is only rarely realized are closed loop systems that couple sensing modalities with actuation or modulation to realize autonomous systems that automatically treat chronic illness, aid in management of disabilities and offer advanced insight into fundamental mechanisms of human and animal physiology (Parastarfeizabadi and Kouzani, 2017; Renard, 2002; Scholten and Meng, 2018; Sun and Morrell, 2014). Current trends in electronic medicine have been focused on development and understanding treatment strategies using stimulation of peripheral nervous system paired with targeted biosensors to refine stimulus delivery (Cameron, 2004; Famm et al., 2013). One organ system that is rarely targeted due to complex anatomy, is the urinary system, specifically targeting bladder dysfunction through closed-loop modulation (de Groat and Tai, 2015; Siegel et al., 2000). Wired systems for this application have been utilized to treat and examine voiding dysfunctions through electrical stimulation, however current systems are highly invasive and require a clinical setting with limited chronic operation appeal (J. et al., 2006; Park et al., 2018). Wireless and battery-free systems provide a favorable alternative due to their robust long-term data collection and transmission capabilities with on-board processors to handle data analysis coupled with the ability of system miniaturization that enables full implantation (Zhong et al., 2020). One such system is shown in Figure 9F this fully integrated, closed-loop system features a wireless control and power module and an optoelectrical stimulation and sensing platform. This system is utilized in small animal model research and uses optogenetic stimulation of the sacral nerve to regulate bladder activity while simultaneously recording strain on the bladder. MRC is used for continuous power deliver to the rodent subjects as discussed in section 2.1 and has been successfully deployed in devices discussed in sections 3.1, 3.2 and 3.3. BLE is used for data communication to adjust and monitor closed loop parameters. A circumferential strain gauge attached to the bladder (as shown in Figure 9E) collects information on extension, which is an indicator of fill level. The strain gauge is made from a carbon black doped elastomer to provide flexible mechanics to enable full implantation and overall soft mechanics of the system. Stimulation is carried out with  $\mu$ -ILED nerve cuff that is comprised of low-modulus silicone to provide soft mechanics in an optically clear platform that seamlessly interfaces with peripheral nerves. Information from the strain gauge is translated to bladder size and computed to determine if micturition events are consistent, hyper-, or hypoactive. If there is variation in the micturition events when correlated to strain gauge values, optogenetic stimulation via  $\mu$ -ILED is used to void the bladder in a closed loop fashion to supplement natural function. Figure 9F shows strain gauge data with correlated micturition events as

detected by the subject's closed loop implant and stimulation events that are computed by the system to return to regular bladder activity.

Demonstrations of closed loop regulation capability highlight advanced computational capabilities that can be accomplished with wireless, battery-free devices and showcase a promising avenue for the realization of systems that automatically treat disease or supplement body function without clinical intervention.

## 4 Conclusion

Wireless, battery-free sensing systems can provide a platform that can be fundamentally advantageous for biosensing applications through the intimate integration opportunities enabled by a highly miniaturized form factor, soft mechanics, low weight and uninterrupted operation. Wireless power supply or power harvesting coupled with suitable data communication strategies can yield highly capable systems in wearable and implantable format. As demonstrated by most recent advances highlighted in this review, this device class quantitatively expands current capabilities over conventional sensing approaches and rapid rate of development suggests increasingly capable bioelectronic systems in the near future. Specifically, improvements to wireless, battery-free power transfer and power harvesting provides opportunities to increase both operational range and the inclusion of power-hungry sensing modalities. This potentially enables the development of sensing platforms that can expand use cases of existing technologies towards sensing modalities not yet realized in wireless and battery-free format. Examples that would expand current sensing capabilities include impedance spectroscopy, continuous blood pressure assessment, and on device continuous analysis requiring multiple streams of high-fidelity data and AI analysis approaches which require more capable computing on the device. Conceptually however, the idea of continuously monitored health with biosensors is only in its infancy. With the expansion and proliferation of wireless and battery free systems, a standardized infrastructure will be needed to support both the continuous powering of these systems and means of data aggregation compliant with current HIPAA requirements. The increased data stream by continuously operating systems and enhanced fidelity enabled by soft mechanics enables advanced disease assessment and prediction if analysis methods can be created that need little human supervision. AI and machine learning offer these attributes if reliable models can be created that take multimodal data streams into account. Assuming increased efficiency of power harvesting and power casting techniques, closed-loop system functionality beyond the boundaries of research paradigms can enable advanced diagnostics and support organ systems. Sensor platforms, as the ones reviewed here, form the basis of progression towards autonomous and integrated healthcare solutions that have the potential to drastically improve the current standard of care and health outcomes.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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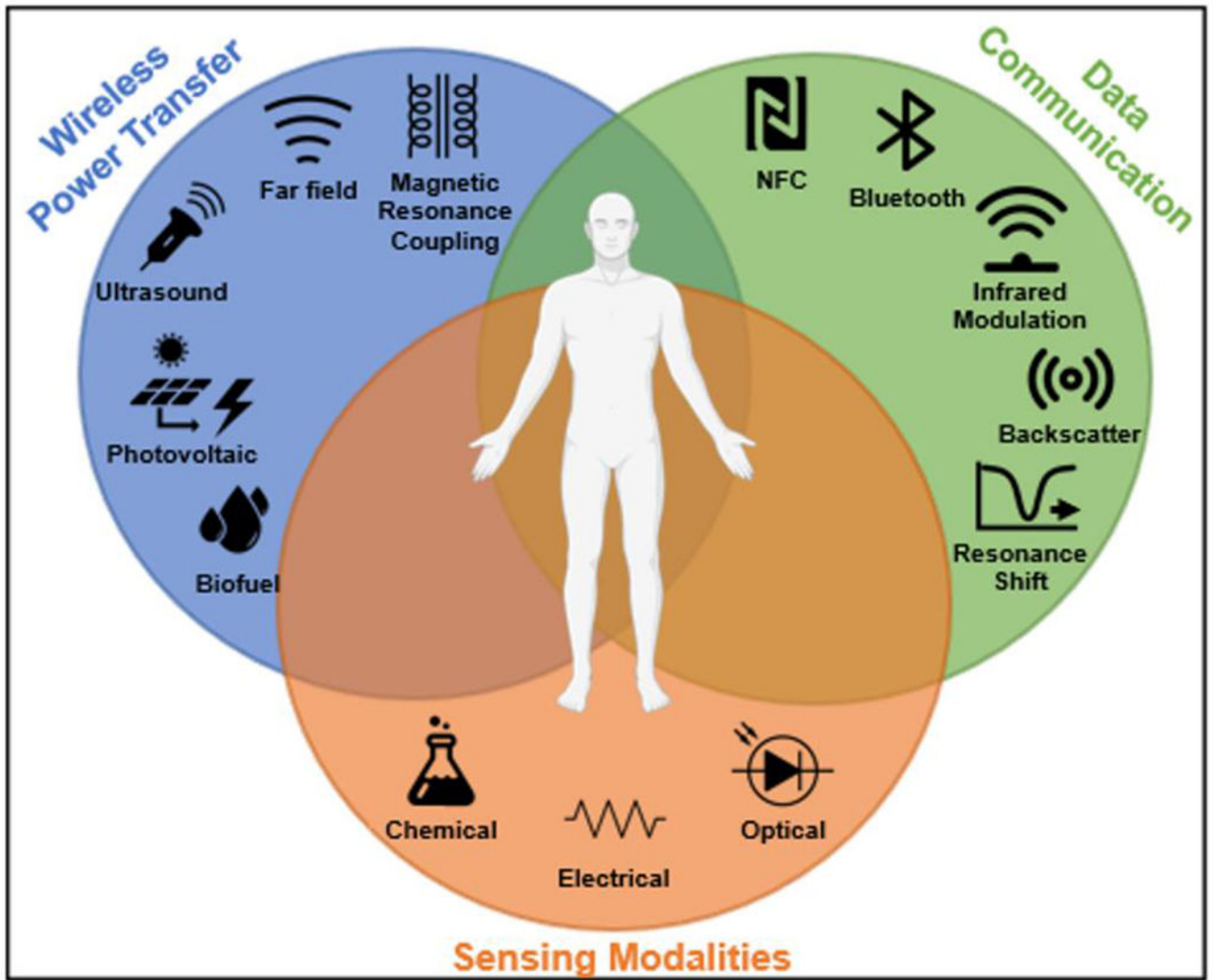
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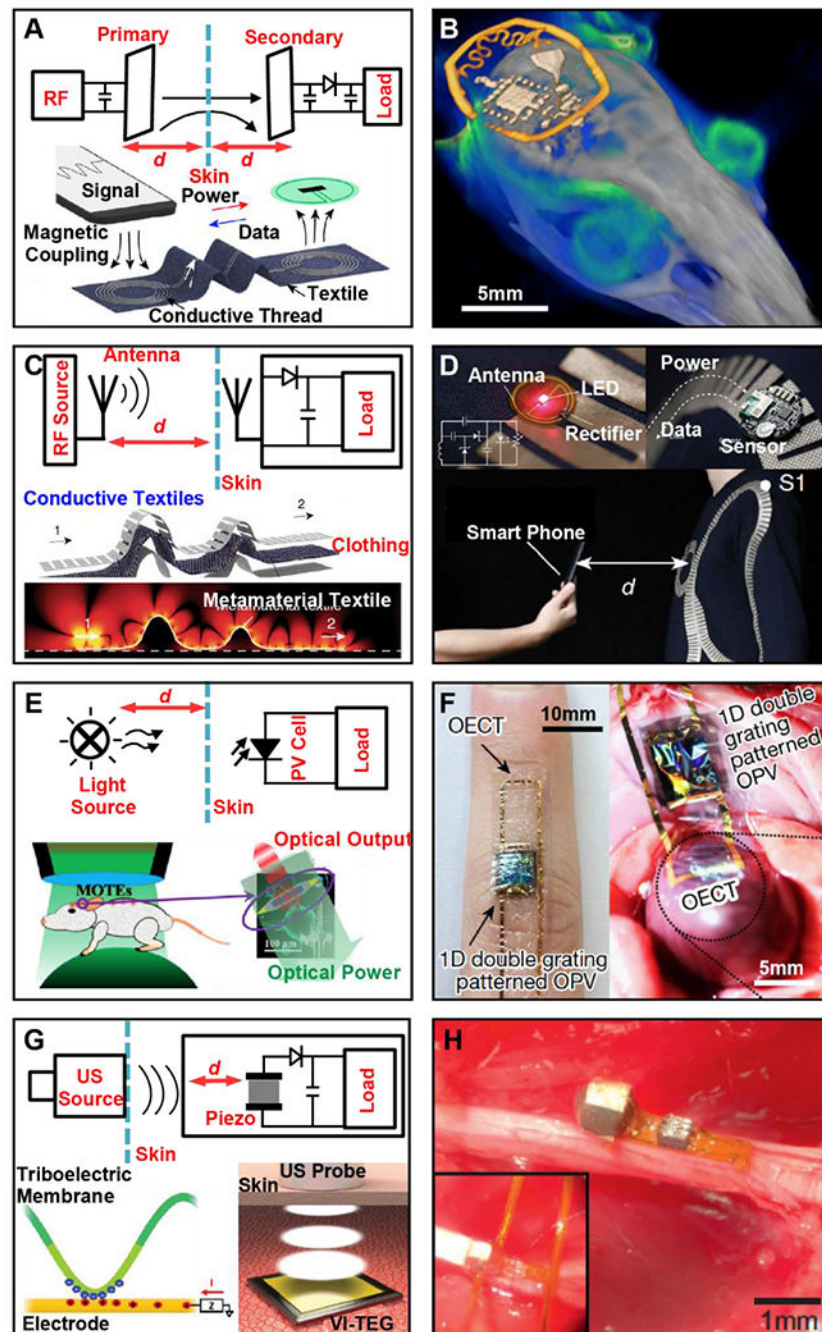
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**Figure 1.**  
Key components of wireless, battery-free sensing systems.



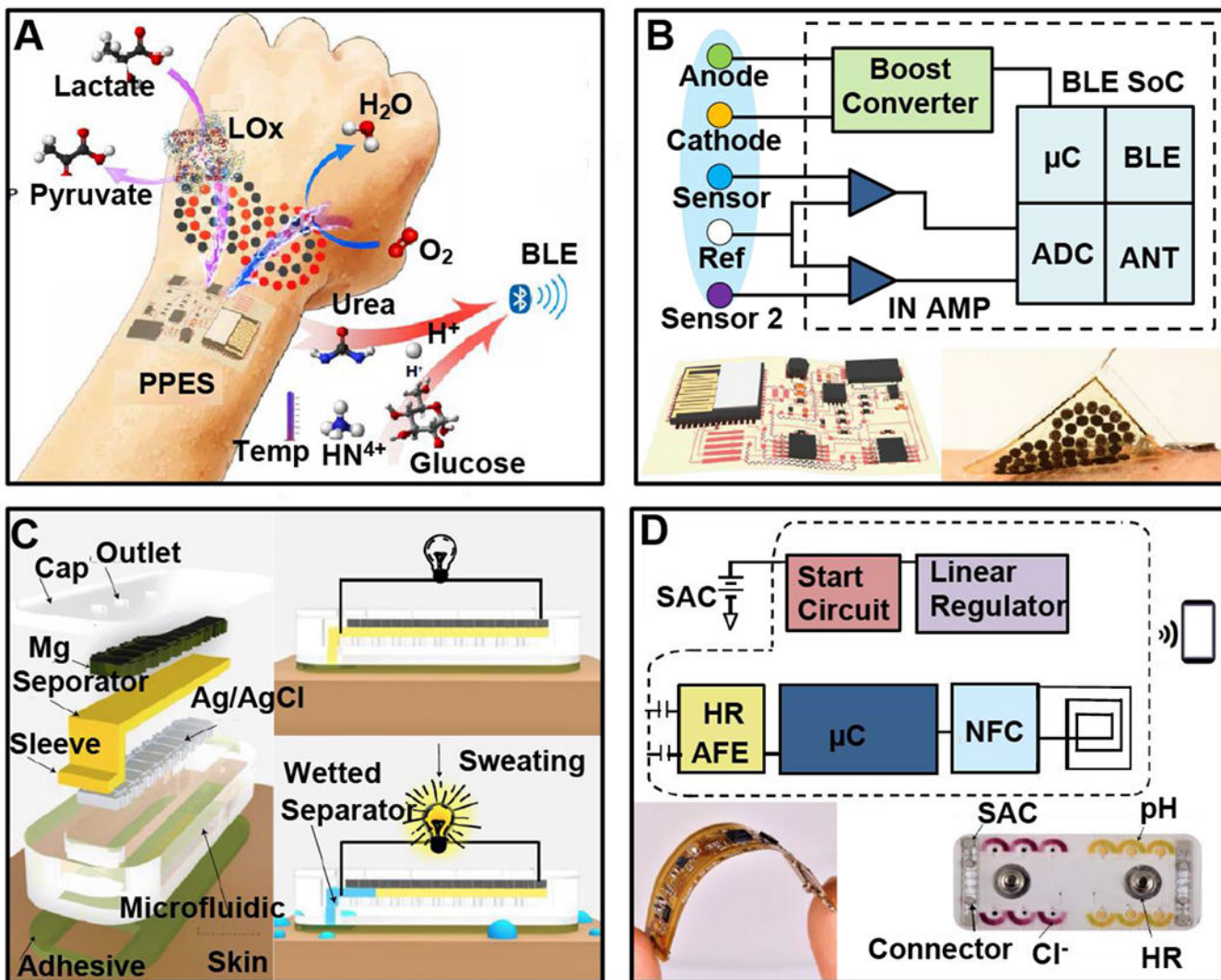


**Figure 2. External power sources for wireless, battery-free sensors.**

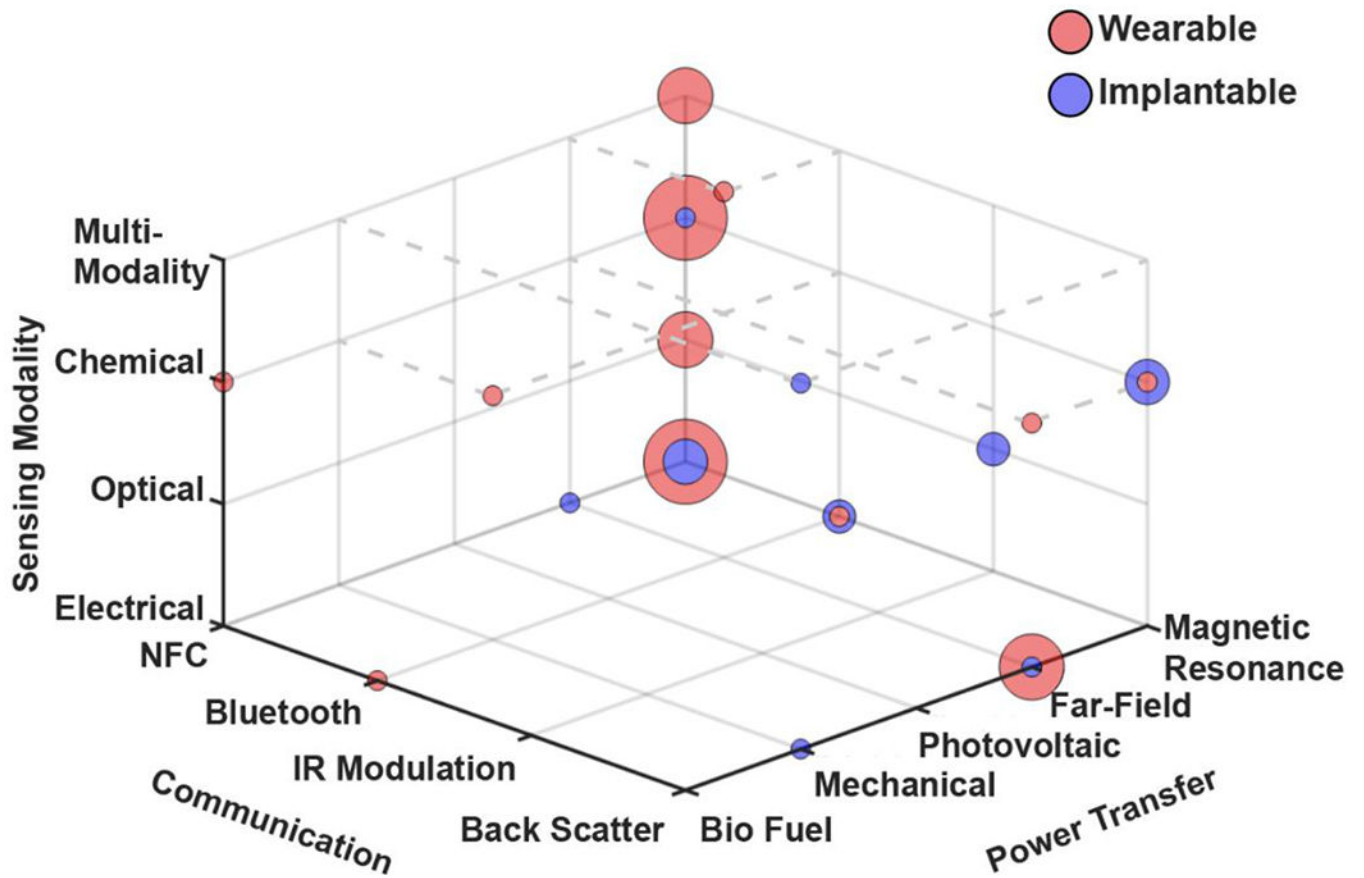
**A**, Operation mechanism of magnetic resonant coupling power transfer (upper half); Illustration of an E-textile-enabled near-field power transfer strategy to drive body sensor networks (lower half). **B**, 3D rendering of a micro-CT scan and MRI scan of a mouse implanted with a wireless photometric probe to monitor the  $\text{Ca}^{2+}$  dynamics in the brain. **C**, Operation mechanism of RF transmission-based power transfer (upper half); illustration and simulated electric field distribution of a wearable body area power transfer network enabled by metamaterial textile. **D**, Photographs of cardiac indicator (upper left) and temperature

sensors (upper right) powered by the metamaterial textile, and demonstration of secure communication using a smartphone (lower image). **E**, Operation mechanism of photovoltaic-powered implantable sensors (upper half); Implementation strategy of a microscale optoelectronically transduced electrode (MOTE) with green light as input power source and red light as output for data communication. **F**, Photographs of sensors comprised of flexible organic photovoltaic (OPV) cells and organic electrochemical transistors (OECT) for wearable (left) and implantable (right) cardiac signal recording. **G**, Operation mechanism of ultrasonic power transfer with a piezoelectric crystal as implantable transducer (upper half); a vibrating and implantable triboelectric generator (VI-TEG) used to harvest ultrasonic energy (lower half). **H**, An ultrasonic-powered miniaturized device for wireless recording in the peripheral nervous system.

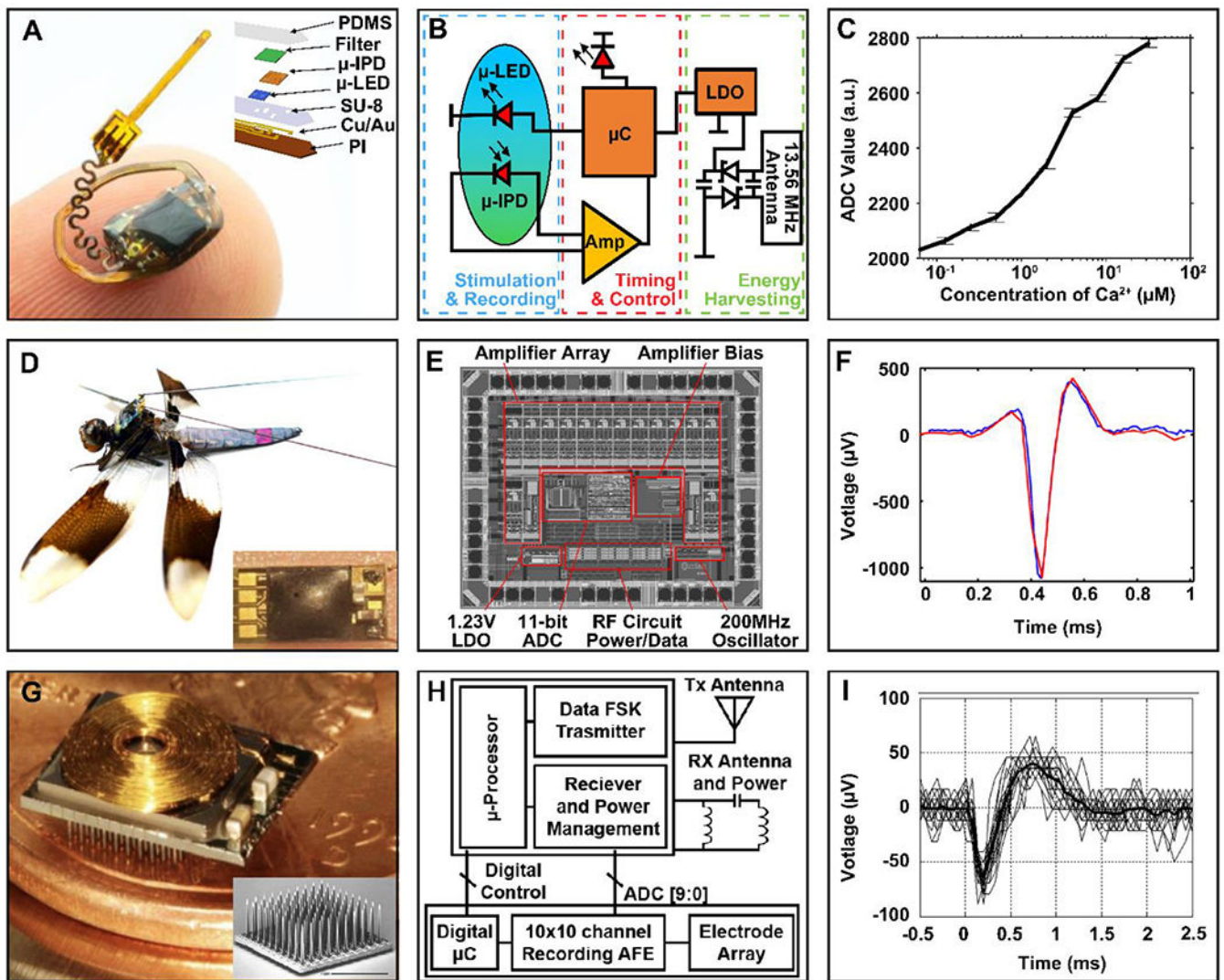




**Figure 3.** Energy harvesting power sources for wireless, battery-free sensors. **A**, Operation mechanism and system construct of a soft electronic skin with multiplexed and wireless sensing functions powered by nanoengineered biofuel cells (BFCs). **B**, Block diagram of the system function (upper), schematic illustration (lower left) and photographs (lower right) of the BFC-powered wireless E-skins. **C**, Device structure and operation principle of sweat-activated batteries for driving epidermal electronic and microfluidic systems. **D**, Block diagram of the system function (upper), and photograph of the electronic (lower left) and microfluidic (lower right) modules.



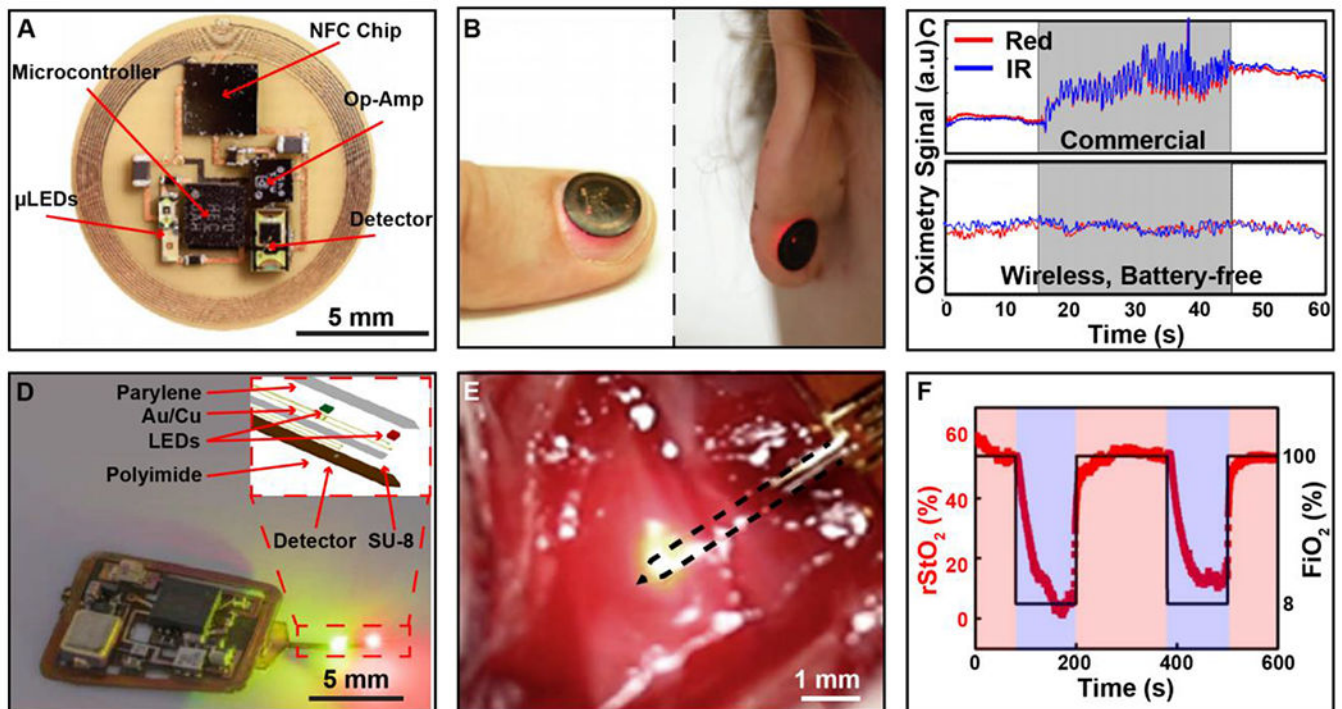
**Figure 4.** 3D scatter plot summarizing recent work in wireless, battery-free sensing devices



**Figure 5. Wireless battery-free neural interfaces.**

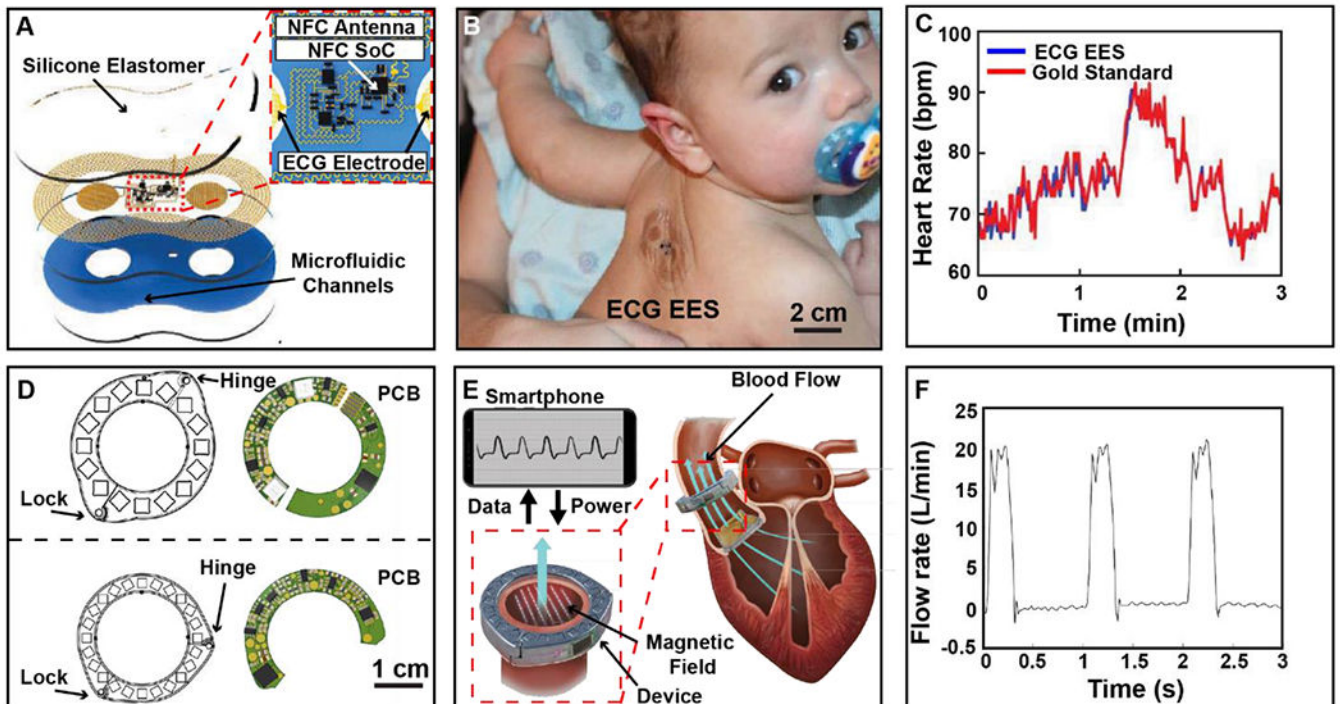
(A) Photograph of a wireless, battery-free photometry device balanced on a finger with an inset of an exploded view makeup of the photometric sensor probe. (B) Block diagram of the photometry device function. (C) Fluorescence recording with standard errors of titrated calcium solutions ( $0.0625 \mu\text{M} - 32 \mu\text{M}$ ) and calcium dye ( $12.5 \mu\text{M}$ ). (D) Photograph of a wireless neural recording system mounted on a dragonfly with an inset of a close-up view of the device. (E) Die layout of the 14-channel digital telemetry IC. (F) Wireless acquisition (red) of a reference neural spike (blue) in a dragonfly. (G) Photograph of a 100-channel wireless neural interface device with inset of a scanning electron micrograph of the 100-channel electrode. (H) Block diagram of the 100-Channel wireless neural recording system. (I) Wireless acquisition of multiple neural signals recorded from auditory cortex of cat.





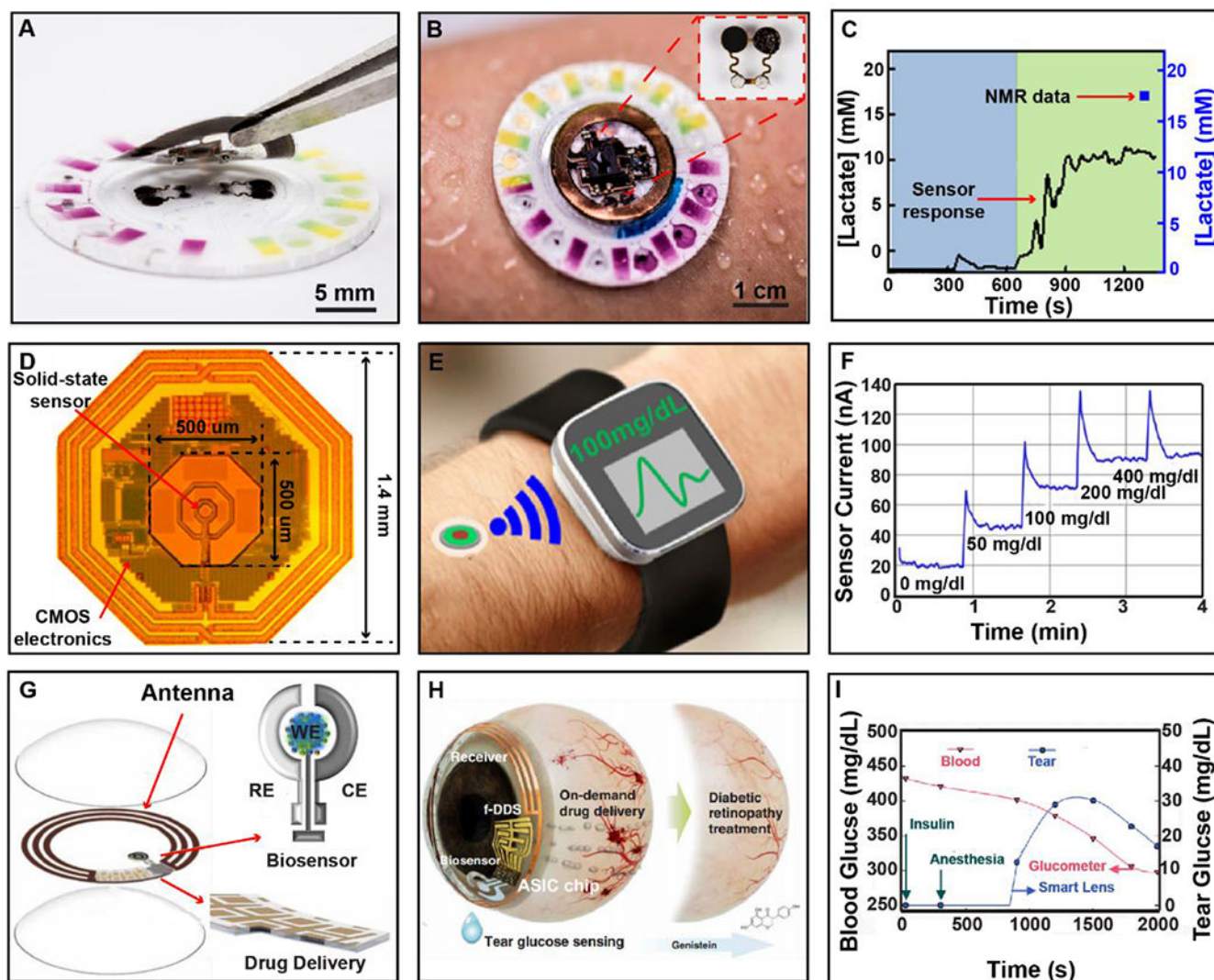
**Figure 6. Wireless battery-free oximetry sensors.**

**A)** Photographic image of oximeter device with key electrical component labeled. **B)** Image of device during operation while applied to the fingernail and earlobe. **C)** Plot of red and infrared (IR) signal from both wireless, battery-free and commercially available devices during user motion. **D)** Image of wireless localized oximeter device during operation. Inset shows exploded view make up of injectable probe. **E)** Image of oximetry probe implanted in tissue region of the femoral artery. **F)** Plot of  $rStO_2$  readout in tissue region while anesthetized rat is exposed to  $FiO_2$  concentrations. of 100% (red) and 8% (purple).



**Figure 7. Wireless battery-free sensors for applications in cardiovascular health assessment.**

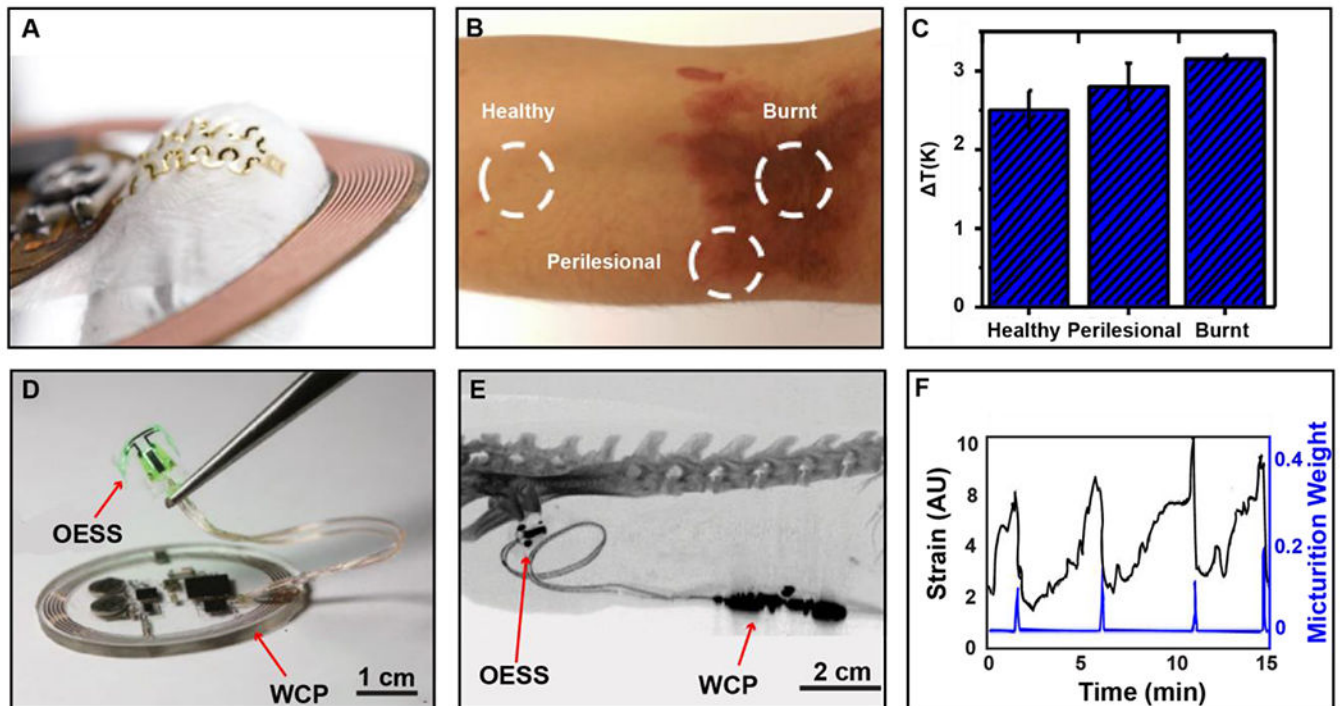
**A)** Schematic illustration of wireless, battery-free ECG system used for epidermal application on NICU patients. **B)** Photographic image of ECG device placed on the back of an infant. **C)** Graph of heart rate data collected using the ECG epidermal electronic system (EES) compared to the gold standard, wired system. **D)** Illustration of two devices with varying magnetic structures and their complementary printed circuit boards. **E)** Illustration of device function showing power and data transfer to the device with implementation on the aortic valve. **F)** Graph showing *in vitro* data collection at physiological conditions.



**Figure 8. Devices for real-time metabolic.**

**A)** Photographic image showing two-part device structure with removable NFC electronics and single use epifluidic patch. **B)** Photographic Image of device on perspiring subject with inset showing biofuel cell for continuous metabolite sensing. **C)** Continuous lactate detection during exercise with comparison to gold-standard, single collection NMR analysis. **D)** Micrographic image of integrated wireless platform with key features labeled. **E)** Illustration of proposed device function. **F)** *In Vitro* response of GOx coated sensor when exposed to varying concentrations of Glucose solution. **G)** Layered makeup of device components for power transfer and data communication, glucose biosensor, and flexible drug delivery system integrated into a contact lens. **H)** Illustration of device function for closed-loop diabetic retinopathy treatment. **I)** *In vivo* response of smart lens compared to glucometer during treatment with insulin.





**Figure 9. Advance applications for wireless, battery-free systems.**

**A)** Photographic image of device showing flexibility of epidermal actuator/sensing combination. **B)** Photographic Image illustrating testing conditions of subject's epidermis. **C)** Thermal characteristics based on health status of epidermis corresponding to panel B. **D)** Photographic image of closed-loop system showing the wireless control and power module (WCP) and optoelectronic stimulation and sensing module (OESS) featuring a strain gauge and  $\mu$ -ILED for optogenetic stimulation. **E)** CT image showing device 1-month post-implantation with sensor and stimulation interface secured circumferentially around the bladder and subdermally implanted wireless battery-free system. **F)** Graph displaying recorded data during closed-loop operation of the system with continuous strain gauge data (black) and micturition events measured by a balance (blue).