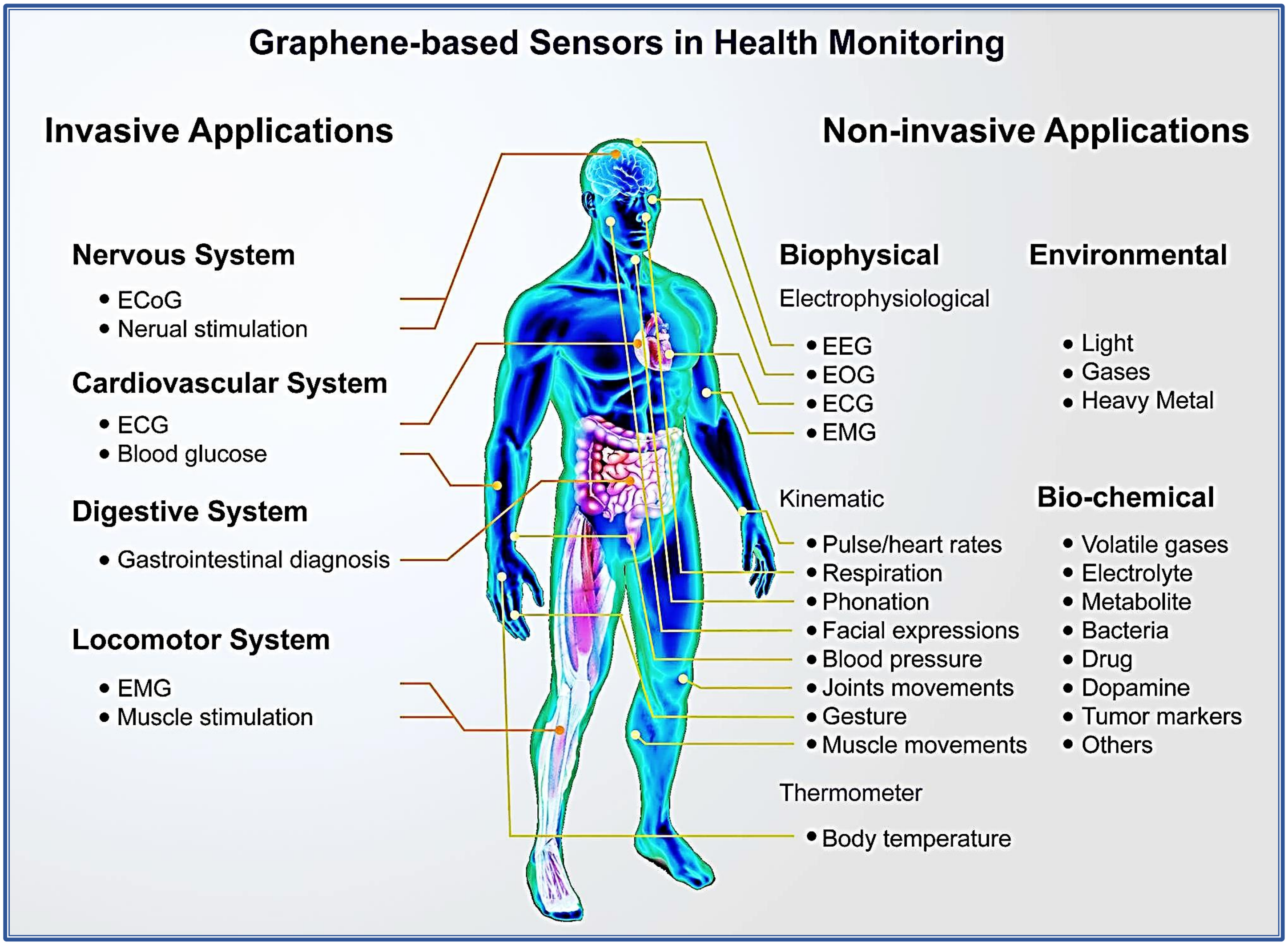

Figure 1. Brief of graphene-based sensor platform for health monitoring. A major distinction can be made between non-invasive and invasive applications, including wearable sensors for monitoring biophysical, biochemical, environment signals, and implantable devices for nervous, cardiovascular, digestive, locomotor system.

Graphene-Based Sensors for Human Health Monitoring

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Front. Chem., 11 June 2019, Sec. Nanoscience, Volume 7 - 2019 | https://doi.org/10.3389/fchem.2019.00399,

EXCERPTS BELOW:

Since the desire for real-time human health monitoring as well as seamless human-machine interaction is increasing rapidly, plenty of research efforts have been made to investigate wearable sensors and implantable devices in recent years. As a novel 2D material, graphene has aroused a boom in the field of sensor research around the world due to its advantages in mechanical, thermal, and electrical properties. Numerous graphene-based sensors used for human health monitoring have been reported, including wearable sensors, as well as implantable devices, which can realize the real-time measurement of body temperature, heart rate, pulse oxygenation, respiration rate, blood pressure, blood glucose, electrocardiogram signal, electromyogram signal, and electroencephalograph signal, etc. Herein, as a review of the latest graphene-based sensors for health monitoring, their novel structures, sensing mechanisms, technological innovations, components for sensor systems and potential challenges will be discussed and outlined.

Introduction

As the global population is growing rapidly and the life expectancy of humans is increasing drastically (Vaupel, 2010; Takei et al., 2015), the healthcare system is facing increasing expenses and burdens, requiring governments to find feasible solutions to render adequate medical care without increasing healthcare costs (Pantelopoulos and Bourbakis, 2010). Preventive and personalized medicine approaches (Ng et al., 2009), which change with health status, can be detected and diagnosed early. Disease-risk can also be predicted, and utilized to overcome challenges by increasing the cure rate and survivability of an at-risk population, while minimizing the overall treatment costs (Narayan and Verma, 2016; Tricoli et al., 2017). By periodically or continuously tracking critical signs and biomarkers, health monitoring systems are capable of comprehensively assessing health conditions which can remarkably benefit the diagnosis and diseases treatment along with postoperative rehabilitation, which can significantly reduce the burden of medical systems and improve quality of life (Yao et al., 2017).

As a critical component of health monitoring systems and the interface to the human body, sensors, including wearable and implantable sensors, are able to detect and measure various signals or analytes with high specificity and sensitivity (Narayan and Verma, 2016). Indeed, due to the mechanical mismatch between the human skin (or soft biological tissues) and conventional rigid silicon-based sensors, mechanical flexibility is notably essential for these invasive or non-invasive sensors (Wang et al., 2017). Moreover, several constraints including biocompatibility, reliability, stability, comfort, convenience, miniaturization, costs, and biofouling should also be considered or even traded for location-unlimited, long-term, multifunctional, real-time, unobtrusive, pervasive, affordable health monitoring (Pantelopoulos and Bourbakis, 2010). Furthermore, recent impressive data management and analysis methods, such as Big Data (Murdoch and Detsky, 2013; Bates et al., 2014; Raghupathi and Raghupathi, 2014), and machine learning (Ravi et al., 2017) technology are applied in data handling and effective information mining (Banaee et al., 2013), since a large amount of data can be collected by these sensors (Someya et al., 2016). Consequently, personal data security and privacy should be effectively guaranteed.

Graphene, owing to its extraordinary multiple properties, such as ultrahigh carrier mobility (Novoselov et al., 2004; Weiss et al., 2012), excellent electrical conductivity, superior thermal conductivity (Balandin et al., 2008; Balandin, 2011), large theoretical specific surface area (Zhu et al., 2010), high optical transmittance (Nair et al., 2008), high Young's modulus (Lee et al., 2008a) and outstanding mechanical flexibility (Yang H. et al., 2018), is a promising 2D material in many applications, especially for the development of wearable sensors and implantable devices in health monitoring. Various and multifunctional sensors can be realized, which benefits from the performance diversities of graphene. The advantages of graphene for sensors are summarized as follows: the first point is that the high specific surface area and the atomic thickness of graphene layers render entire carbon atoms directly in contact with analytes, as a result, graphene-based sensors have superior sensitivity compared to silicon (Justino et al., 2017). In addition, conformal, intimate contact with organs of interest such as the skin (Ameri et al., 2016), brain (Park et al., 2017) and eyes (Kim et al., 2017) can be achieved by graphene-based sensors, because of the mechanical flexibility and ultrathin thickness of graphene, which is essential in acquiring high-quality signals without irritation, motion artifacts, or contamination (Ray et al., 2018). Moreover, high optical transparency and electrical conductivity renders graphene an ideal material for bio-tissue observation with clear images and without visual disturbances (Lee et al., 2015). Furthermore, a high signal-to-noise ratio (SNR) can be achieved in electrophysiological signals recording by the conformal integration and the efficient signal transmission depending on the high electrical conductivity (Ameri et al., 2016). Additionally, the superior performance of graphene in biosensors, such as large specific surface area, convenient functionalization, wide potential window as well as high electron transfer rate, allows receptors such as enzymes, antibodies and deoxyribonucleic acid (DNA) to be efficiently immobilized on the surface of graphene (Szunerits and Boukherroub, 2018). More discussions on the properties, synthesis, characterization, and other applications of graphene and its derivatives have been reported in previous review papers and are not included in this review due to limitations in space (Soldano et al., 2010; Huang M. et al., 2011; Huang X. et al., 2011).

As shown in Figure 1, a lot of graphene and its derivatives, including graphene oxide (GO), reduced graphene oxide (rGO), and graphene composites based sensors for human health monitoring have been reported, including wearable sensors, and implantable devices, which can realize the real-time measurement of body temperature (Trung and Lee, 2016; Wang et al., 2018a), heart rate (Karim et al., 2017), wrist pulse (Yang et al., 2017; Pang et al., 2018), respiration rate (Boland et al., 2014; Xu et al., 2018c), blood pressure (Pang et al., 2016), blood glucose (Pu et al., 2018), electrocardiogram (ECG) signal (Ameri et al., 2016), electromyogram (EMG) signal (Yun et al., 2017; Sun et al., 2018) and electroencephalograph (EEG) signal (Ameri et al., 2016; Yun et al., 2017), etc.

Invasive Sensors

While non-invasive wearable sensors are promising in human health monitoring, they do not have the ability to obtain data on the entire complexity of organ systems and long-term monitoring biological events continuously. Invasive sensors, which are close to the target organs or tissues, significantly increase the sensing accuracy and the curative effect in comparison to non-invasive counterparts. Thus, it is attracting a huge surge of interest in the monitoring, diagnosis, treatment, and management of diseases, which shows its potential in medical application (Eckert et al., 2013). As described previously, challenges including biocompatibility, biofouling, biodegradability, power supply, device minimization, integration, durability and lifetime, also exist in designing invasive sensors (Narayan and Verma, 2016; Gray et al., 2018). Although a large amount of work on implantable sensors for health monitoring has been done, graphene-based invasive sensors have been developed in limited aspects, such as neural recording and stimulation (Blaschke et al., 2017), glucose monitoring (Pu et al., 2018), cardiac monitoring (Chen et al., 2013) and EMG signals recording (Kim et al., 2016), which to date mainly focus on neural implants. The feasibility of graphene-based implants has been demonstrated *in vivo* in physiological systems, including the nervous system, cardiovascular system, digestive system and motional system.

Implants for Nervous System

Active neural implants that stimulate and/or record the electrical activity of the nervous system, can highlight the prospects for the clinical interventions and treatments of various diseases, such as Parkinson's disease, epilepsy, retinitis pigmentosa, pain or even psychiatric conditions (Kostarelos et al., 2017; Kireev et al., 2018). Moreover, brain-machine interfaces with neural implants allow for direct communication between the brain and machines (Choi J. et al., 2018). Although conventional non-invasive electrodes are capable of recording EEG signals (slow rhythms, 5–300 μV, < 100 Hz) from single or multiple sites on the scalp, the spatial resolution and SNR are undesired due to the filtering of different media, such as the skull and cerebral spinal fluid, which may not provide sufficient information to decode nerve signals. As an alternative, electrocorticography (ECoG) (medium rhythms, 0.01–5 mV, < 200 Hz) can achieve better spatial and time resolution and high SNR in an invasive way, by placing electrode arrays directly on the intracranial cortex. Penetrating electrodes are also utilized to record local field potentials (< 1 mV, < 200 Hz) and action potentials (ca. 500 μV, 0.1–7 kHz) (Fattahi et al., 2014). In order to improve the spatiotemporal resolution, microelectrode arrays (MEAs) with electrode diameters in tens of micrometers and electrode-to-electrode separation down to dozens of microns have been employed (Hebert et al., 2017). As with any implant, biocompatibility and non-immune responses are fundamental for electrodes. In addition, high flexibility (reaching conformability and stretchability) or Young modulus matching are crucial to minimize the movement within the soft tissue and to avoid shear-induced inflammation as the body moves, which cannot be achieved when utilizing rigid electrodes, such as silicon or noble metals. Furthermore, biochemical stability and electrical properties are also critical, indicating that the conductivity of electrodes must be high enough to enable safe stimulation or efficient recording signals in slightly salty, gel-like, and 37°C environments. Additionally, as the impedance and noise of the electrode are inversely proportional to electrode size, a trade-off is required between spatial resolution and SNR (Blaschke et al., 2017).

With the combination of extraordinary conductivity, electrochemical stability, flexibility, mechanical conformability and transparency, graphene is almost perfect in addressing many current challenges in neural interface design, where very few conductive polymers can claim all these features. Moreover, optical transparency of graphene is favorable for the study of neural networks and cortical features, where optogenetics, and calcium imaging at the same site can render complementary information (Kuzum et al., 2014; Park et al., 2014; Lu et al., 2018). Therefore, graphene microelectrode arrays (GMEAs) and graphene field effect transistors (GFETs) have been widely utilized for neural stimulation, recording and local preamplification (Thunemann et al., 2018). High surface-to-volume ratio makes graphene sensitive to charges at its surface. Furthermore, high transconductance and low intrinsic noise of GFETs, which require directly or extremely close to the electrode site, render capabilities in high SNR ratios recording with preamplification. As a consequence, the sensitivity to external noise is minimized.

Several structural innovations have been exploited in graphene-based materials for GMEAs and GFETs. For instance, wet-spun rGO fibers have been developed as free-standing penetrating electrodes in an early study (Apollo et al., 2015). Futhermore, highly crumpled all-carbon transistors with graphene channels and hybrid graphene/carbon nanotube electrodes have been achieved *in-vivo* recording of brain activity, with high sensitivity and substantially improved spatial resolution through aggressive in-plane compression (Yang L. et al., 2016). In addition, platinum nanoparticles (PtNPs) electrodeposited on monolayer graphene have been developed to overcome the quantum capacitance limitation and the lack of Faradaic reaction for the graphene electrodes (Du et al., 2018).

Furthermore, operating *in-vivo* was recently performed (Liu T.C. et al., 2016; Park et al., 2017; Du et al., 2018; Lu et al., 2018). One study has employed flexible arrays of graphene solution-gated field-effect transistors to record brain activity *in vivo*, which shows a SNR of up to 72 compared to classical metal Pt electrodes of similar sizes (Blaschke et al., 2017). These graphene transistors have advantages such as intrinsic signal amplification, the possibility for down-scaling and high-density integration, which can compete with state-of-the-art MEAs technologies. The biocompatibility of the graphene implants has also been confirmed without any significant changes of circularity or solidity at any of the time points tested, compared to naive rats or polyimide samples without graphene (Figures 8A,B). Furthermore, imaging spatiotemporal neural responses to electrical stimulation with minimal artifacts can help to better understand the mechanisms of electrical stimulation in neural tissue and allow for various studies, which cannot be accomplished with existing opaque neural electrodes. Therefore, several studies (Liu X. et al., 2018; Lu et al., 2018; Thunemann et al., 2018) have developed fully transparent graphene electrodes for electrical brain stimulation and simultaneous optical monitoring of the underlying neural tissues.

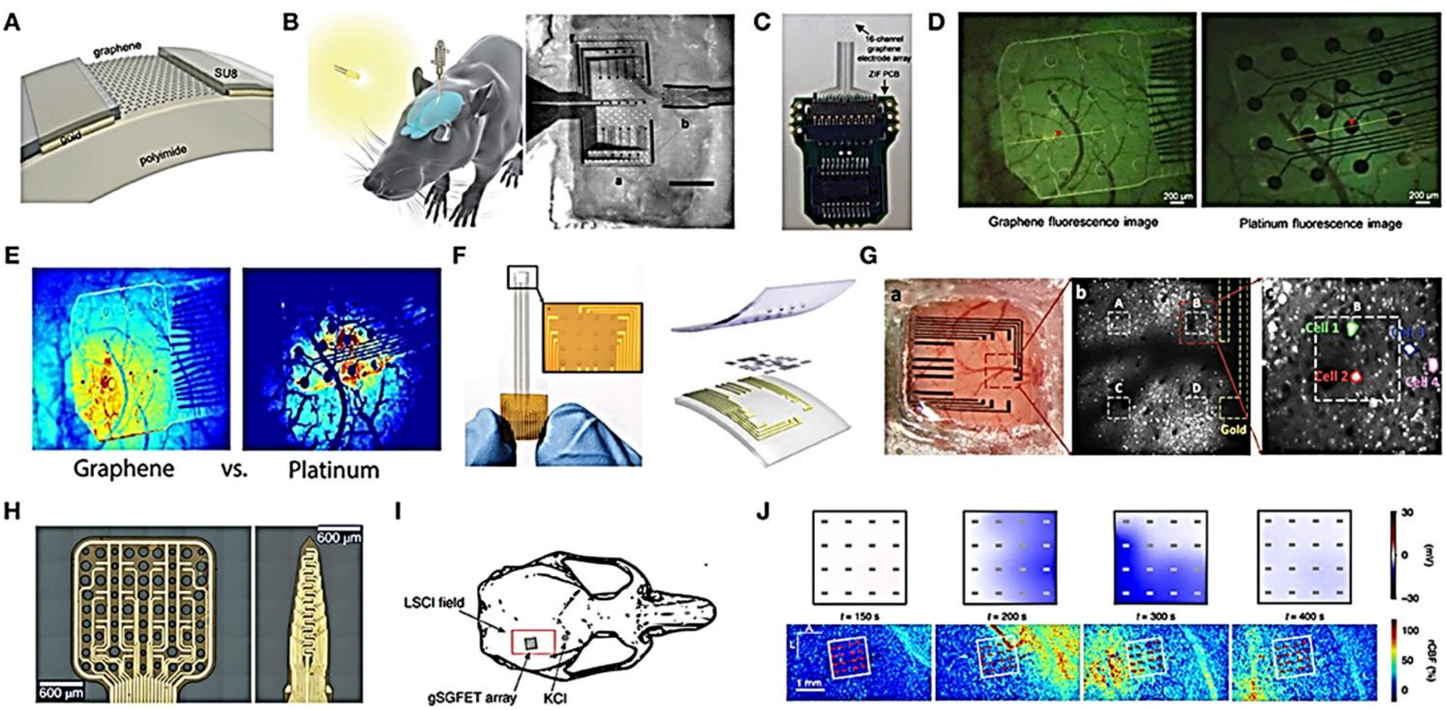

Figure 8. Graphene-based implants for nervous system. **(A)** Schematic of cross section of a graphene transistor. **(B)** Schematic of the implant placed on the surface of the rat's brain (left) and microscope image of a MEA with Pt electrodes and the graphene device next to it (right). Adapted with permission from Blaschke et al. (2017). **(C)** Graphene microECoG array with 16 transparent electrode sites and a ZIF PCB connector. **(D)** Visualization of the fluorescent neural response after stimulation with graphene electrodes (left) and platinum electrodes (right). **(E)** Visualization of the intensity of neural response to electrical stimulation with graphene electrode array and the same platinum electrode array. Adapted with permission from Park D. W. et al. (2018). **(F)** Photograph and Schematic of the array. **(G)** The PtNP/graphene electrode array placed on the cortex (left), two-photon microscope for cell bodies detection

(middle) and image of multiple cells (right). Adapted with permission from Lu et al. (2018). **(H)** Optical microscope images of the active area of a 4 × 4 gSGFET array and a 15-channel intracortical array. **(I)** Schematic of a rat skull depicting the LSCI field of view and the position of the gSGFET array. **(J)** Electrical recordings and optical imaging were performed directly on the cortical surface. Color maps represent the spatial value of the extracellular voltage as measured by the gSGFET array and the rCBF at a given set of times after the induction of a CSD event. Adapted with permission from Masvidal-Codina et al. (2018).

For example, Park D. W. et al. (2018) developed a transparent graphene neural electrode, implanted in GCaMP6f mice, with capabilities in electrical stimulation and optical full-field monitoring of the neural tissues concurrently. With the employment of these transparent electrodes, fluorescence imaging of neural activity with minimal image artifacts was carried out in different electrical stimulation parameters, which also showed that more efficient neural activation could be obtained with cathode leading stimulation compared to that of anode. These graphene electrodes showed potential in therapeutic electrical stimulation of the nervous systems (Figures 8C–E). Although transparent graphene electrodes could enable simultaneous electrical stimulation and optical monitoring, the high impedance of the graphene obstructed wide application. Lu et al. (2018) demonstrated that quantum capacitance is the reason for high impedance of graphene electrodes. By electrodepositing platinum nanoparticles (PtNPs) on monolayers, the impedance of the PtNPs/graphene electrodes were dramatically reduced without a decrease in transparency. By utilizing transgenic mouse models, concurrently cortical activity recording with optical imaging was available with the PtNPs/graphene electrodes, which rendered the possibilities in figuring out the cellular dynamics as well as brain-scale neural activity (Figures 8F,G).

Monitoring brain activities below 0.1 Hz, commonly known as infralow activity (ISA), is valuable for clinical diagnosis, prognosis and therapy in neurocritical care, which can indicate brain states, such as sleep, or a coma. Cortical spreading depression (CSD), a slowly propagating wave of near-complete depolarization of neurons and astrocytes followed by a period of electrical activity suppression, occurs at infralow frequencies in brain pathophysiology, which is usually provoked in persons suffering a stroke, brain injury, and migraines. In order to record ISA *in-vivo*, Masvidal-Codina et al. (2018) exploited graphene solution-gated field-effect transistors (gSGFETs) arrays for both the epicortical and intracortical mapping of CSD. The results showed that graphene transistors were superb in recording ISA with spatially resolved mapping and could record in a wide frequency bandwidth from an infralow frequency to the typical local field potential bandwidth. With the employment of gSGFETs and optical techniques, such as laser speckle contrast imaging, 2D maps of neurovascular coupling could be obtained, which were significant in for a deep understanding of the neurovascular coupling phenomena (Figures 8H–J).

Implants for Cardiovascular System

In cardiovascular system, oxygenated blood is pumped to the whole body by the heart through the network of blood vessels. Diseases or even life threats may occur due to heart failure or a change in blood. Therefore, monitoring the biomarkers in blood and heart diseases is significant.

The concentration of blood glucose is a critical parameter in blood; hence blood glucose monitoring is significant, especially in diabetics. The glucose concentration of the venous plasma is regarded as the gold standard for glucose measurement. Although conventional glucose self-monitoring devices based on single-use test strips has been widely applied to improve the life quality for diabetes patients, it still has limitations such as pain, failure in measuring at sleep, as well as problems in continuous monitoring. Consequently, continuous glucose monitoring (CGM) is considered to be an optimized approach to obtain the illness state of diabetics for management of diabetes and complications. As discussed previously, biofluids-based non-invasive painless wearable glucose sensors are capable of continuous monitoring, however, they are still less accurate compared to direct blood glucose monitoring. Therefore, in order to measure blood glucose continuously, implantable glucose sensors and microdialysis-type devices have been developed (Lee et al., 2018). Several commercial state-of-the-art CGM systems do exist however, containing a minimally invasive needle-type sensor to monitor the glucose in the ISF, as the glucose concentrations in the ISF are closely related to those in the blood, and most of them rely on enzyme-based electrochemical detection (Bobrowski and Schuhmann, 2018). The implantable glucose sensors are also accompanied by some difficulties, including a short lifetime, biofouling and poor biocompatibility.

Unfortunately, few invasive graphene-based glucose sensors have recently been reported. One recent study (Pu et al., 2018) proposed an inkjet printing based cylindrical flexible enzyme-electrode sensor for implantable CGM, to minimize signal drift and implement hypoglycemia detection. With the employment of a large surface area working electrode with 3D nanostructures consisting of graphene and platinum nanoparticles, the sensitivity was significantly enhanced with a detecting range of 0–570 mg.dL^{-1}. An *in vivo* rat experiment showed that this sensor was promising in implantable CGM in subcutaneous tissue, which is comparable with commercial glucometers, even under hypoglycemic conditions (Figures 9A,B).

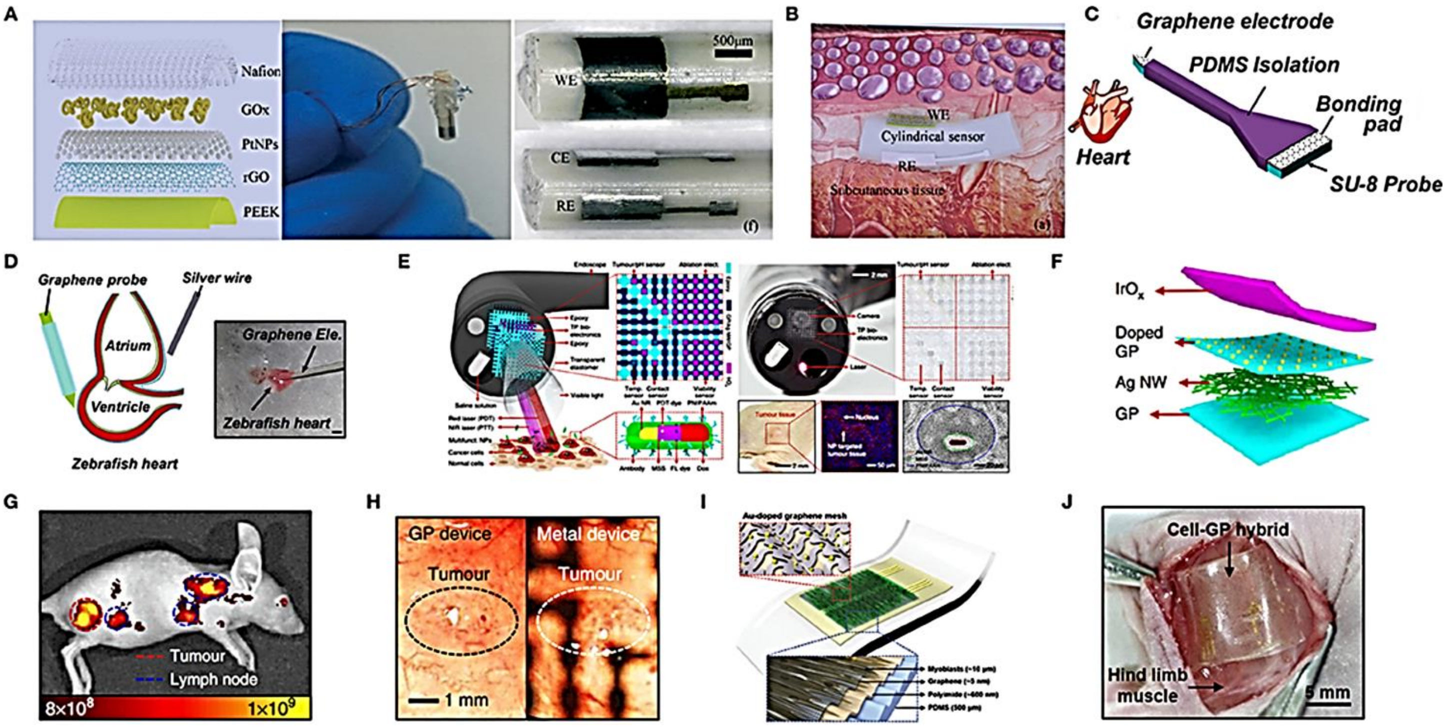

Figure 9. Other applications of invasive graphene-based sensors. **(A)** Schematic of the WE (left) and photos of the fabricated sensor (middle and right). **(B)** Schematic of implantable application of the flexible sensor in the subcutaneous tissue. Adapted with permission from Pu et al. (2018). **(C)** Schematic and optical micrographs of a flexible microprobe. **(D)** Schematic and actual view of the cardiac recording system for zebrafish. Adapted with permission from Chen et al. (2013). **(E)** Schematic illustrations and images of the multifunctional endoscope system based on transparent bioelectronic devices and theranostic nanoparticles. **(F)** Schematic illustration of the graphene hybrid in the exploded view. **(G)** Merged fluorescence image of the colon cancer on the mouse sub-dermis 6 h after intravenous injection of NPs. **(H)** Images of the tumor, captured by the camera of the endoscope through electronic devices (left: through transparent bioelectronic devices; right: through control metal devices). Adapted with permission from Lee et al. (2015). **(I)** Architecture of the stretchable and transparent cell-sheet-graphene hybrid. **(J)** Implantation of the cell-sheet-graphene hybrid onto target site of a nude mouse *in-vivo*. Adapted with permission from Kim et al. (2016).Heart failure is still a major public health problem, with a higher mortality rate than that of most cancers (Park et al., 2016a).

Heart failure is still a major public health problem, with a higher mortality rate than that of most cancers (Park et al., 2016a). As a primary organ of the cardiovascular system, heart activities can be recorded *in-vitro* and *in-vivo* for the early diagnosis and treatment of cardiovascular diseases. Until now, cardiac implanted devices including pacemakers and defibrillators, are capable of long-term sensing and pacing, diagnosis and treatment of rhythms and resynchronization, which can hardly be realized outside of the body (Freedman et al., 2017). Traditional pacing only activates the myocardium in leads, which may also face complications including lead failure, infection or tricuspid valve insufficiency (Bussooa et al., 2018). Leadless pacing is an alternative with a subcutaneous pocket and transvenous lead, which reduces complications (Merkel et al., 2017). Recently, electromechanical cardioplasty with an epicardial mesh has been employed to reconstruct cardiac tissue (Park et al., 2016a; Choi S. et al., 2018).

However, few studies are related to cardiac monitoring *in-vivo* with graphene-based electrodes. An early study (Chen et al., 2013) utilized steam plasma to treat the surface of a graphene-based flexible microprobe, which decreased the interfacial impedance, and thus high resolution and high SNR was obtained during neural and cardiac recording. The CVD prepared graphene electrode was in contact with a zebrafish heart to record the electrocardiographic signals. The signaling recording results exhibited that the QRS complex, *P* wave, and *T* wave were significantly increased in amplitude. The total noise of this microprobe was 4.2 μV_{rms} for hydrophilic the graphene-based sensor and 7.64 μV_{rms} for the hydrophobic graphene-based sensor (Figures 9C,D).

Implants for Digestive System

The digestive system supplies nutrients to the entire body, thus disorders of this system may lead to various associated diseases. the gastrointestinal tract is the largest structure of the digestive system and gastrointestinal diseases have become extremely common among the population (Yang N. et al., 2016). Minimally invasive surgical endoscopes with imaging and therapies are widely used to diagnose and treat gastrointestinal diseases. However, they lack spatial resolution in detecting and treating tiny cancers or other abnormalities. Thus, integrating electronic devices on the limited surface of cameras is required with transparent bioelectronics to avoid visual or light blockage. An early study (Lee et al., 2015) demonstrated a multifunctional endoscope system to diagnose and treat diseases like colon cancer, which contained graphene-based hybrid transparent electronic devices such as tumor, pH, viability, temperature sensors. Moreover, this closed-loop system contained radio frequency ablation as well as localized photo/chemotherapy, which could be utilized for colon cancer treatment *in-vivo*. This endoscope system enabled remarkable compatibility between the camera and the devices, accurate detection, delineation and fast targeted therapy (Figures 9E–H).

Implants for Locomotor System

The locomotor system provides the human body with the capability of movement through the muscular and skeletal systems. Accurate and continuous monitoring of EMG signals with instant feedback treatment is significant in diagnosing neuromuscular disorders, such as Duchenne muscular dystrophy and spinal muscular atrophy. Thus, one study (Kim et al., 2016) proposed a cell-sheet-graphene hybrid stretchable, transparent, implantable device with a high quality bio-interface to record EMG signals and stimulate muscles and nerves, which includes a sheet of C2C12 myoblast (~10 μm), Au-doped graphene mesh electrodes (~5 nm) with wrinkles, a polyimide (PI) membrane (~600 nm) and a PDMS substrate (500 μm). The cell-sheet-graphene hybrid with highly conductive Au doping graphene mesh electrodes was highly transparent, which could be employed to optically stimulate the modified muscle tissues. This device could be used *in vitro* for monitoring and stimulation of the C2C12 myoblasts. Moreover, *in-vivo* recordings of the EMG signals of hind-limb muscles in mice and electrical/optical stimulation of the implanted sites were applied without any immune reactions. This multifunctional device exhibited immense potential in soft bioelectronics (Figures 9I,J).

Challenges and Future Outlook

The focus of human healthcare has shifted gradually from hospitals to communities (families, individuals). Tremendous effort has therefore been devoted toward sensors and devices for health monitoring. Due to its unique features, including chemical and physical properties, graphene is extremely attractive for flexible electronics and sensors. In this review, recent achievements in graphene-based sensors for human health monitoring, including both non-invasive flexible wearable sensors and invasive devices have been reviewed. The graphene-based sensors have been explored to measure a wide range of vital signs and biomarkers of the human body, which are highly promising in the foreseeable future for applications in healthcare, personalized/preventive medicine, disease treatment, human-machine interaction, as well as brain computer interfaces. Novel structures have been employed to improve performance, while their sensing mechanisms and technological innovations were also thoroughly discussed.

Non-invasive wearable sensors are more acceptable and desirable in healthcare applications, as they are less invasive, and reduce risks while maintaining their function and performance. Public attitudes toward wearable devices have changed from curiosity to clinical-grade healthcare (Rogers et al., 2019). However, there is still a long way to go before meeting the requirements of medical devices. With the progress of materials and manufacturing techniques, implantable medical devices are becoming increasingly attractive, because of their capability in long-term real-time accurate monitoring of the state of tissues, organs, system, while also further providing guidance/assistants/prognoses for diagnosis and therapeutics, which gradually replace traditional portable and wearable devices. However, for implantable devices, several challenges such as biocompatibility, biofouling, as well as power supply should be solved. Transient/biodegradable electronics show immense potential in implantable applications, which can be degraded in a manner of controlled triggers and/or self-triggering without secondary surgeries or risks of infection. Furthermore, the exciting thing is that the highly dispersed GO sheets can be biodegraded by myeloperoxidase which is derived from human neutrophils, which may be employed in biodegradable electronics for implants (Kurapati et al., 2015). In general, sensors for human health monitoring, whether being invasive or non-invasive sensors, can be considered as an "augmented sense," which is an extension of human senses.

Considerable amounts of data will be generated with the development of sensor technologies and material science due to ubiquitous sensing ranging from the internet of things (IoT) to health care. Thus, statistical and computational methods, such as a range of machine learning techniques, can be utilized in data processing and effective information mining. Real-time data analytics capabilities are desired for robust data management (Paulovich et al., 2018). Ethical and moral issues in data collection, analysis and storage, particularly the data concerning personal health, must be properly resolved to protect personal privacy.

Although tremendous efforts have been devoted toward graphene-based sensors in recent years, a number of scientific and engineering challenges should be addressed before practical applications can proceed. For a start, human health risks such as the biocompatibility, biological toxicity, along with the environmental impact of graphene and its derivatives, need to be further assessed, especially in long-term *in-vivo* tests. Whole devices, with graphene as the core, are also required to be carefully checked. In addition, conformal, functional biotic/abiotic interfaces are crucial for robust sensing. Sensors on the epidermis and other organs with permeability to gases and moisture are desired. Moreover, high selectivity is required for multiple stimuli or ultra-low concentration biomarkers detection. The sensor may also be sensitive to stimuli other than the targeted stimulus to some extent, especially for integrated multifunctional sensors. For example, most sensors are affected by the environmental temperature floating. Crosstalk may exist in integrated multifunctional sensors, which can detect multi-signals simultaneously or separately. Long-term stability and mechanical durability are also demanded. Furthermore, integrated multifunctional sensors with feedback point-of-care therapy to construct a closed-loop system are significant in disease management. Power sources are essential for these devices, especially for implantable devices in long-term applications. Additionally, sensors combined with energy-harvesting technologies, such as triboelectrics nanogenerators (TENGs), photovoltaics, thermoelectrics, radio frequency (RF) and biofuel cells, are becoming a growing trend in the formation of self-powered systems (Liu et al., 2019). Finally, price and cost control are always an inevitable topic in commercialization. Therefore, cost-effective and facile fabrication methods with excellent uniformity should be developed for the large-volume high-throughput production of graphene and graphene-based sensors.

Each material has its unique advantages and limitations, and the requirements in different applications are also different, thus trade-offs are required. Although graphene provides a variety of distinctive characteristics in one, limitations also exist. First, a zero-gap structure of graphene results in the relatively low on/off ratio as FETs, which hinders its usability in biomedical applications. A possible way to open its bandgap is with functionalized organic molecules. Other attempts such as strain engineered lattice distortions, spintronics have also been explored. In addition, graphene is absent of selectivity toward target analytes of interest, owing to its excessive sensitivity to external stimuli. One possible approach to improve selectivity is to modify its surface with specific functional groups, bioreceptors or to cover it with a thin selective layer such as metal-organic frameworks (MOFs) (Tan et al., 2017). Furthermore, graphene has relatively low long-term stability induced by the moisture absorption and ultrathin nature. The solution may be to coat the surface with stable thin layer materials. Furthermore, the employment of graphene for functional devices in different applications requires a close integration with other functional materials; the intrinsic properties of graphene could be easily (usually negatively) impacted by these material integrations, device fabrication, and processing steps. Primary challenges including control, quality, scalability, and durability, should be resolved before commercially significant devices with graphene move forward.