elasticity of hydrogels plays an important role in controlling transport. Future opportunities may focus on the synergistic role of network elasticity and reversible interaction in independently controlling the transport of various biomolecules in hydrogels. Such fundamental knowledge may also aid in understanding the selective transport mechanisms employed in biological systems, such as sperm selection by mucus layers.

1.4.2 Electrochemical Design of Hydrogel-2D Material Interfaces

The other challenge faced by *in-situ* electrochemical biosensors is their inability to detect biological events in high ionic strength solutions, ubiquitous in body fluids [166, 175]. The presence of 0.9 wt% mobile ions (Na^+, K^+, Cl^-) in body fluids leads to significant screening of electrical fields, which greatly reduces the sensitivity of electrochemical detection. For instance, the Debye length for 2D sensing materials in body fluids is typically below 1 nm, making it almost impossible to detect proteins (typically around 10 nm) above the Debye length [168]. A potential solution is to engineer the interface between the hydrogel and 2D material to enhance the field-effect sensing performance. Recent studies have shown that surface-functionalized 2D materials can achieve a 10-fold increase in Debye length from 0.82 to 9.6 nm in high ionic strength solutions [170]. One possibility is to graft crosslinked polymer networks of hydrogels onto existing sensing materials and explore the potential of optimizing the network topology and charge density in hydrogels to push the limits of electrochemical properties such as Debye length, surface capacitance, and band gap.

1.5 Flexible Hydrogel Biobattery

A flexible biobattery is a device that converts low-grade energy within the human body into usable energy and is essential for developing self-powered *in-situ* bioelectronic devices [176–179]. Hydrogels are a promising material for use in these devices because they are porous and can modulate ion and electron transport while minimizing potential leakage compared to traditional organic aqueous electrolytes. Furthermore, hydrogels are biocompatible and soft, which reduces damage to surrounding tissues. However, the power outputs of flexible hydrogel biobatteries are still relatively low and do not meet the power requirements of most *in-situ* bioelectronic devices. Figure 1.10a shows the power range and operation time requirements of common biomedical devices [180]. To develop the next generation of self-sustaining *in-situ* bioelectronic devices, high-performing hydrogels must be leveraged to harness various forms of energy within the human body (Figure 1.10b). This potential remains largely unexplored but is highly desirable. This section will discuss recent efforts in exploring the potential of powering *in-situ* bioelectronic devices through mechanical, chemical, and thermal energy harvesters (Figure 1.10c).

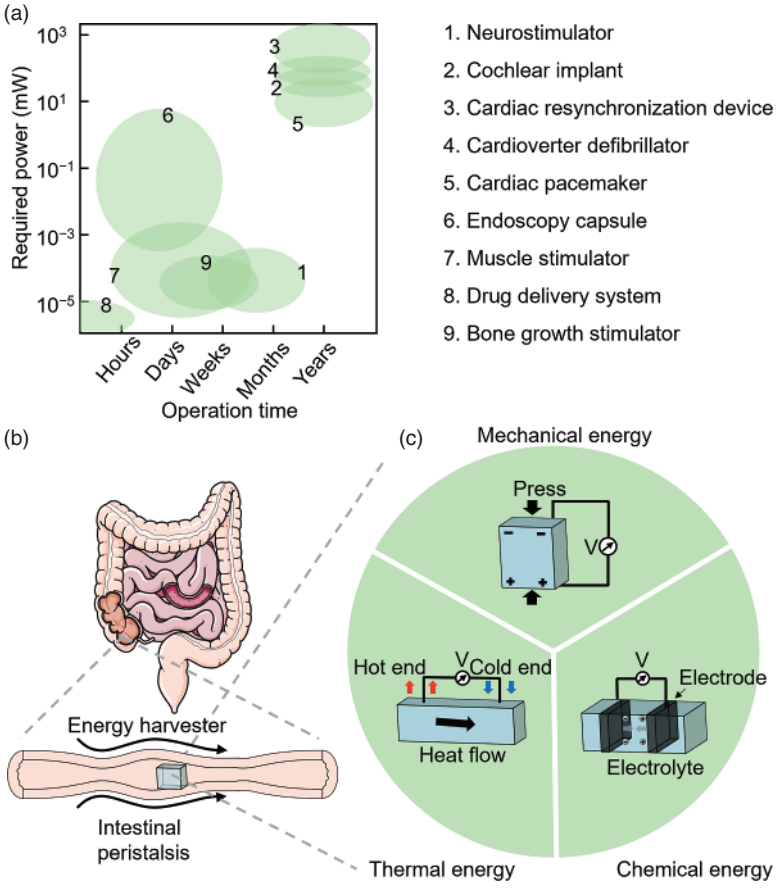

Figure 1.10 Flexible hydrogel batteries to self-power *in-situ* bioelectronic devices. (a) Examples of common implantable medical devices, with their required power supply and operation time (Source: Ref. [180]/Oxford University Press). (b) Schematic illustrations of the energy harvester working inside the intestine and (c) three forms of energy harvesting, including mechanical, chemical, and thermal energy, generated within the human body.

1.5.1 Mechanical Energy Harvester

Mechanical energy harvesters are devices that can convert the mechanical energy of the human body or organs into electrical energy for powering *in-situ* bioelectronic devices. One prime example of a mechanical energy harvester is the triboelectric nanogenerators (TENGs) [181–183], which generates an electrostatic potential difference between two materials of diverse polarities due to the triboelectric effect, causing a transfer of charges and the formation of an electric potential difference between them (Figure 1.11a) [177, 190–192]. Figure 1.11b presents a representative example of using ultrasound to induce vibrations and harness triboelectricity for in-body powering [184, 185]. Another way to harvest mechanical energy in the body is by leveraging the fluid-electro-mechanical coupling

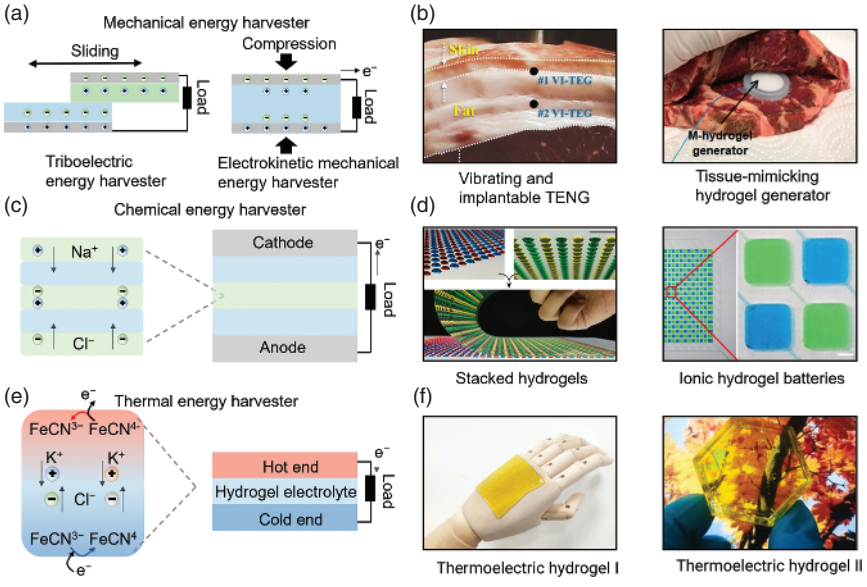

Figure 1.11 Schematic illustration of the working mechanism of (a) mechanical energy harvester with (b) examples (Source: Ref. [184] and Ref. [185]), (c) chemical energy harvester with (d) examples (Source: Ref. [186] and Ref. [187]), and (e) thermal energy harvester with (f) examples (Source: Ref. [188] and Ref. [189]. © 2022/Elsevier).

of electrokinetic streams in porous materials to generate electricity [193, 194]. Electrokinetic mechanical energy harvesters typically involve applying external forces, such as pressure, to drive the movement of micro-/nanofluidic water across a porous membrane, thereby causing the motion of ions to produce electricity. Unlike conventional TENGs, electrokinetic mechanical energy harvester can harvest low-frequency body motions while potentially producing high power output [195].

1.5.2 Chemical Energy Harvesters

Chemical energy harvesters are devices that convert chemical energy into electrical energy through chemical reactions in an electrolyte (Figure 1.11c) [196, 197]. These devices usually have two electrodes and an electrolyte, where the electrolyte acts as a mediator for the chemical reactions. The chemical reactions that occur between the positive and negative electrodes cause the flow of electrons within the electrolyte, thus generating electrical energy that can be used in the circuit. Hydrogel, with its watery nature, is an excellent carrier for chemicals, and acts as the electrolyte [198–200]. Drawing inspiration from the electric eel's power generation mechanism, Yang and Mayer and coworkers harnessed the gradients of ions in hydrogels to develop soft, flexible, transparent, and biocompatible hydrogel biobatteries, generating 110 V at open circuit or 27 mW/m^2 per hydrogel cell, which

is a significant achievement in the realm of electrochemical energy harvesting via hydrogels (Figure 1.11d) [186, 187]. Despite the abundant chemical reactions that occur within the human body (such as those that occur during digestion resulting in pH differences), there has been no significant progress in *in-situ* chemical energy harvesting. The main barriers are related to unstable ion concentrations and uncontrolled ion types in body fluids. The stability and size of the device are still the main challenges.

1.5.3 Thermal Energy Harvesters

Thermal energy harvesters using thermoelectric materials (Figure 1.11e), such as thermoelectric hydrogels, offer the potential to harvest low-grade body heat and power *in-situ* bioelectronic devices. These soft and biocompatible thermoelectric hydrogels are regarded as favorable alternatives to conventional thermoelectric materials [201–205]. Recent studies by Chen and Liu and coworkers have demonstrated a giant positive thermopower of 17 mV/K in an ionic thermoelectric hydrogel by harnessing synergistic thermo-diffusion and thermo-galvanic effects. The thermos-diffusion effect is dominated by the presence of ions (KCl, NaCl, and KNO_3), while the thermo-galvanic effect is governed by a redox couple $(Fe(CN)_6^{4-})/(Fe(CN)_6^{3-})$, also adopted in other thermoelectric hydrogels (Figure 1.11f) [188, 189]. While thermoelectric hydrogels have significant potential for *in-situ* bioelectronics, the low power output and poor mechanical properties of these materials remain key limitations. Overcoming these limitations through further research and development will be crucial to fully exploit the unique advantages of thermoelectric hydrogels in *in-situ* bioelectronics.

1.6 Concluding Remarks

Over the past few years, we have seen many exciting advances and examples in the field of *in-situ* hydrogel bioelectronics that suggest great potential of high-performing hydrogels for many important applications. We will conclude this chapter with a set of opportunities by integrating interdisciplinary efforts in various areas of *in-situ* hydrogel bioelectronics, including ingestible sensors, neural interfaces, miniature robots, and data analytics. Ingestible sensors are one area where hydrogel-based bioelectronics can be leveraged (Figure 1.12a). These sensors can be designed to be swallowed and pass through the gastrointestinal tract, allowing for noninvasive monitoring of various biomarkers in real time. With the integration of hydrogel-based sensors, these devices can provide more accurate and reliable data, as hydrogels can respond to changes in pH, temperature, and other environmental factors [32]. Neural interface technology is another area where hydrogel-based bioelectronics can be applied (Figure 1.12b) [206–209]. By using hydrogels as a platform for neural interfaces, these devices can be made more biocompatible and less invasive, reducing the risk of rejection or other complications. With the integration of hydrogel-based sensors and actuators, these

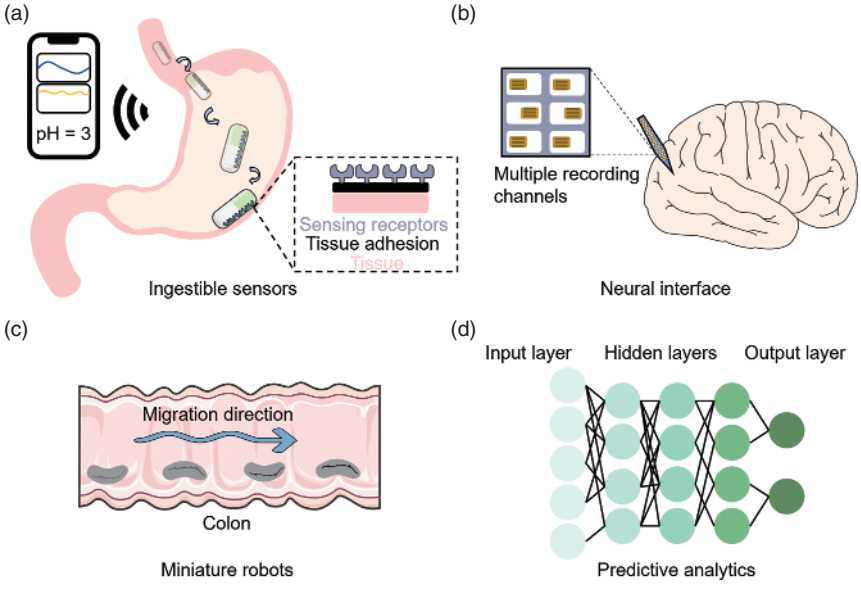

Figure 1.12 Future opportunities of *in-situ* hydrogel bioelectronics. Schematic illustrations of (a) ingestible sensors, (b) neural interfaces, (c) miniature robots, and (d) predictive analytics.

interfaces can provide more accurate and precise control over prosthetic devices or assistive technologies, allowing for more natural movements and interactions with the environment. Miniature robots are also an exciting area of research for *in-situ* hydrogel bioelectronics (Figure 1.12c) [210, 211]. With the use of hydrogels, these robots can be made more flexible and compliant, allowing for safer and more effective integration with the body. By incorporating hydrogel-based sensors and actuators, these robots can be controlled and manipulated to perform targeted drug delivery, tissue engineering, and surgical procedures. Finally, the integration of data analytics and machine learning algorithms is crucial for unlocking the full potential of *in-situ* hydrogel bioelectronics (Figure 1.12d) [212, 213]. With the vast amounts of data generated by these devices, there is a need for advanced analytics tools to help interpret and make sense of the data. By leveraging these tools, we can gain new insights into biological systems and develop more effective treatments and therapies.

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