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Functional Hydrogel Interface Materials for Advanced Bioelectronic Devices

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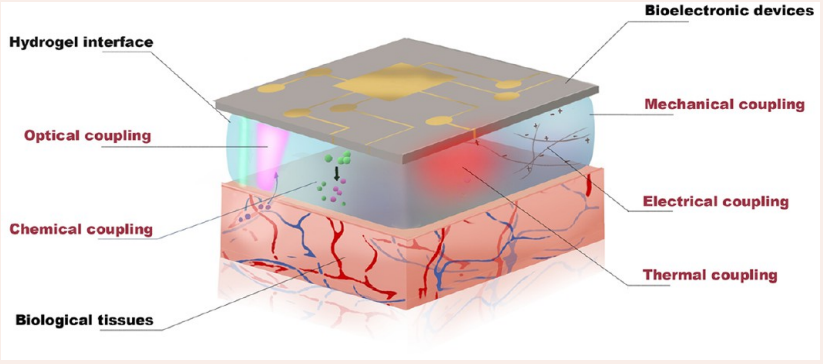

CONSPECTUS: A frontier area of modern research focuses on emerging classes of implantable bioelectronic devices with unique modes of operation that are relevant both to research studies and to medical practice. These advanced technologies have the potential to enable revolutionary diagnostic and therapeutic capabilities relevant to a wide spectrum of disorders, where seamless integration onto the surfaces of vital organs allows for accurate sensing, stimulation, or even concurrent sensing and stimulation. Materials for tissue-like interfaces, such as hydrogels, that enable soft mechanical coupling and multifunctional, bidirectional exchange between these technology platforms and living systems are critically important. Functional hydrogels offer significant promise in this context, as illustrated in recent demonstrations of interlayers that support optical, mechanical, electrical, optical, thermal, and biochemical modes of interaction, with chronic biocompatibility and stable function in live animal models.

This Account highlights recent progress in hydrogel materials that serve as interfaces between bioelectronics systems and soft tissues to facilitate implantation and to support sensing and stimulation. The content includes materials concepts, compositions, chemistries, and structures that allow for bioelectronic integration. Use as interfacial adhesives and as surface coatings to support mechanical, electrical, optical, thermal, and/or chemical coupling highlight the broad range of options. The Account begins with hydrogels that exploit advanced chemistries to control internal hemorrhage, prevent bacterial infections, and to suppress foreign body responses. Subsequent sections summarize strategies to exploit the mechanics of hydrogels, such as their mechanical, tunable modulus, lubricating surfaces, and interface adhesion properties, to facilitate interactions between bioelectronic and biological systems. Discussions of functional characteristics begin with the electrical conductivity of different types of conductive hydrogels and their long-time stability, with applications in bioelectronic sensing and stimulation. Following sections focus on optical, thermal, and chemical properties, also in the context of device operation. A final passage on chemistry outlines recently developed photocurable and bioresorbable hydrogel adhesives that support multifunctional interfaces to soft biological tissues. The concluding paragraphs highlight remaining challenges and opportunities for research in hydrogel materials science for advanced bioelectronic devices.

1. INTRODUCTION

Advanced implantable electronic/optoelectronic systems have the potential to offer revolutionary diagnostic and therapeutic capabilities relevant to a broad spectrum of diseases and disorders. Many such bioelectronic technologies require seamless integration onto the surfaces of vital organs, where the interfaces provide soft mechanical coupling and efficient electrical/optical/thermal/chemical exchange. Hydrogels represent an attractive class of interface material for such applications because they can (1) offer chemical and structural properties similar to those of biological tissues, (2) support chemical and physical interactions required for robust adhesive

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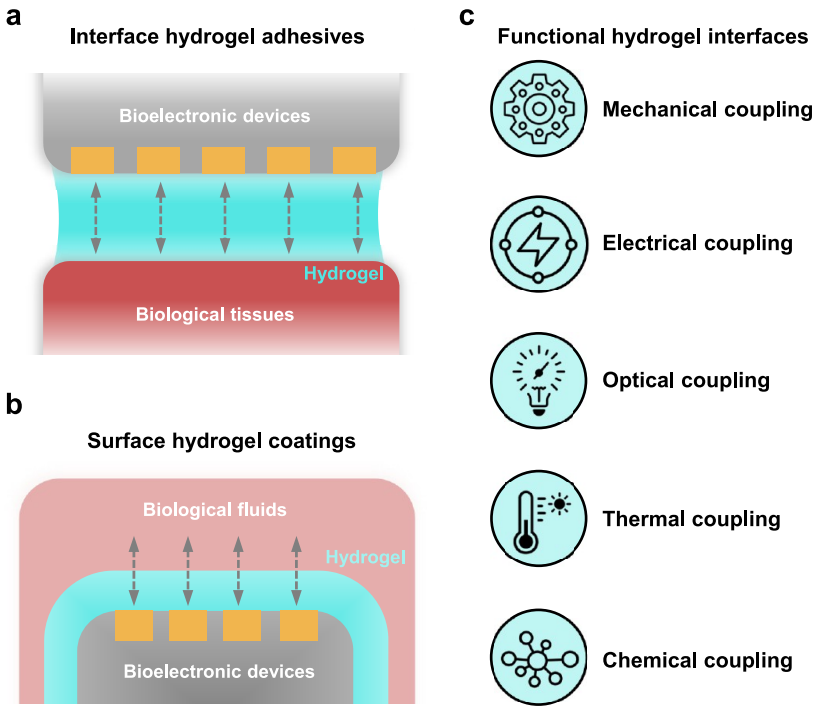

Figure 1. Functional hydrogel interfaces and coatings for advanced bioelectronics technologies. a, Schematic illustration of a hydrogel tissue/device interface. b, Schematic illustration of a hydrogel device coating. c, Functional hydrogels offer capabilities in mechanical, electrical, optical, thermal, and chemical coupling.

bonding, (3) enable functional, bidirectional interfaces, and (4) alleviate foreign body responses. Although recent work on hydrogels applied to living systems defines routes for achieving high electrical conductivity, strong interface adhesion, optical transparency, and stimuli-responsive properties, further study and optimization of these materials for advanced, implantable bioelectronic devices that meet specific operational requirements and lifetimes will likely lead to further opportunities and improvements in key characteristics.

This Account summarizes recent advances in hydrogels designed for bioelectronics interfaces of relevance to biological research and clinical medicine. The content focuses on two main schemes: (1) interfacial hydrogel adhesives that merge bioelectronic devices with biological tissues and support functional exchange between the two (Figure 1a) and (2) surface hydrogel coatings that encapsulate bioelectronic devices and efficiently couple them with surrounding biological fluids (Figure 1b). The content begins with a presentation of biocompatible characteristics of hydrogel interfaces, with a focus on systems that offer favorable mechanical properties and an ability to alleviate the formation of fibrous capsules. The following sections emphasize properties relevant to bioelectronics systems of various types with requirements for device fixation and multifunctional operation, including mechanical, electrical, optical, thermal, and chemical coupling with biological tissues. A final section describes these and other modes of exploiting hydrogel interfaces with emerging bioelectronic devices. Concluding remarks highlight some remaining challenges and opportunities for future research.

2. HEMOSTASIS AND BIOCOMPATIBILITY

Implantation of any type of device, including bioelectronic systems, can cause bleeding and inflammation,[1] with the possibility infections and adverse immune responses. Natural reactions can also lead to the formation of fibrous capsules that physically isolate the devices from the surrounding biology. Advanced hydrogel materials can provide immediate hemostatic, acute antibacterial, and chronic fibrous capsule-resistant effects that are beneficial in this context. For hemostatic function, a representative development is catechol-conjugated chitosan (CHI-C) hydrogel coatings (Figure 2a).[2,3] Partially cross-linked dry coatings of this type absorb blood and transform into thin adhesive hydrogel layers via an *in situ* solid-to-gel transition process, often resulting in a complete stoppage of bleeding. Antibacterial hydrogels include those that incorporate antibacterial agents as dopants as well as those that are inherently antibacterial.[4,5] Figure 2b presents a hyaluronic acid (CHA) hydrogel containing chlorhexidine (CHX) antibacterial for cardiovascular implantable electronic devices.[6] The CHX binds to the CHA network through electrostatic interactions that permit sustained release during an acute period after implantation. This material can efficiently reduce the probability of infection 1 week postsurgery when applied in a pacemaker pocket infection model.

The formation of fibrotic capsules can be minimized by using thin, mechanically compliant device designs in miniaturized geometries.[7] Eliminating nonspecific protein adsorption on the surfaces of such implants can further suppress the first steps in the processes of foreign-body reactions.[8] Hydrogels that offer such characteristics and support nonfouling properties can prevent recognition by macrophages and consequently resist the formation of fibrous tissues. Hydrogels based on zwitterionic materials, such as carboxybetaine, sulfobetaine, and phosphorylcholine chemistries, represent an emerging class of materials with ultralow biofouling properties due to the charge interactions on the surfaces (e.g., zwitterionic groups).[9] The solvation of the charged terminal groups, along with hydrogen bonds, forms a

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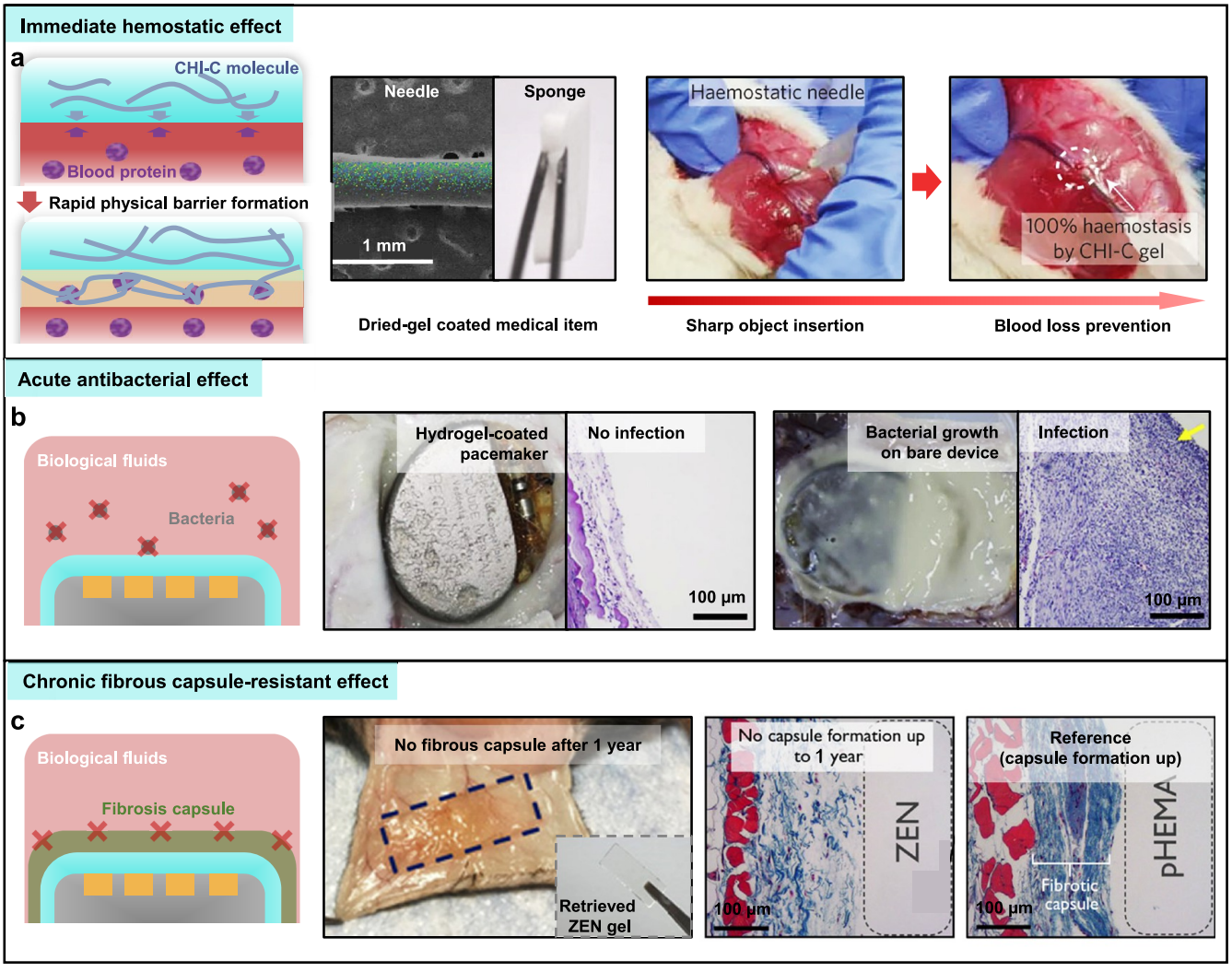

Figure 2. Hemostasis and biocompatibility provided by hydrogel interfaces. a, Immediate hemostatic effect. Reproduced with permission from refs 2 and 3. Copyright 2017 Springer Nature and 2021 American Academy for the Advancement of Science, respectively. b, Acute antibacterial effect. Reproduced with permission from ref 6. Copyright 2020 Elsevier. c, Chronic fibrous capsule-resistance effect. Reproduced with permission from ref 11. Copyright 2021 American Academy for the Advancement of Science.

hydration layer bound to resist nonspecific protein adsorption.[10] For example, zwitterionic hydrogel and elastomer hybrid films exhibit stable mechanical strength and resistance to fibrous capsule formation for up to 1 year after subcutaneous implantation in mice.[11] This behavior follows from the combination of two components contained in this material, poly(carboxybetaine) (pCB) hydrogel, which has a high swellability and hydrophilicity, and poly(sulfobetaine) (pSB) elastomer, which is the major component and provides elastic mechanical response. This zwitterionic hydrogel and elastomer hybrid film represents a promising antifibrotic encapsulation material for implantable bioelectronics.

Bacterial cellulose is another attractive hydrogel material for antifouling applications, attributed to the strong hydrophilicity of cellulose nanofibers. The surface microstructures may further interfere with surrounding cells. Pacemakers coated with bacterial cellulose hydrogel in microscale geometries on the surface alleviate fibrotic tissue formation with an average thickness reduction of 66% around the pacemakers after 12 months postimplantation in porcine models. This characteristic enhances the process of cardiac implantable electronic device exchange, upgrade, or revision surgeries.[12]

3. MECHANICAL PROPERTIES

Mechanical flexibility of the three-dimensional (3D) polymer network of the hydrogel and the amount of water content determine the bulk modulus and the surface lubricity. Interfacial bonding to bioelectronic devices and biological tissues rely on functional groups in the polymer. Hydrogels with tissue-like mechanical properties can serve as compliant, stable interfaces to soft living systems. Simple demonstrations include monitoring of deformations of biological tissues without significant mechanical constraint through the use of strain-sensitive circuits embedded into the hydrogel matrix.[13,14] Figure 3a shows a stretchable polyacrylamide-alginate-based double network hydrogel embedded with liquid metal as conducting elements in a hybrid device designed to record movements of the surface of a beating heart in a rabbit model.[15] These hydrogel microfluidic devices (modulus: ~30 kPa) interface with the cardiac tissues with little mechanical constraint (modulus: 10−50 kPa). The devices exhibit a linear dependence of resistance on strain up to 550%, with a gauge factor (GF) of ~0.5. To match the stiffness of ultrasoft tissues, such as brain cortex (~1 kPa), alginate hydrogels can be used,

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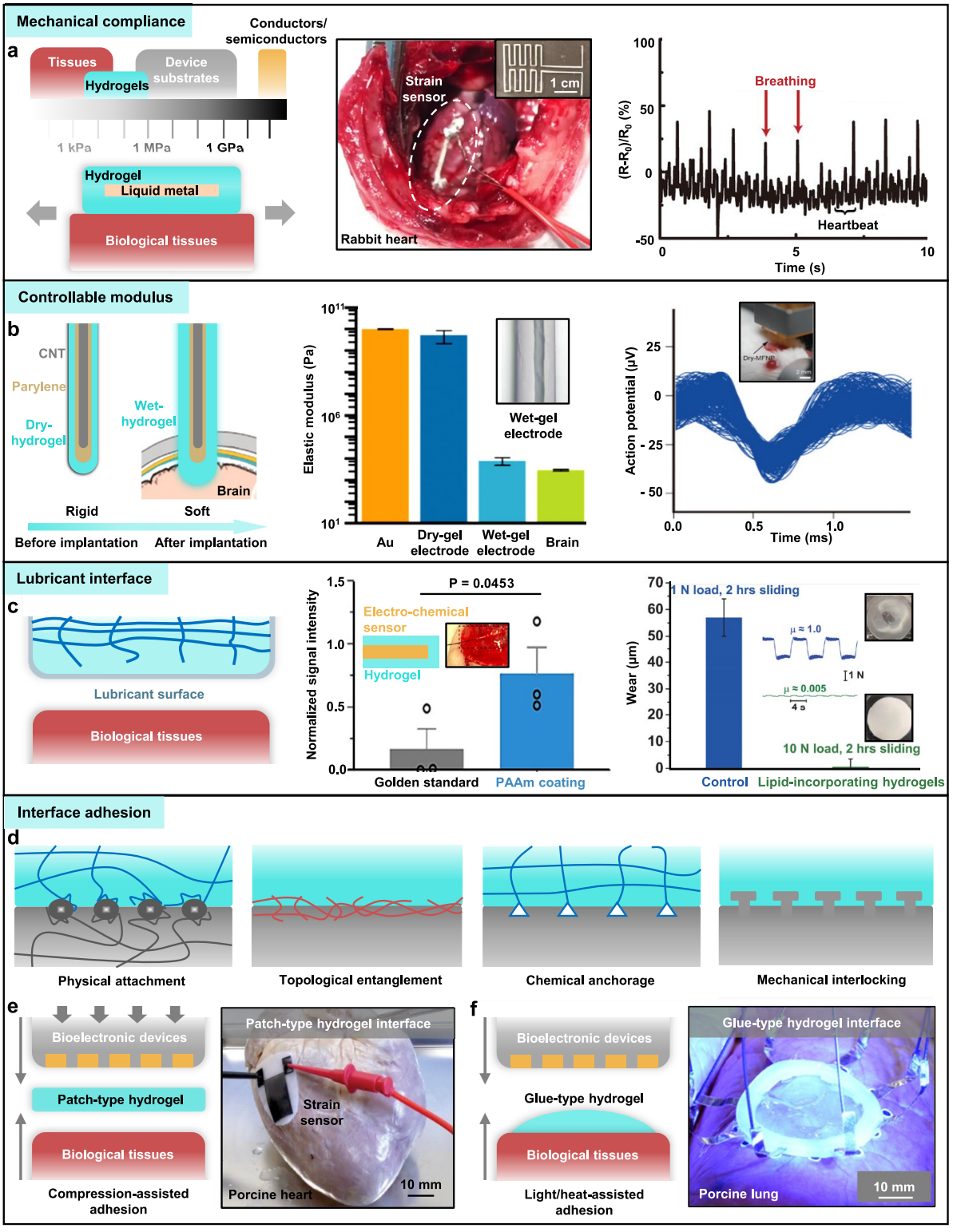

Figure 3. Mechanical coupling supported by hydrogel interfaces. a, Mechanically compliant hydrogel-encapsulated strain sensor for monitoring heart movements. The dry-state hydrogel has a high elastic modulus and allows for direct tissue penetration during implantation. After implantation, the hydrogel absorbs surrounding water and softens, as an adaptable interface that alleviates inflammatory responses and enables long-term monitoring of neuron signals. Reproduced with permission from ref 15. Copyright 2019 Wiley-VCH. b, Adaptable modulus before and after implantation for precise positioning and reduced inflammatory response. Reproduced with permission from ref 18. Copyright 2020 Royal Society of Chemistry. c, Lubricating hydrogel interface to reduce friction at the tissue interface and to prevent biofouling. Reproduced with permission from ref 22. Reproduced with permission from ref 23. Copyright 2020 American Academy for the Advancement of Science. d, Strategies for promoting adhesion of hydrogels to bioelectronics devices and tissue surfaces. e, f, Two approaches for initiating hydrogel adhesion during the application process. Compression-assisted patch-type hydrogels (e) and light/heat-induced glue-type hydrogels (f). Reproduced with permission from refs 27 and 31. Copyright 2019 Springer Nature and 2020 American Academy for the Advancement of Science, respectively.

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as demonstrated in encapsulating layers for a microelectrode array (electrode number, 8; dimensions, 700 × 700 μm; space, 800 μm). The carboxyl groups on the surface of the alginate hydrogels conjugate with the primary amines on the devices to form an ultrasoft encapsulation layer, with an elastic modulus of 0.1−10 kPa. This alginate material suppresses the responses of neurons to the microelectrode array, which presents minimal astrocyte activation and enhanced neurite spreading *in vitro*, and contributes to a high signal-to-noise ratio (∼17) *in vivo*.[16]

The modulus of these materials varies across a wide range from kPa to GPa, depending on water content. Engineered changes in the modulus achieved through control of hydration level can be exploited in procedures for device implantation.[17] Figure 3b shows a neural probe encapsulated with a calcium ion cross-linked sodium alginate (0.5 wt % Ca^{2+}) that exhibits a high modulus (∼10 GPa) in its initial dry state (water content: <1.5 wt %) to facilitate insertion into the brain followed by subsequent transformation into a low modulus (∼10 kPa; water content, >98 wt %) state after hydration by cerebrospinal fluid associated with the surrounding tissues postimplantation.[18] The low modulus minimizes the mechanical mismatch and, correspondingly, reduces the inflammatory response. Another example involves a soft polyacrylamide-alginate hydrogel matrix that integrates multiple fibers in a single platform capable of multifunctional sensing and actuation in the brain.[19] This system has a bending stiffness of 53 N/m in the dehydrated state, comparable to that of the reference polycarbonate fibers (103 N/m). The value decreases to 7 N/m after complete hydration by cerebrospinal fluid. The device enables monitoring of isolated single neuron potentials over 6 months in mouse models, with minimal inflammatory response.

Changes in volume associated with this process of hydration/dehydration can have utility in ingestible electronic devices. One example involves a commercially available telemetry temperature transmitter (DST nanoRF-T, Star-Oddi; length, 1.5 cm; diameter, 0.5 mm) that includes capabilities for wireless data communication using near-field communication (NFC) protocols, incorporated in a hydrogel structure.[20] The hydrogel contains superabsorbent particles (poly(acrylic acid)) that lead to high swelling speeds and ratios (∼160 times in volume within 5−10 min). A porous hydrogel as an encapsulating membrane (poly(vinyl alcohol)) maintains the mechanical stability of the system under repeated mechanical loads over 2 weeks *in vitro*. Such a device can be ingested as a standard-sized pill (diameter: 1−1.5 cm) that subsequently swells into a soft sphere in the stomach and records the gastric temperature for up to one month, as demonstrated in a porcine model.

Another attractive mechanical property of hydrogels is in their ability to lubricate surfaces via thin, interfacial layers of water.[21] Such layers can prevent the aggregation of platelets from the blood onto an underlying device (i.e., biofouling), thereby extending the lifetime for stable operation (Figure 3c).[22,23] In one case, a hydroxyethyl/diethyl polyacrylamide copolymer hydrogel coating on an implantable electrochemical sensor eliminates biofouling and improves signal levels significantly compared to those of probes without this type of coating after 5 days in a rat model.[22] This interfacial lubricating function can be enhanced via self-renewing, molecularly thin lipid-based boundary layers enabled by incorporating small amounts of lipids into the hydrogel matrix.[23] These lipid-based hydrogels reduce friction and wear by a factor of 100 relative to lipid-free hydrogels.

An additional mechanical characteristic of interest relates to adhesive bonding between the surfaces of bioelectronics devices and biological tissues. The adhesion mechanisms include physical attachment, topological entanglement, chemical anchoring, and mechanical interlocking (Figure 3d). Physical attachment follows mainly from electrostatic, van der Waals, and hydrophobic interactions, sometimes accompanied by hydrogen bonding. These noncovalent mechanisms apply to scenarios that do not demand strong adhesion (<10 J/m^2) or extended periods of operation. Nanoparticles at the interface can further enhance these bonds by physically adsorbing polymer chains from both sides due to hydrogen bonding.[24] Polymer chains adsorbed onto the nanoparticle surfaces can reorganize and dissipate energy under stress, to enhance the adhesion energy by retarding interfacial failure during the desorption or detachment process. Alternatively, if the surfaces exhibit some degree of porosity, the interpenetration of interfacial bridging polymers or hydrogels results in entanglements at the molecular level, which elicits hysteresis at the interface (10−400 J/m^2).[25] Chitosan is a representative bridging polymer that enables robust and repeatable adhesion without requirements for chemical functional groups of the joining surfaces.[25]

Chemical anchoring yields interfacial energies (up to 1000 J/m^2) that can be higher than those associated with such mechanisms of physical attachment.[26,27] A disadvantage is in requirements for specific hydrogel chemistries and chemical modifications of the surfaces of bioelectronic devices.[28] For example, grafted *N*-hydrosuccinimide (NHS) ester-activated functional groups in a hydrogel matrix can yield robust adhesive joints between tissues and electronic surfaces pretreated with primary amine functionalization due to the formation of covalent amide bonds.[27]

Patterning hydrogels into micro/nanoscale structures can also be effective in promoting adhesion. Specifically, surface architectures with hexagonal facets separated by interconnecting grooves that allow fluid exclusion at regions of contact with wet surfaces, and materials that support energy-dissipative dynamic ionic and hydrogen bonds, can lead to strong and reversible levels of wet adhesion (10−50 J/m^2).[29] These strategies can be exploited separately or in a combined collection to further enhance the bonding strength.

Independent of the mechanisms, hydrogel adhesives can be divided into two main categories defined by the process for their application. Patch-type hydrogels exist in cured and/or patterned forms prior to their application. Because the quality of bonding depends strongly on efficient surface contact, such patches are typically pressed against a contacting surface for several seconds or minutes to allow adequate time for the formation of physical or chemical bonds at the interface (Figure 3e). For example, certain hydrogels with interfacial bonding rely on the diffusion of bridging polymers into both sides formed by compression for at least 5 min *in situ*.[26] For uses in bioelectronics, this required compression can deform or damage fragile device structures or interfaced tissues.[30] Sliding at the interface during this period of application can also lead to bonding failure. One recent improvement utilizes carboxylic acid groups on the hydrogel surface to form temporary cross-links with tissues through hydrogen bonds and electrostatic interactions with compression for only ∼5 s, followed by covalent cross-linking between NHS ester groups on the

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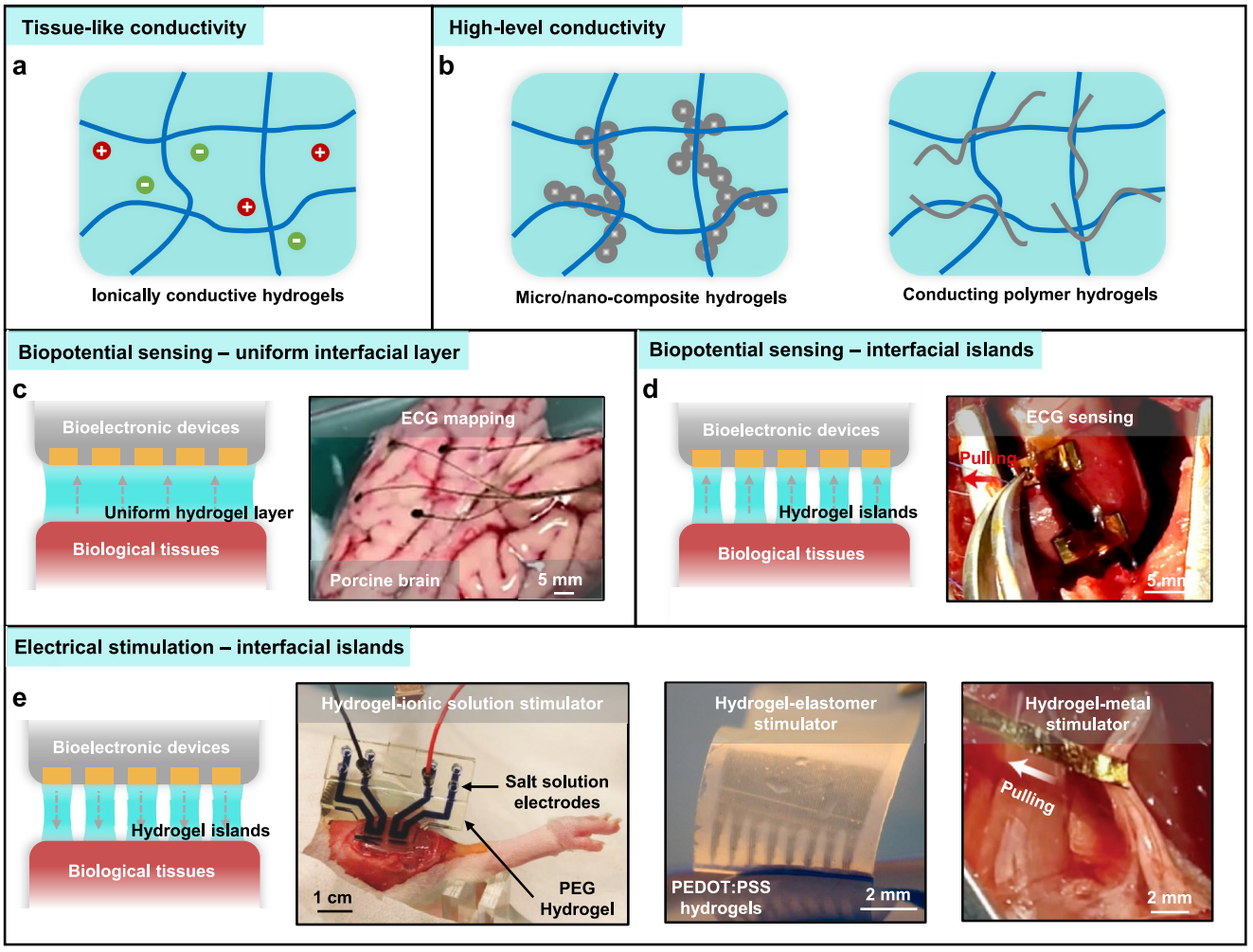

Figure 4. Electrical coupling supported by hydrogel interfaces. a, b, Engineered hydrogels that enable tissue-like ionic conductivity (a; ionically conductive hydrogels) and combined ionic and electronic conductivity (b; micro/nanocomposite hydrogels and conducting polymer hydrogels). c, A uniform interfacial hydrogel layer with tissue-like conductivity that enables electrophysiological mapping across the epicardium with a multielectrode array. Reproduced with permission from ref 38. Copyright 2019 Springer Nature. d, Hydrogel islands with high conductivity for electrophysiological sensing between discrete electrodes and the epicardium. Reproduced with permission from ref 39. Copyright 2021 Springer Nature. e, Hydrogel islands with high conductivity for electrical stimulation of muscles and nerves. Reproduced with permission from refs 13, 35, and 39. Copyright 2018 Wiley-VCH, 2019 Spring Nature, and 2021 Springer Nature, respectively.

hydrogels and primary amine groups on the tissues after several minutes.[27]

The second type of hydrogel applies as a liquid that subsequently transform into a solid form *in situ* and *in vivo* process of with or without exposure to light or mild heat (Figure 3f).[30−32] The chitosan-based hydrogel adhesive is a representative example of a material that allows *in situ* adhesive formation without exposure to light or heat.[32] For liquid-type systems, the viscosity of the uncured state is critically important, to allow controlled, patterned delivery without unwanted flowing and spreading to adjacent areas. One example utilizes high molecular weight polyacrylamide (5000 kDa) as a rheology modifier in a mixture with acrylamide monomer precursors to enable an initial viscosity of 10−40 Pa·s, before free radical polymerization.[31]

4. ELECTRICAL PROPERTIES

Many types of bioelectronic devices demand efficient electrical coupling to adjacent tissues for electrophysiological sensing or stimulation. Introducing electronically or ionically conductive components into the hydrogel network can yield desired levels of field or current coupling for such purposes. Ionically conductive hydrogels utilize mobile ions in the hydrogel matrix to achieve conductivities in ranges similar to those of biological tissues (Figure 4a; conductivity: 0.1−10 S/m).[33] High salt concentrations in the hydrogel matrix can, however, lead to biocompatibility concerns. Alternative approaches involve micro/nanocomposites that rely on a hydrogel matrix (Figure 4a). For example, polyacrylamide-alginate hydrogels embedded with silver flakes (concentration: ∼5 vol %) can achieve conductivities of >35000 S/m while maintaining tissue-like mechanical properties (modulus: <10 kPa; stretchability: >250%).[34] A reduced graphene-polyacrylamide hydrogel exhibits a conductivity of 10^4 S/cm and a Young's modulus of 50 kPa. In experiments on enhancing myogenic gene expression, the material supports stable electrical stimulation of myoblasts for 7 days.[40] Conducting polymers, such as poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS), can also significantly improve the conductivity of the hydrogel matrix. PEDOT:PSS hydrogel electrodes (thick-

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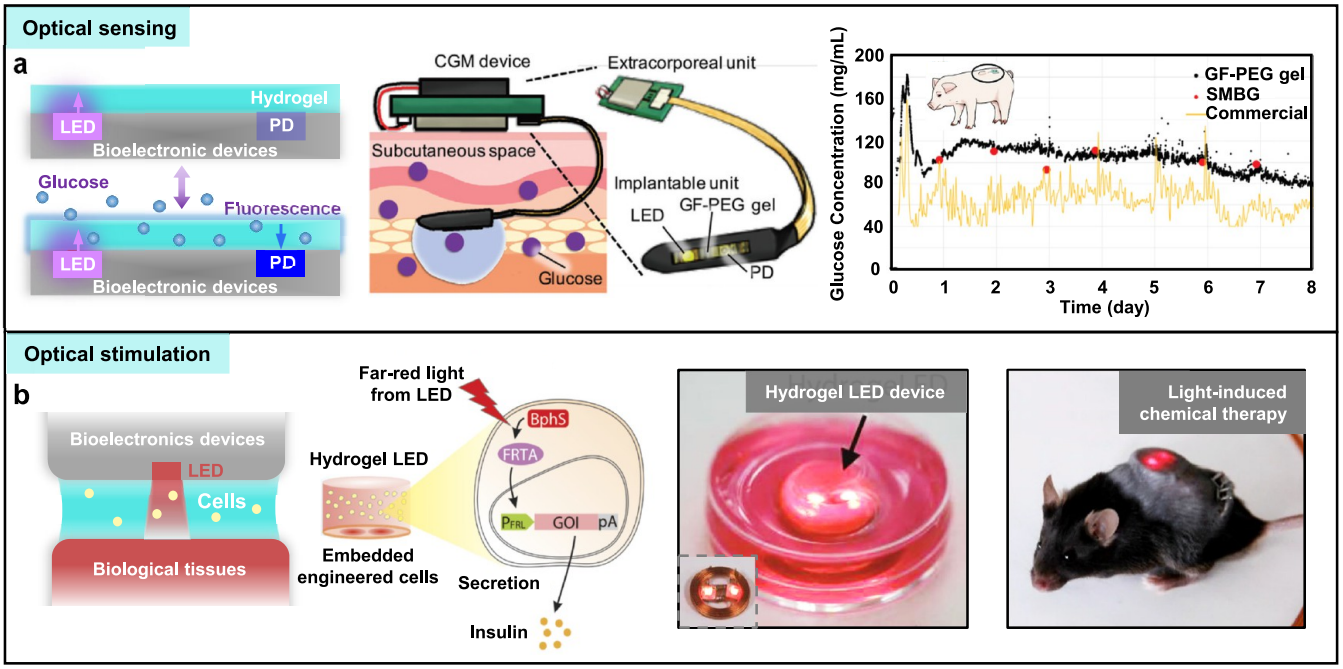

Figure 5. Optical coupling supported by hydrogel interfaces. a, Glucose-induced changes in fluorescence intensity from a hydrogel for continuous monitoring of glucose concentration. A light-emitting diode (LED) excites a glucose-responsive fluorescent dye (GF-dye) immobilized in the polyethylene glycol (PEG) hydrogel and triggers the fluorescence of the GF-dye in the presence of glucose. The fluorescence intensity is related to the glucose concentration and can be detected by a photodiode (PD). The hydrogel is transparent, thus allowing optical measurements of glucose concentration in this manner. Reproduced with permission from ref 42. Copyright 2021 Wiley-VCH. b, High light transmission through a hydrogel for light-induced chemical therapy. Reproduced with permission from ref 44. Copyright 2017 American Academy for the Advancement of Science.

ness: 100 μm) with a conductivity of 47.4 S/cm and Young's modulus of 30 kPa can provide sciatic nerve electrical stimulation in mice for 6 weeks, with minimized damage and inflammation response of the neural tissue compared results from a sham group with plastic cuff electrodes.[35]

The simplest form of electrical coupling interface involves a uniform layer of hydrogel between electrodes and a targeted tissue (Figure 4c).[36,37] Hydrogels that have tissue-like conductivity allow for spatially resolved biopotential sensing and local electrical stimulation, with efficient electrical coupling but without significant effects of shorting between adjacent electrodes even for uniform, unpatterned layers of a hydrogel.[30] For sensing, a recent study reports a system that embeds an array of PEDOT-modified carbon fabric electrodes (number: 2; diameter: 5 mm; spacing: 2 mm) into two uniform layers of poly(vinyl alcohol) (PVA) hydrogel as a sandwich structure.[38] Such PVA hydrogel interfaces include 88 vol % saline solution, which supports tissue-like ionic conductivities (0.3−0.5 S/m at 1 kHz). The impedances for tissue interfaces are similar to those of Pt electrodes at 1 kHz, and high signal-to-noise ratios of 20 and 30 dB in rat and porcine brains, respectively, for electrocorticography (ECoG) monitoring.

Hydrogels that possess conductivities significantly higher than those of biological tissues must be patterned into island structures aligned with the electrodes to avoid shorting between them (Figure 4d).[39,40] One case exploits graphene-based hydrogel composites (conductivity: 2.6 S/m) formed into islands at locations between gold electrodes (number: 2; dimensions: 1.3 mm × 2 mm; thickness: 20 μm; spacing: 5 mm) and epicardial tissues.[39] The device allows stable ECG recordings without significant baseline shift or high-amplitude noise on day 0 and day 14 postimplantation in rat models. The high signal-to-noise ratio follows from the low impedance at frequencies relevant to brain activity, resulting from the large double-layer capacitance of the PEDOT-modified carbon fabric hydrogel electrodes, and minimized contact impedance due to the ultrasoft PVA hydrogel substrate. The shape conformability of the hydrogel electrode enables tight adhesion even to the curved, grooved surfaces of the brain, thereby suppressing baseline shifts.

Such types of conductive hydrogel islands are particularly attractive for electrical stimulation (Figure 4e). Experiments that use high concentrations of salt solutions introduced into the hydrogel matrix as efficient electrodes have the ability to stimulate rat tibialis anterior muscles.[13] Alternatively, PEDOT:PSS mixed into hydrogels can offer remarkably low impedance electrical interfaces, with a current-injection density that can be ∼30 times higher than that of platinum electrodes.[35] The results allow low-voltage electrical stimulation (∼50 mV) of peripheral nerves, as demonstrated in mouse models. Hydrogels with graphene fillers offer similar electrical stimulation capabilities, in experiments on sciatic nerves in rat models.[39] Current progress is limited to short-term animal trials for device validation; continuous electrical monitoring and treatment for days and weeks to months require further attention and validation through chronic studies. Challenges can arise from chemical instabilities and performance inconsistencies at the hydrogel interfaces.

5. OPTICAL PROPERTIES

For optoelectronic devices, interfaces with relevant optical properties are essential. Nearly all hydrogels are transparent, as an attractive feature in this context. The optical properties can be tailored for specific requirements by controlling the chemical structure, molecular weight, and cross-linking density.

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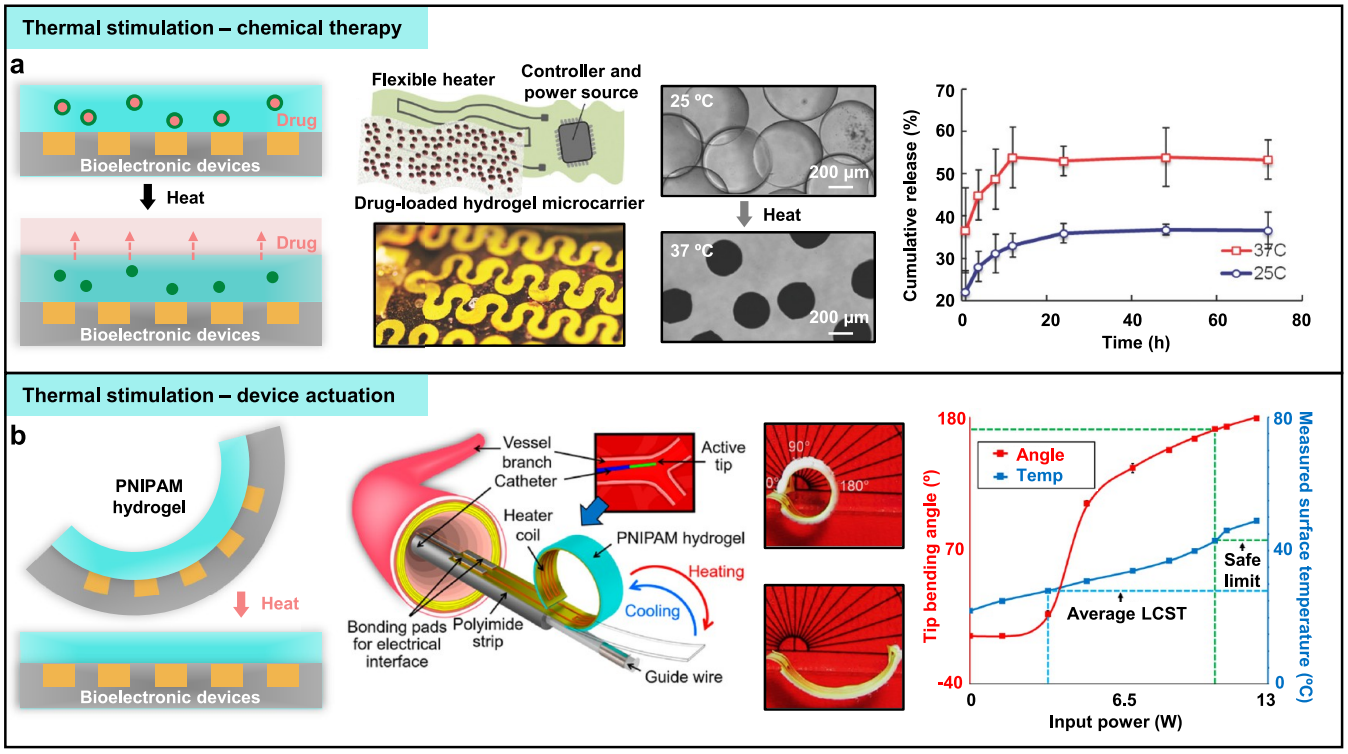

Figure 6. Thermal coupling supported by hydrogel interfaces. a, Thermoresponsive hydrogel with an integrated thin-film heater for on-demand delivery of drugs and growth factors. Reproduced with permission from ref 47. Copyright 2016 Wiley-VCH. b, Uniform layer of a thermoresponsive hydrogel as the basis for bimorph thermal actuators in catheters that can be maneuvered to a target vessel branch. Reproduced with permission from ref 49. Copyright 2020 Molecular Diversity Preservation International.

Transmission losses are typically less than 1 dB/cm in the visible light spectrum. Conformal contact to the light source (commercial optical fiber or LEDs) with robust adhesion facilitates optical coupling with low loss.[19] Furthermore, fluorescent dyes sensitive to physiological parameters, such as glucose and pH (Figure 5a),[41] can be immobilized in surface hydrogel coatings, where they can interact with ions, molecules, and proteins in the biological environment as the basis for sensing. One study reports a scheme for measuring glucose concentration in rat and pig models using a wireless implantable device that incorporates a glucose-responsive fluorescent dye into a four-arm polyethylene glycol hydrogel (GF-PEG-gel).[42] The GF-PEG-gel mounts on top of a light-emitting diode (LED) and a photodiode (PD) for excitation and fluorescence detection, respectively. The hydrogel effectively mitigates foreign body reactions and suppresses fibrous capsule formation based on mechanisms described previously, thereby minimizing any diffusive delays in sensing. Such hydrogel-integrated devices can detect glucose concentrations in a diabetic rat model for 45 days, with an accuracy (average of absolute error: 11.8%) better than that of a representative commercial glucose monitoring device (average of absolute error: 14.6%).

In addition to applications in optical sensing, the transparency of hydrogels can be exploited for purposes of optical stimulation. Recent studies report that hydrogel-based optical fibers designed to deliver light into the primary motor cortex in mouse models can be used for chronic optogenetic forms of neuromodulation.[43] Fully swollen polyacrylamide-alginate hydrogel fibers possess low propagation loss (0.249 dB/cm) in the spectral range of interest (blue light in this case) for light-evoked, frequency-dependent responses of hippocampal neurons. An interesting additional example embeds optoelectronic devices and optogenetically modified cells in a hydrogel interface for controlled optical and drug therapy. Figure 5b shows a hydrogel-encapsulated device that includes wirelessly controlled far-red LEDs and engineered cells to control the release of insulin produced by these cells.[44] The result supports glucose homeostasis in diabetic mouse models over several weeks, where the intensity and duration of light from the LEDs serve as the control mechanism. Long-term stability in these optical properties can, however, be influenced by chemical exchange with biological fluids and mechanical effects associated with swelling in vivo. An additional cladding layer may be used to mitigate such effects.

6. THERMAL PROPERTIES

Thermal characteristics of hydrogels, and specifically the physical chemistry of their response to changes in temperature, can also be important in functional interfaces for implantable devices. Reversible and dramatic changes in dimensions of thermal-responsive hydrogels occur as a result of their temperature-triggered interaction between chain moieties and the surrounding water, which causes water uptake/release in hydrogels. The most common system of this type is poly(*N*-isopropylacrylamide) (PNIPAM)-based hydrogels.[45] Above the lower critical solution temperature (LCST), the hydrogels tend to shrink and precipitate from an aqueous solution due to weakened interchain hydrogen bonding, where changes in volume can be as large as ~40%.[46] The hydrogels return to their fully hydrated state when the temperature is below the LCST, relying on the solvation of the amide groups by the water molecules. Emerging uses of thermoresponsive hydrogels in bioelectronics focus on controlled drug delivery and

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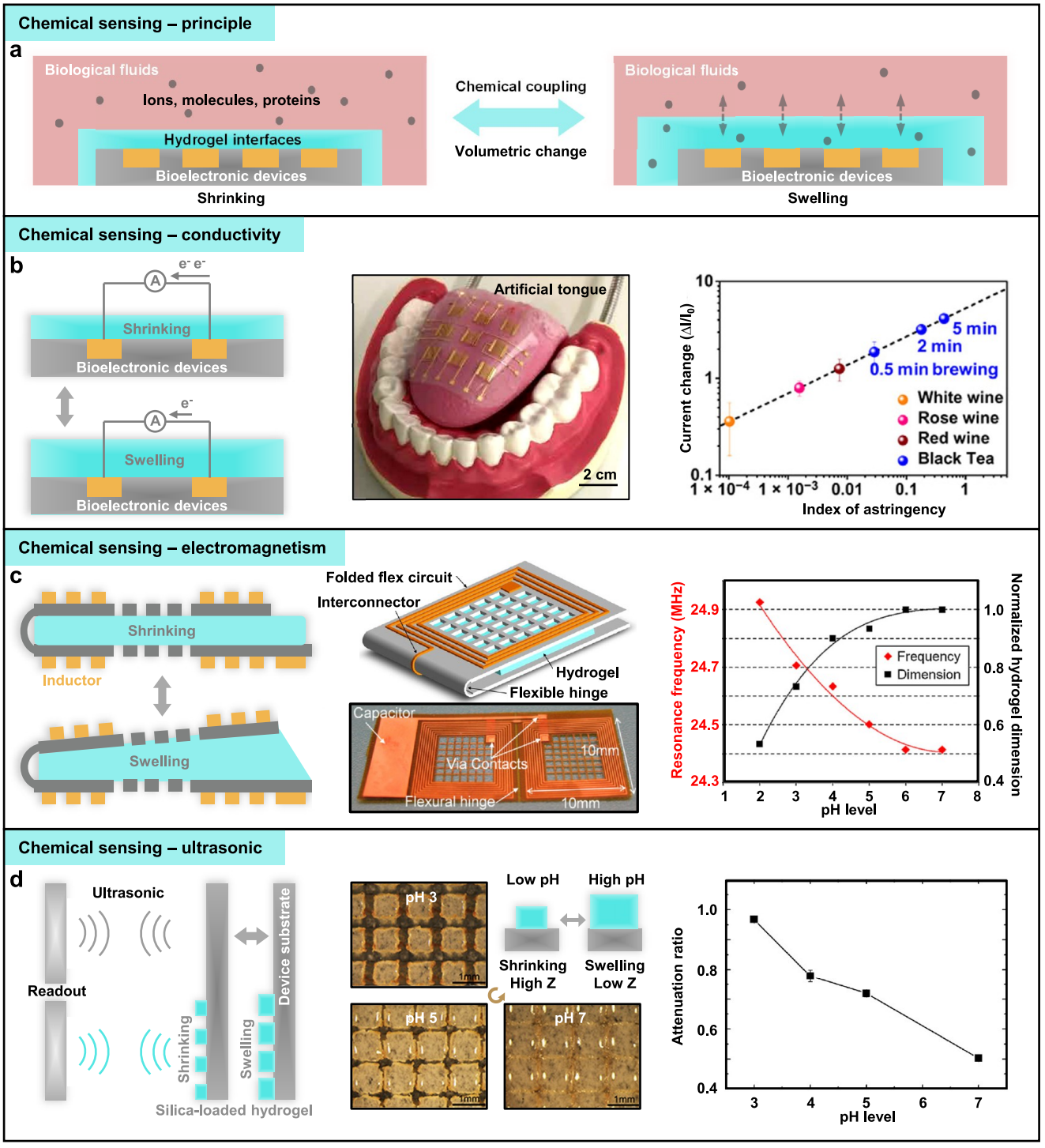

Figure 7. Chemical coupling supported by hydrogel interfaces. a, Chemical coupling leads to a volumetric change in hydrogel interfaced bioelectronics. b–d, Volumetric changes lead to changes in conductivity as the basis for resistive sensing (b), changes in electromagnetism as the basis for wireless passive LCR sensing (c), and changes in ultrasonic attenuation as the basis for sensing with ultrasound (d). Reproduced with permission from refs 51, 53, and 56. Copyright 2020 American Academy for the Advancement of Science, 2009 Elsevier, and 2020 Frontiers, respectively.

electrothermal surgical manipulation. For example, Figure 6a shows a drug-loaded PNIPAM surface hydrogel coating that integrates a flexible thin-film heater for wireless, on-demand delivery of drugs and growth factors.[47] In this case, shrinkage that occurs above the LCST leads to the release of penicillin/streptomycin/vancomycin antibiotics or vascular endothelial growth factors. These agents increase the deposition of granulation tissue in the wound bed compared to controls by more than three times and accelerate the chronic diabetic impaired dorsal wound healing in a mouse model. Similar dimensional changes can be exploited for mechanical actuation and controlled deformation of bioelectronic devices (Figure 6b). Combining compliant electrode arrays in open, serpentine mesh layouts with PNIPAM hydrogels yields a class of soft

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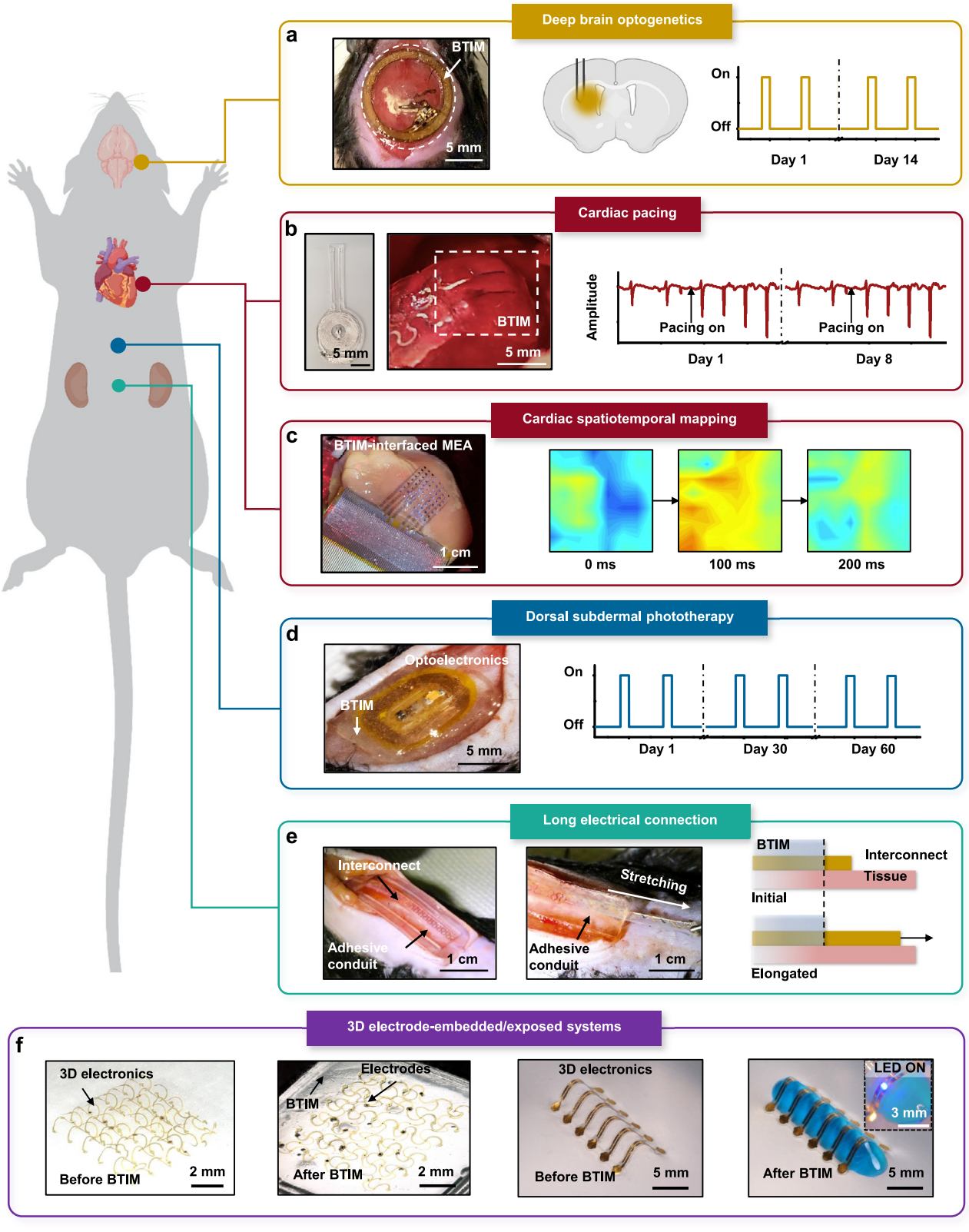

Figure 8. Multifunctional hydrogel interfaces for advanced implantable bioelectronics systems. Hydrogels as interfaces for multifunctional electronic/optoelectronic devices, with robust adhesion to dermal, neuronal, and cardiac tissues for several days to months. a, Wireless, battery-free deep brain optoelectronic stimulators. b, Wireless, millimeter-scale cardiac pacemakers. c, High-density flexible epicardial multielectrode arrays. d, Wireless subcutaneous phototherapeutic devices. e, Hydrogel adhesive tunnels for long interconnects/cables. f, Hydrogel-integrated 3D electrode-embedded and electrode-exposed electronic systems. Reproduced with permission from ref 30. Copyright 2021 Springer Nature.

actuators, capable of complex and programmable three-dimensional shape transformation.[48] Use of PNIPAM applied onto the tip of a medical catheter with a thin-film metal heater[49] enables active, steering across a wide range of bending

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angles for maneuvering through complex vascular networks to target regions of interest. Another class of thermal functionality involves evaporative cooling. Commercially available hydrogel dressings possess cooling effects due to water evaporation, which occurs rapidly upon application on the skin (15−30 s). Such hydrogel pads have potential for various additional applications.

7. CHEMICAL PROPERTIES

Further functionality of hydrogels relevant to bioelectronics follows from their capability for converting chemical stimuli, such as changes in concentrations of ions, molecules, and proteins, into volumetric changes (Figure 7a).[50] Recent progress utilizes surface hydrogel coatings to create corresponding changes in conductivity or capacity in an electrical sensing element,[51,52] or in electromagnetic properties in a wireless module,[53,54] or in the attenuation ratio associated with ultrasonic interactions.[55,56] Examples of the first mode of interaction involve chemiresistive ionic hydrogels integrated onto flexible interdigital electrodes as the basis for a soft artificial tongue (Figure 7b).[51] Exposure to astringent compounds leads to the formation of hydrophobic aggregates that transform the hydrogel from a microporous network into a hierarchical micro/nanoporous structure with enhanced ionic conductivity. This change in conductivity can be detected by the underlying electrodes.

The resulting device offers a sensing range for tannic acid detection in aqueous solution from 0.0005 to 1 wt %, which is comparable to the human taste receptor. The second mode of interaction can be exploited in passive wireless sensors that rely on chemical-sensitive hydrogels incorporated into inductor-capacitor-resistor (LCR) resonators (Figure 7c).[53] A pair of coplanar dual spiral coils sandwich a layer of hydrogel for wireless pH sensing through magnetic resonance coupling. The chemical-sensitive poly(vinyl alcohol)-poly(acrylic acid) hydrogel in between modulates the distance between the coils and consequently the inductance and resonance frequency of the device.

Other strategies for wireless sensing rely on ultrasonic waves. Figure 7d presents an example of the former, enabled by a silica-nanoparticle-embedded hydrogel on a thin glass substrate.[56] Volumetric changes caused by environmental stimuli alter the concentration of the silica scattering agents and thus the attenuation coefficient for the ultrasound. By considering changes in attenuation coefficient and hydrogel dimensions, a linear relationship can be established between the lateral expansion of the hydrogel and the pH value. Benchtop experiments with this system in a water tank demonstrate sensing distances of 10 cm with ultrasonic intensities (200 mW/cm^2) that are several times below limits set by the FDA (720 mW/cm^2), with a resolution of 0.2 pH units. One limitation of these and other types of responsive hydrogel sensors is in relatively slow response speeds (seconds to minutes) associated with diffusive transport of chemical species or heat.

8. HYDROGELS IN MULTIFUNCTIONAL BIOELECTRONIC SYSTEMS

Active areas of research focus on the integration of the sorts of functional hydrogel materials described in previous sections with implantable bioelectronics platforms for continuous diagnosis and therapy. The most advanced systems include miniaturized battery-free wireless communication moduli,[57] closed-loop feedback controls,[58] ultrathin/soft sensing/stimulation units,[59] mechanically compliant interconnects,[60] and physically transient/bioresorbable forms.[61] Hydrogel interfaces between such technologies and living tissues can provide mechanical coupling and functional exchange. Key materials design considerations include (1) robust adhesion not only to biological tissues but also to electronics surfaces, (2) minimally invasive processes for application and activation, (3) general utility across diverse classes of technologies, including those that adopt three-dimensional layouts and/or complex surface features,[62] (4) appropriate levels of electrical conductivity and/or light transmission to enable functional electronic and/or optical exchange between devices and tissues,[63] and (5) bioresorbability with rates that match use cases in temporary implants for diagnostic or therapeutic purposes.[64]

Recent work focuses on the development of bioelectronic/tissue interface materials (BTIMs) with these features.[30] One example from our group combines photocurable covalent networks, formed by PEG-LA-DA macromers cured via free radical polymerization, with alginate networks ionically cross-linked by calcium ions that quickly form upon application onto tissue/electronics surfaces. The resulting material has a honey-like initial viscosity (2−3 Pa·s) to allow it to flow and conform to complex devices and tissue surfaces. The chemical designs in the hydrogel matrix support robust bonding to the biological tissues and bioelectronics *in situ*. Conformal coverage across complex tissue/electronics surfaces enables use as encapsulating coatings, interfacial layers, or supporting matrices, to address various applications. The polymerization of the PEG-LA-DA covalent network under ultraviolet (UV) exposure (wavelength: 365 nm; density: 20 mW/cm^2; duration: 3 min) allows for a liquid−solid transformation and bonding without the application of force, thereby facilitating surgical processes and reducing the potential for tissue damage or excessive deformations of fragile tissues or delicate electronic devices.

The PEG-LA-DA of the BTIM with high molecular weight (35 kDa) enables optical transparency and, therefore, optical exchange between optoelectronic devices and biological systems. The transmittance of the samples (thickness: 2 mm) is between 60 and 80% for wavelengths between 395 and 475 nm and remains higher than 80% between 475 and 900 nm. The ionic conductivity, which arises from transport of Ca^{2+} and Cl^- ions in the sodium alginate network, is in the range of ∼0.5 S/m at 1 kHz, similar to that of most biofluids. Additionally, the BTIM can resorb entirely in the body due to the hydrolysis of the lactide in the backbone aided by enzymatic reactions and the surrounding biofluids at well-defined rates, which can be tuned from ∼20 days to several months in PBS (pH 7.4) at 37 °C determined by the lactide numbers in the backbone, thereby addressing opportunities in temporary implants.

Figure 8 presents demonstrations with various types of electronic/optoelectronic devices interfaced to the surfaces of different vital organs, with optical and electronic models of stimulation and measurement in live animal models, from days and weeks to months. Examples include battery-free optoelectronic platforms that wirelessly deliver light stimuli to regions of the deep brain (Figure 8a) or subcutaneous tissues (Figure 8d), stably and without inciting inflammation. In other experiments, the BTIM forms adhesive "tunnels", or conduits, for interconnects/cables that join different components of implantable devices to span large distances across the

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anatomy (Figure 8e). Further demonstrations highlight the applicability to highly dynamic organs such as the heart, where wireless millimeter-scale pacemakers and high-density flexible multielectrode arrays mount directly onto the epicardial surfaces of rat models (Figure 8b) and Langendorff-perfused rabbit hearts (Figure 8c). Pacemakers implanted with sutures and with hydrogel interfaces achieve 5- and 8-day functional lifetimes, respectively. The shorter lifetime in the case of sutures is mainly due to an increased level of disorganized nonconductive connective tissue that develops at the surface of the myocardium, which highlights the performance improvements enabled by hydrogel-integrated bioelectronics. The BTIM can fill the interior spaces of 3D bioelectronic systems without damaging fragile features, to achieve 3D electrode-embedded and electrode-exposed electronic structures (Figure 8f). In all cases, the devices remain in their desired positions and retain their performance characteristics throughout the period of study. Although hydrogels have been successfully utilized in bioelectronics applications, challenges remain for many practical applications. One issue is the long-time stability in interface adhesion. Also, optimizing the manufacturing processes and reducing the costs are prerequisites for clinical trials.

9. CONCLUSIONS AND OUTLOOK

This Account highlights recent advances in hydrogel materials as functional tissue interfaces for implantable bioelectronics systems. The content includes guidelines for hydrogel design choices, from the perspectives of chemistry in the context of mechanical, electrical, optical, thermal, and chemical coupling between bioelectronic devices and living organisms. Progress in biocompatible and functional hydrogels present opportunities for the use of such technologies in chronic diagnostic operation and therapeutic treatment with minimized foreign body responses.

Although recent advances enable efficient signal transmission through hydrogel interfaces, from bioelectronics to biology and vice versa, synergistic operations that exploit both modalities simultaneously represent additional interesting possibilities. Simultaneous, dynamic adaptions to chemical or physical changes in both biology and bioelectronics may be possible. For example, a future adaptive hydrogel interface might automatically regulate its conductivity according to the amplitude of the cardiac cycle, and therefore, adjust the current density provided by the pacemaker for optimized cardiac pacing. Such intelligent and adaptive hydrogels could potentially initiate a time-dependent evolution in the nature of communications between bioelectronics and biology. Another possibility is in cellular/tissue-engineered living hydrogel interfaces that not only provide coupling between bioelectronics and biology but also impart biological function to bioelectronics and active, engineered interactions to biology. In these and other cases, systems that adopt complex, 3D architectures across a range of biologically relevant length scales represent the most natural and extensive levels of interaction, beyond anything that is possible with conventional interfaces across surfaces. Here, stereolithography, extrusion techniques, and multiphoton methods may define 3D hydrogel frameworks that support interconnected or isolated collections of active semiconductor components distributed across this volumetric space by guided or deterministic assembly approaches. The broad diversity of options in the materials science of hydrogels suggests a promising future for these and related directions in research.

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