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Review

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Emerging Modalities and Implantable Technologies for Neuromodulation

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Techniques for neuromodulation serve as effective routes to care of patients with many types of challenging conditions. Continued progress in this field of medicine will require (1) improvements in our understanding of the mechanisms of neural control over organ function and (2) advances in technologies for precisely modulating these functions in a programmable manner. This review presents recent research on devices that are relevant to both of these goals, with an emphasis on multimodal operation, miniaturized dimensions, biocompatible designs, advanced neural interface schemes, and battery-free, wireless capabilities. A future that involves recording and modulating neural activity with such systems, including those that exploit closed-loop strategies and/or bioresorbable designs, seems increasingly within reach.

The nervous system controls body processes through a complex pattern of action potentials across neural networks that innervate all regions of the anatomy. Elaborate mechanisms of chemical and electrical signal transduction and propagation across interconnected cell bodies, axons, dendrites, and synapses work together to process a wide array of stimuli, including pain, pleasure, hunger, vision, somatosensation, and more, as the basis for regulating organ function through the peripheral and central nervous systems. Capabilities for modulating such types of neural function have potential to address health conditions with significant societal burden, including neurological, neuropsychiatric, neuromuscular, and sense organ disorders. Although a fundamental understanding of many aspects of the causes and consequences of the associated biological mechanisms is limited, studies suggest that many effects arise from aberrant or uncontrolled activity in neural circuits (Bonelli and Cummings, 2007), thereby presenting potential pathways for treatment based on stimulating, inhibiting, repairing, and/or replacing neurons. A potentially important opportunity, then, is to utilize miniaturized implantable devices that automatically detect and selectively control neuronal activity as an engineering-based treatment without side effects encountered with traditional medicines (Dorey, 2016). Technologies in this context span those that repair and replace impaired neural function (i.e., neuroprosthetics) to those that regulate disordered neural activity (i.e., neuromodulation).

The adaptation of cardiac pacemaker technology into platforms to treat chronic pain in the late 1960s (Gardner, 2013) led to the development of techniques for electrical neuromodulation in the context of many other conditions, including deep-brain stimulation (DBS) for Parkinson's disease, spinal cord stimulation (SCS) for chronic pain (Verrills et al., 2016), and vagus nerve stimulation (VNS) for epilepsy and depression (Johnson and Wilson, 2018), each now with regulatory approval for widespread use in human subjects, as shown in Figure 1. Although they rely on approaches and systems designed in a largely empirical fashion with limited understanding of the fundamental mechanisms, these and other successful therapies motivate development of related approaches for other challenges in patient care and for research into underlying phenomena. For example, the efficacy of DBS for addressing the effects of Parkinson's disease suggests potential in other contexts such as obsessive compulsive disorder and depression (Gardner, 2013), with qualitative improvements in operation and broadened scope of applications that could likely follow from advances in basic knowledge of mechanisms and specificity in neuromodulation. In fact, neuromodulation is one of the fastest growing areas of medicine and has already been deployed in hundreds of thousands of patients with diverse neurological disorders. The associated opportunities for research and technology development are significant, as evidenced by federal

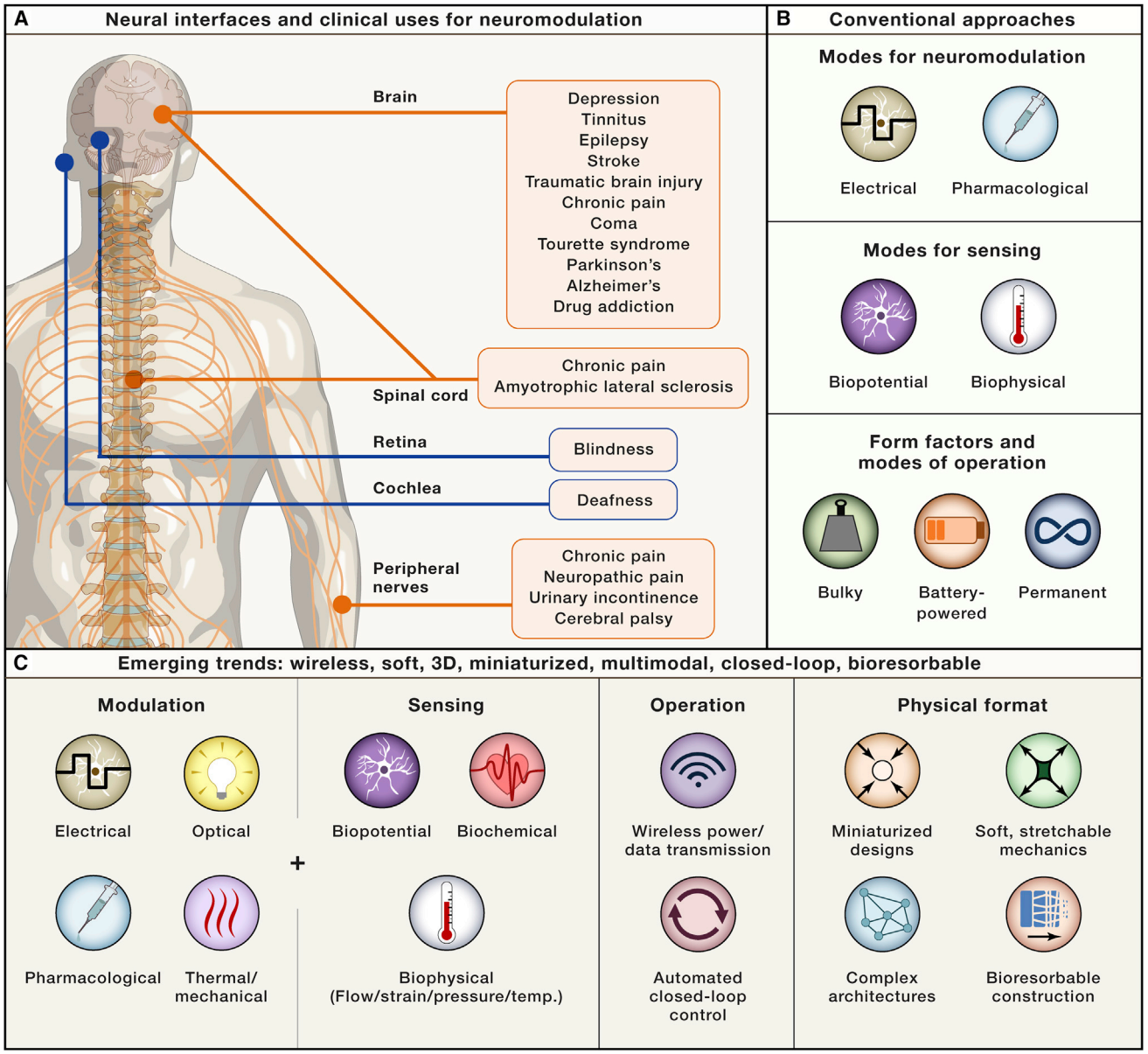

Figure 1. Past, Present, and Future of Implantable Technologies for Neuromodulation

(A) Scope of uses of implantable devices for neuromodulation, with interfaces in the brain, the spinal cord, and the peripheral nervous system.

(B) Conventional approaches rely predominately on electrical and pharmacological stimulation in systems that adopt rigid, bulky form factors, with control provided by discrete external hardware and sensors.

(C) An important future is in expanded modalities for modulation and sensing, through devices that provide improved precision, fidelity, and long-term viability. Multimodality and closed-loop feedback define the frontier for technologies demonstrated in animal model studies. Platforms that offer intimate integration of device function with soft tissue systems, with biocompatible construction (e.g., soft, stretchable, bioresorbable), embedded sensing and control units (i.e., closed-loop feedback), and untethered formats (i.e., wireless power and communication) will create many opportunities for personalized therapeutics, when used as alternatives or complementary approaches to traditional pharmaceutical treatments.

funding allocations in this area through agencies such as the US National Institutes of Health (NIH; stimulating peripheral activity to relieve conditions [SPARC] program, since 2014) and the US Defense Advanced Research Projects Agency (DARPA; bioelectronics, since 2015), by corporate spending (e.g., Galvani, a joint effort between GlaxoSmithKline and Verily since 2016) and by broader venture capital investment (Dorey, 2016). The market for neuromodulation technologies, including those that interface to the central and the peripheral nervous systems, is expected to reach ~6 billion USD in 2020 (Tomycz et al., 2019).

This review focuses on research progress in this broader area, with an emphasis on recently reported pre-clinical technologies that improve the durability, efficiency, and/or functionality of interfaces for neuromodulation across all parts of the nervous

system. We highlight advances in materials science, electrical engineering, and mechanical design that enable minimally invasive, highly functional devices with biophysical properties and geometrical configurations that enhance chronic stability in programmable operation across large collections of neurons. Our discussion covers a breadth of modalities in neuromodulation, from electrical, thermal, and optical to pharmacological and multimodal combinations of these, in tissue-compliant and wireless platforms with demonstrated utility in animal model studies and clear promise in clinical translation. Research on closed-loop systems that regulate body processes in dynamic response to physiological measurements and on fully bioresorbable platforms that operate over time frames defined by natural biological processes are included as important frontiers. A concluding section summarizes the state of the field and highlights topics for continued fundamental research and translational development.

Neuromodulation Modalities

Many active research programs in neural interface technologies focus on modes for neuromodulation that offer capabilities beyond those supported by electrical stimulation. These include effects based on thermal, optical, and pharmacological stimulation, often in programmable, multimodal configurations. Immediate opportunities are in the use of the resulting systems as tools to facilitate scientific studies of the operation and function of neural networks in animal models and human studies. The ultimate goal is for technologies that can perform neuromodulation in the brain for treatment of neurological (e.g., neurodegeneration, dementia, Parkinson's disease, epilepsy, essential tremor) and neuropsychiatric (e.g., addiction, depression) disorders, and in the spinal cord and/or peripheral nervous system for addressing acute/chronic pain, organ dysfunction (e.g., urinary incontinence, blindness, deafness) and movement disorders (e.g., cerebral palsy, paralysis), where safety, reliability, and fidelity of the neural interface are key considerations. The following subsections summarize different stimulation modalities, their capabilities in neuroscience and clinical research and associated potential for translation, beginning with electrical methods due to their wide prevalence.

Electrical

Approaches based on electrical stimulation or inhibition are well established in this context and many are approved for clinical treatments (e.g., DBS, SCS, VNS), where electrodes in the form of cuffs or probes physically interface to adjacent neural tissues. Modulation involves inducing potential gradients across neurons, to initiate functional responses (i.e., action potential) by depolarizing (for stimulation) and hyperpolarizing (for inhibition) the cell membrane (Cogan, 2008; Luan et al., 2014; Parodi and Choi, 2019). Here, the detailed parameters (e.g., amplitude, width, frequency, polarity) affect outcomes such as the rate of excitation of nerves and nerve bundles, and they also define the spatial selectivity within the bundle (Brocker and Grill, 2013; Parodi and Choi, 2019). For example, spatially targeted transcranial electrical stimulation in a short pulsed (2.5 or 10 μs pulse width) mode injects spatially focused currents to affect neuronal spiking, with relatively low charge densities and sensations on the scalp surface (Vöröslakos et al., 2018). Advanced systems exploit programmable electronics for active control, to allow dynamic changes in affected behaviors (O'Leary et al., 2018; Yuan et al., 2016). The temporal and spatial resolution follow from the refractory times of the neurons (typically ~1 ms) and the sizes of the electrodes (typically between several millimeters to tens of microns), respectively (Luan et al., 2014). A key metric is the charge injection capacity (CIC) of the electrodes, defined as the maximum deliverable charge per unit area. A combined set of considerations in materials, surface texture, and geometry define this parameter; its value determines, in part, the ability to reduce the electrode sizes for improved spatial resolution. Additional details on principles and applications of electrical stimulation appear in other review articles (Brocker and Grill, 2013; Cogan, 2008; Luan et al., 2014).

Noble metals (e.g., Pt, Au, Ir, Pd, Rh) are attractive materials for such purposes due to their biocompatibility and high resistance to corrosion in biofluids. The relatively modest values of CIC (0.05–0.26 mC/cm^2 [Cogan, 2008]), however, represent limitations that motivate the development of alternative materials and of strategies to increase the electrochemical surface areas. Examples of the former include ceramics (e.g., titanium nitride, TiN: ~1 mC/cm^2; iridium oxide, IrO_x: 1–5 mC/cm^2 [Cogan, 2008]), where high surface roughness in TiN and reversible Faradaic reactions associated with reduction and oxidation in IrO_x contribute to charge injection (Jeong et al., 2015b; Wang et al., 2009; Won et al., 2018), and conducting polymers (e.g., 1–3 mC/cm^2 for poly(3,4-ethylene dioxythiophene) doped with poly(styrenesulfonate) (PEDOT:PSS), poly(3,4-ethylene dioxythiophene) doped with carboxyl functionalized multiwalled carbon nanotubes (PEDOT:CNT), poly(3-4-ethylene cioxythiophene) doped with perchlorate (PEDOT:ClO_4), and poly(3,4-ethylene dioxythiophene) doped with paratoluene sulfonate (PEDOT:pTS) [Gerwig et al., 2012; Green et al., 2012; Kozai et al., 2016; Venkatraman et al., 2011]), where volumetric interactions follow from permeation of biofluids into the polymer and mixed electronic/ionic transport occurs at the electrode-electrolyte interface (Rivnay et al., 2016; Won et al., 2018). Adding a plant-based hydrogel (i.e., aloe vera hydrogel) to the conductive polymer (i.e., PEDOT:PSS) also provides a relatively high charge capacity with attractive adhesive properties (Spyropoulos et al., 2019). Electrodes that use micro/nanostructure to increase the effective surface areas include nanotextured Pt (Pt black; 0.3–2 mC/cm^2 [Zhang et al., 2015]), nanoporous Pt (3 mC/cm^2 (Park et al., 2010) and Au (1 mC/cm^2 [Kim et al., 2015]), and needle-shaped surface features in Pt (Pt grass; 0.3 mC/cm^2 [Boehler et al., 2015]). Nanoscale forms of carbon such as carbon nanotubes (1.6–6.5 mC/cm^2 [Vitale et al., 2015]) and graphene (0.05–0.20 mC/cm^2 [Kostarelos et al., 2017] or in laser pyrolyzed form [Lu et al., 2016], 3.1 mC/cm^2) are also of interest, due to their chemical stability, mechanical strength, wide electrochemical window, and high surface area. Combinations of these various materials and of structured forms of them can also be valuable, such as graphene fibers coated with Pt, where the CIC can reach ~10.3 mC/cm^2, three orders of magnitude higher than Pt alone, owing to the high surface area (2,210 m^{2}g^{-1}, compared to Pt black with ~30 m^{2}g^{-1} [Xu et al., 2007]) at the exposed tip (Figure 2A) (Wang et al., 2019).

Fundamental constraints in the use of electrical stimulation for neuromodulation follow partly from difficulties in engaging

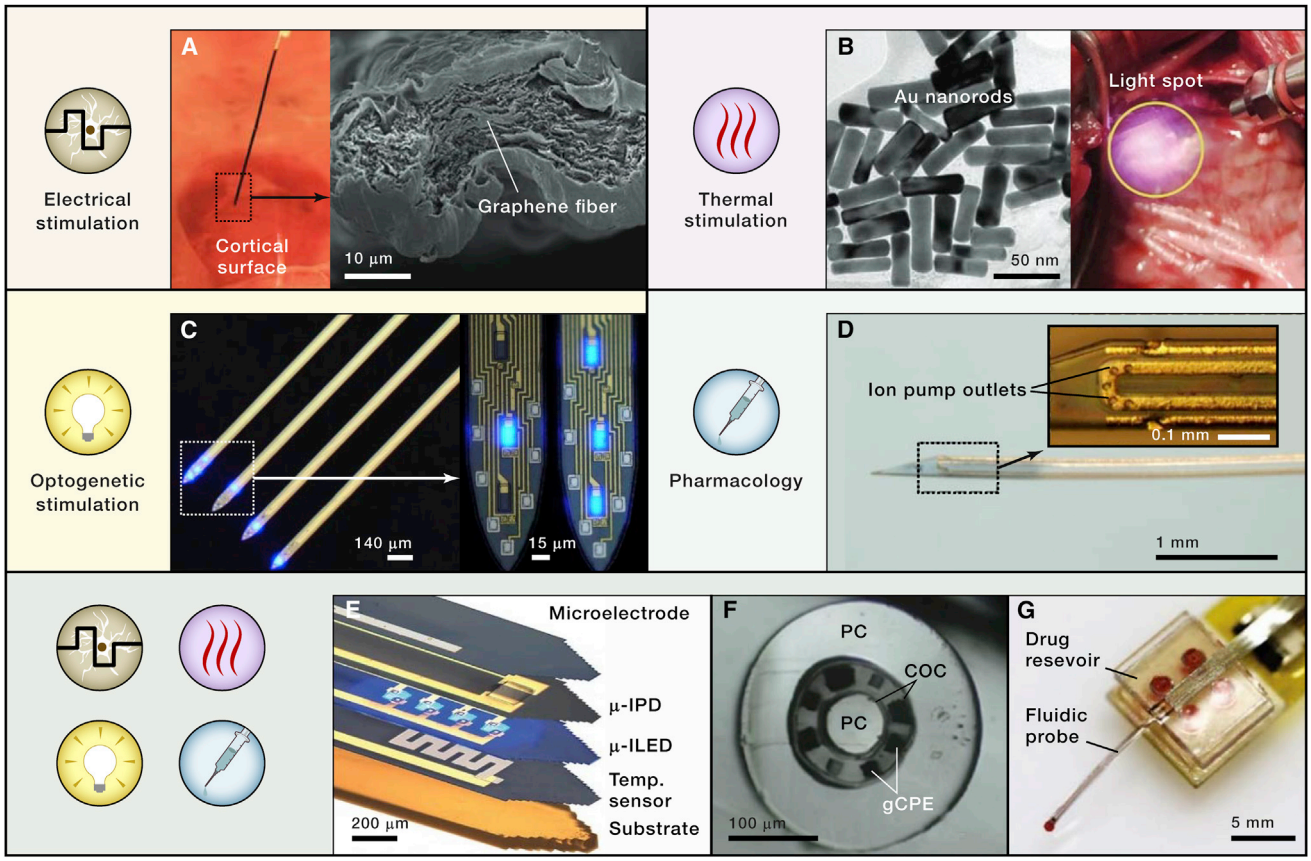

Figure 2. Neuromodulation Pathways

(A) Optical (left) and scanning electron microscope (right) image of a porous graphene microfiber with a charge injection capacity of ~10.3 mC cm^{-2} (Wang et al., 2019).

(B) Gold nanorods (left) with tailored absorption in the near-infrared (NIR) region of the spectrum for photothermal modulation. In this example, temperatures reach ~47°C after 5 min NIR laser irradiation (right) (Ye et al., 2019).

(C) Optical images of a monolithic multi-shank with InGaN (indium gallium nitride) microscale inorganic light-emitting diodes (μ-ILEDs) for optogenetic stimulation (Wu et al., 2015).

(D) Injectable microfluidic ion pump for electrophoretic drug delivery across an ion exchange membrane (Proctor et al., 2018). In (A)–(D), the insets are zoomed-in images of the dashed line box.

(E) Optoelectronic probe with a Pt electrode for physiological recording or electrical stimulation, μ-ILEDs for optogenetic stimulation, and a thin film element for thermal stimulation and temperature sensing. μ-ILED, microscale inorganic light-emitting diode; μ-IPD, microscale photodetector (Kim et al., 2013).

(F) Cross-sectional microscope image of a polymer fiber probe that incorporates an optical waveguide, electrical interconnects, and microfluidic channels for multimodal modulation via optical, electrical, and pharmacological means. PC, polycarbonate; COC, cyclic olefin copolymer; gCPE, composites of graphite and conductive polyethylene (Park et al., 2017).

(G) Optofluidic system with rechargeable battery and replaceable drug cartridge for programmable pharmacology and optogenetics (Qazi et al., 2019).

specific types of cells and confined regions, with associated limitations in control of targeted therapeutic outcomes (Chen et al., 2017; Kringelbach et al., 2007; Lozano et al., 2019; McIntyre et al., 2004; Lim et al., 2015). Also, chronic implantation can result in fibrotic responses and the development of scar tissue, thereby leading to time varying properties of the contacting interface and thus in required stimulation parameters (Lotti et al., 2017; Sridharan et al., 2013). Further complications can follow from parasitic Joule heating and associated unintended effects on the targeted tissue (Elwassif et al., 2006).

Thermal

Recent studies demonstrate that careful control of thermal effects can be leveraged as an alternative methodology for neuromodulation, with relevance in treating neuropathic pain (Brito et al., 2014; Patapoutian et al., 2009), epilepsy (Fernandes et al., 2018), and peripheral neuropathy (Xing et al., 2007). The underlying mechanisms follow from temperature induced changes in the cell membrane capacitance and/or changes in the conductance of thermosensitive transient receptor potential ion channels (e.g., TRPV1 with activation temperature of >~41°C, TRPM8 with activation temperature of <~30°C), both resulting in ionic transport (Luan et al., 2014). The former and latter effects are believed to arise from brief (on the order of milliseconds) spatiotemporal temperature gradients and from slow heating or cooling of the baseline temperature, respectively (Luan et al., 2014). Some of the most thoroughly explored means to deliver thermal energy involve absorption of light (e.g., infrared

[IR] [Duke et al., 2013; Lothet et al., 2017] or visible light [Owen et al., 2019]) directly by targeted tissues or indirectly by injected materials that affect conversion into thermal energy. Here, the efficacy of energy conversion determines the latency periods between stimulation onset and neuronal manipulation; optically induced heating can reach response times on the order of milliseconds (Lothet et al., 2017; Owen et al., 2019), whereas heating associated with absorbing materials can vary from milliseconds (e.g., IR to thermal conversion via mesostructured silicon particles [Jiang et al., 2016] and gold nanorods [Eom et al., 2014]) to seconds (e.g., magnetic wave to thermal conversion via magnetic nanoparticles (MNPs) [Chen et al., 2015; Huang et al., 2010]), depending on the detailed mechanisms.

Among these options, thermal stimulation based on upconverting nanoparticles (i.e., nanoparticles that absorb two to more incident photons of relatively low energy and emit a single photon of higher energy) are of recent interest due to their capacity for minimally invasive neuromodulation, with localization that can match the length scales of subcellular components (e.g., neuronal membrane, ion channels) (Wang and Guo, 2016). Gold nanoparticles/nanorods represent one example, where NIR illumination leads to thermal stimuli largely localized to the area of illumination though plasmonic effects (e.g., optical intensities of ~10 mW/mm^2 in the NIR can lead to temperatures of ~45°C, above TRPV1 activation) (Figure 2B) (Ye et al., 2019). Functional demonstrations include stimulation of action potentials in cultured hippocampal neurons and in sciatic nerves of rodent models, stimulation of cultured rat primary auditory neurons, and prevention of ventricular arrhythmias within the left stellate ganglion of canine models. An alternative, but related, scheme uses Fe_3O_4 MNPs for thermal stimulation as a consequence of hysteresis effects upon exposure to an oscillating magnetic field (Chen et al., 2015). Injection of such materials in the ventral tegmental areas of mice enables activation of nearby neurons within ~5 s via increases in temperature to >43°C. Additional approaches utilize mesostructured silicon particles (~1–2 μm) for fast photothermal effects (e.g., 5.8°C increase in temperature within 1.8 ms of illumination with 532 nm laser light), causing transient capacitive currents from the phospholipid bilayer (Jiang et al., 2016), with negligible cytotoxicity in cultured mammalian cells. In all cases, the materials must maintain close proximity to the cells of interest, without diffusion or movement through the tissue. Independent of the specific approach, thermal stimulation demands tightly controlled dosing to achieve activation without cell damage (Luan et al., 2014).

Optical

Optical methods that do not rely on heating overcome many of these and other limitations through the use of photosensitive ion channels or proteins expressed in genetically modified neurons, as a highly targeted form of neuromodulation known as optogenetics (Chen et al., 2017; Deisseroth, 2011; Shin et al., 2017). Here, changes in the conformation of light-sensitive proteins, or opsins, occur under light illumination with specific wavelengths (390–700 nm) (Erofeev et al., 2016). The resulting ionic (e.g., Ca^{2+}, Na^+, Cl^-, H^+) current flows through the cell membrane can stimulate or inhibit opsin-expressing cells. These effects allow for high temporal precision, limited by cellular dynamics (1 ~10 ms) (Gunaydin et al., 2010; Luan et al., 2014), and single-cell-type precision within the illumination volume. *In vivo* demonstrations, ranging from those in cultured neuronal networks (e.g., human embryonic kidney cells), small worms (e.g., *C. elegans*), and mammalian species such as rodents or non-human primates (Fenno et al., 2011), support uses of optogenetics for treating depression, spinal cord injury, chronic pain, and epilepsy (Ahmad et al., 2015; Cela and Sjöström, 2019; Liu et al., 2019a). Common opsins include Channelrhodopsin-2 (ChR2, responsive to ~470 nm wavelength for stimulating responses), Archaerhodopsin (Arch, responsive to ~570 nm wavelength for inhibitory responses), and Halorhodopsin (Hr, responsive to ~580 nm wavelength for inhibitory responses) (Erofeev et al., 2016). Reviews of the genetic expression of these and other opsins that operate across a range of absorption wavelengths with varied photocycle kinetics can be found elsewhere (Camporeze et al., 2018; Fenno et al., 2011; Gholami and Sayyah, 2018).

As with IR induced heating, the most straightforward means to introduce light into targeted tissues for optogenetics relies on optical fibers or planar silica waveguides coupled to external light sources. Although effective in many contexts, the associated physical tethers can alter natural behaviors and prevent certain types of experimental protocols. Recent advances in miniaturized and/or wireless platforms, discussed in greater detail in subsequent sections, utilize implanted, highly efficient inorganic light-emitting diodes with microscale (i.e., sub-millimeter) dimensions (μ-ILEDs), first demonstrated in wireless, flexible multifunctional probes. Here, the μ-ILEDs can be selected for emission in the ultraviolet, blue, yellow, and/or red regions of the spectrum (Shin et al., 2017), with small thermal loads that limit increases in temperature to a few tenths of a Celsius degree (<0.4°C for optical power of 15 mW/mm^2, stimulation frequency of 1.25 Hz, and duty cycle of 10% [Gutruf et al., 2018]) and with optical intensities that can reach levels (>50 mW/mm^2 [Shin et al., 2017; Wu et al., 2015]) suitable for most opsins. Recent work exploits semiconductor processing techniques and silicon shanks as high modulus, a widely used parameter for the stiffness of a solid material, yet durable guides for deep tissue implantation of arrays of blue (wavelength of 460 nm) μ-ILEDs that allow for ChR2-mediated optical stimulation of hippocampal pyramidal cells via ChR2 photoactivation in mice (Figure 2C) (Wu et al., 2015).

Alternatively, materials oriented strategies, conceptually similar to those for thermal stimulation, rely on mechanoluminescent nanoparticles to provide optogenetic stimulation (wavelength of 470 nm and optical power of 1.2 mW/mm^2) of ChR2 upon excitation with focused ultrasound (Wu et al., 2019). A functional demonstration shows activation of unilateral limb movement through neuromodulation of the secondary motor cortex in mice. Although such schemes significantly reduce adverse effects of device load and associated chronic foreign body reaction, disadvantages follow from toxicity concerns (Khalili Fard et al., 2015), the potential for parasitic heating, and the need for body-mounted external systems to generate focused ultrasound (O'Brien, 2007; Nelson et al., 2009). More generally, optogenetics is limited by translational challenges that include the

need to express non-mammalian proteins in the nervous system and to implant devices for illumination of the opsins. Continued studies focus on the safety and efficiency for use in humans (Luan et al., 2014). A related but distinct set of methods, known collectively as chemogenetics, avoid some of these disadvantages through the use of engineered receptors in cells to produce pharmacological sensitivity that is normally absent. A discussion of chemogenetics appears in the next section.

Pharmacological

Pharmacological techniques represent the oldest and most well-established means for cell-specific neuromodulation without concerns associated with genetic modifications. A variety of excitatory (e.g., neurotropic factors [Mohtaram et al., 2013]) and inhibitory (e.g., receptor antagonists [Jeong et al., 2015a; Qazi et al., 2019; Shin et al., 2019a]) pharmacological agents have applications in chemically refined DBS (Creed et al., 2015), seizure control (Devinsky et al., 2018; Mitchell et al., 2012), pain (Turk et al., 2011), depression (Robbins, 2019; Russo et al., 2011), and schizophrenia (Robbins, 2019). The power of pharmacology lies in its ability to target specific endogenous systems to either enhance or diminish activity at specific chemical junctions. Multiple routes of administration, including oral, intravenous, and intramuscular avenues create flexibility in treatment protocols. Development of schemes to overcome the limited temporal resolution and the inability to program and selectively modulate specific somatic sites represent topics of current work. Also, systems for local, precise delivery are needed to reduce off-target effects. For example, benzodiazepines offer therapeutic effects for anxiety by activating γ-aminobutyric acid (GABA) receptors and reducing brain activity in limbic areas such as amygdala (Ngo and Vo, 2019; Nuss, 2015; Jonsson et al., 2016). However, stimulation of GABA receptors in other areas of the brain, such as the primary motor cortex, reduces motoric technical abilities (Kolasinski et al., 2019; Stagg et al., 2011). Metal guide cannulas and microinjectors can support infusion of pharmacological agents into specific brain sites, simultaneously overcoming the blood-brain barrier but posing practical difficulties for clinical use (Sim et al., 2017). Recent work demonstrates that complete microfluidic systems with drug reservoirs, pumps, and fluidic-probes can deliver multiple distinct pharmacological or fluidic agents in a highly targeted manner (Jeong et al., 2015a; McCall and Jeong, 2017; Noh et al., 2018; Qazi et al., 2019; Zhang et al., 2019a; Zhang et al., 2019b). When constructed in soft, compliant materials with active (programmable) micropumps, these platforms can be suitable for effective chronic use, as shown in various publications (Qazi et al., 2019; Zhang et al., 2019a, 2019b). Another recent example illustrates active delivery of pharmacological agents via electrophoresis across an ion exchange membrane, thereby eliminating the need for a solvent (Figure 2D) (Proctor et al., 2018). Such schemes also avoid local pressures associated with conventional syringe injection or convection-enhanced delivery methods and their associated risks in formation of edemas.

The challenges associated with microfluidic pharmacological techniques are safe chemical storage, limited spatial and temporal resolution, as dictated by metabolism and diffusion, and engineering difficulties in refilling depleted reservoirs (Luan et al., 2014; Sim et al., 2017). An emerging set of strategies relies on engineered receptors in cells to yield pharmacological sensitivity that is not present naturally. These genetically modified receptors can be selectively activated on demand with an exogenous ligand (Atasoy and Sternson, 2018), such that drugs delivered systemically via injection or oral administration induce biological effects only at the sites of receptor expression. In some cases, these receptors can be activated by drugs with pre-existing FDA approval (Weston et al., 2019) or via pathological levels of endogenous compounds (Lieb et al., 2018). A key advantage of the methods of chemogenetics relative to optogenetics is that they avoid the need for expression of non-mammalian proteins and they do not require implantable devices. Chemogenetic approaches could lead to powerful treatment options for conditions such as epilepsy (Lieb et al., 2019), although many of safety concerns associated with optogenetics and genetic modifications remain.

Multimodal

An important future in neuromodulation exploits multimodal operation via an engineered combination of electrical, thermal, optical, and pharmacological stimuli, in some cases with recording modalities for improved levels of control. Experimental demonstrations include recovery of locomotion capabilities in paralyzed rodents through combined electrical and pharmacological stimulation in the spinal cord (L2 and S1 segments) (Minev et al., 2015), strong place aversion and preference through optical stimulation with concurrent blocking of this behavior through pharmacological (dopamine receptor antagonist, SCH23390) delivery in the ventral tegmental area of wild-type mice (Jeong et al., 2015a), and abolishment of the drug-adaptive behavior through combined electrical and pharmacological (dopamine receptor antagonist, SCH23390) stimulation in the medial prefrontal cortex regions of mice (Creed et al., 2015). Figures 2E–2G highlights examples of platforms with relevant capabilities in this context.

Figure 2E shows an advanced multimodal system that includes a Pt electrode for electrophysiological recording, a microscale photodetector for measurement of light exposure, μ-ILEDs for optical stimulation (ChR2 at wavelength of $\sim$450 nm), and thin metal films for both temperature sensing and thermal stimulation, all heterogeneously integrated in a multilayer injectable probe (Kim et al., 2013). Optical stimulation with this system in mice can modulate anxiety-like behaviors and induce place-preference. An alternative multimodal platform, highlighted in Figure 2F, relies on a thermal drawing process to yield a cylindrical structure that includes an optical waveguide, electrical interconnects (conductive polyethylene), and microfluidic channels, with capabilities in optical and pharmacological stimulation and electrophysiological recording (Park et al., 2017). Experiments in mice show recording of neural activity during optical (ChR2 at wavelength of $\sim$470 nm) and/or pharmacological stimulation (receptor antagonist) in the prefrontal cortex. Other recently reported technologies utilize wireless powering and control strategies to deliver multiple pharmacological agents to localized targets (e.g., deep brain, spinal cord) via soft, shape conformal microfluidic neural probes with arrays of μ-ILEDs for concurrent optical stimulation (Figure 2G) (Qazi et al., 2019). Experiments with such systems in mice demonstrate multimodal

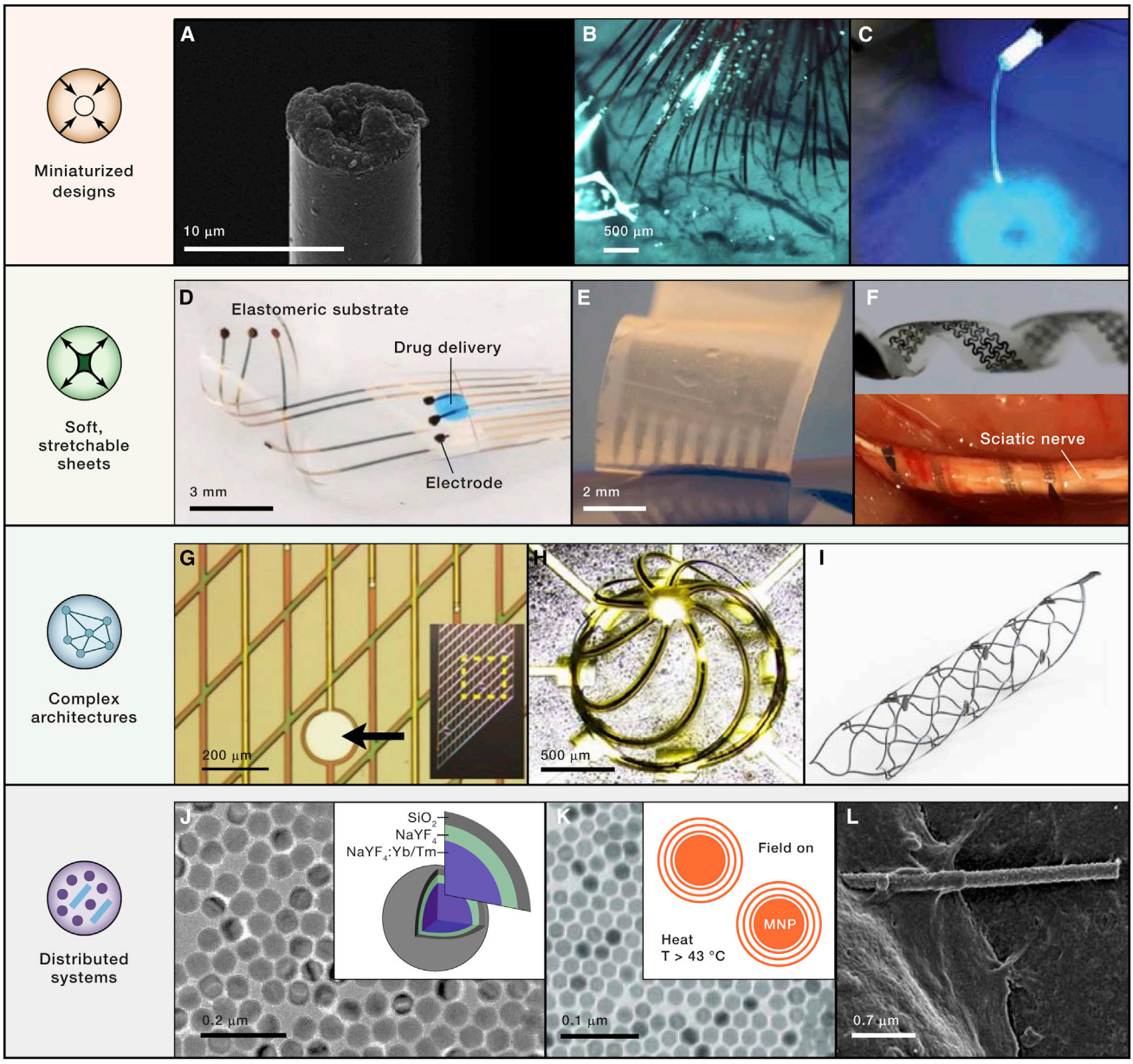

Figure 3. Advanced Materials and Architectures for Neural Interfaces

(A) Penetrating carbon microfiber (diameter of ~7 μm) coated with PEDOT:PSS (Kozai et al., 2012).

(B) Array of polymer filaments (length of 20 mm, width of 5–50 μm, thickness of 4–6 μm) implanted in rat cerebral cortex (Musk and Neuralink, 2019).

(C) Ultrasoft (effective modulus ~60 kPa) hydrogel optical fibers for optogenetic stimulation (Wang et al., 2018).

(D) Thin, soft (effective modulus ~2 MPa), stretchable electronic dura mater (thickness ~120 μm) that supports gold interconnects, platinum-silicone composite electrodes, and microfluidic channels for multimodal interfaces to the spinal cord (Minev et al., 2015).

(E) Ultrasoft (effective modulus ~30 kPa), electrically conductive hydrogels (thickness 30–100 μm) designed for electrical stimulation of sciatic nerves in rodent models (Liu et al., 2019b).

(F) Soft (effective modulus of ~300 kPa), stimuli-responsive nerve cuff that gently wraps onto peripheral nerves, triggered by a thermal process upon exposure to body temperatures (37°C) (Zhang et al., 2019c).

(G) Macroporous mesh electronic that consists of recording and stimulating electrodes (Pt, 20 μm diameter for recording sites and 150 μm diameter for stimulating sites [black arrow]) (Fu et al., 2016).

(H) Optical image of a 3D scaffold with separately addressable passive electrodes (Au, diameter of 50 μm) for electrical stimulation and recording of neuronal activity (Yan et al., 2017).

(I) Self-expanding scaffold that supports 6–12 passive electrodes (Pt, diameter of 500–750 μm) for endovascular stimulation within the superior sagittal sinus of an ovine model (Opie et al., 2018).

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operation through optical stimulation (ChR2 at wavelength of ~470 nm) in the lateral hypothalamus to yield place preference behavior, with separate, wireless control of infusion of a gabazine receptor antagonist that can block this response.

These current efforts seek to expand on established methods in electrical stimulation to provide modalities with increased spatiotemporal control, cellular specificity, and safety profiles appropriate for clinical translation. Mature schemes for electrical stimulation serve as the successful basis for treating variety of conditions, but with limitations that follow from a lack of cellular specificity, from difficulties in controlling interaction volumes and from adverse effects of device-related mechanical and thermal loads on soft, fragile tissues. Thermal stimulation provides localization that can approach the length scales of subcellular components, constrained by thermal diffusion, but with requirements for tightly controlled dosing to achieve activation without cell damage. Genetic techniques enable cellular specificity through the expression of light-sensitive proteins (optogenetics) or engineered receptors with specific pharmacological sensitivity (chemogenetics). The need for genetic modifications, however, create uncertainties in the safety and efficacy for use in humans. Delivery of exogenous pharmacological compounds represents an alternative that can target specific endogenous systems but with comparatively poor temporal resolution and an inability to program and selectively modulate specific cellular sites. Combining multiple stimulation modalities has the potential to circumvent many of these separate limitations and to provide improved levels of control and recording capabilities. Regardless of the stimulation pathway, the materials and the device form factors dictate, in large part, the safety, reliability, and fidelity of the neural interface. Such considerations are therefore essential in widespread use of these neurotechnologies in humans.

Advanced Materials and Architectures for Neural Interfaces

Sophisticated neural interfaces that can support various schemes for neuromodulation described in the preceding sections are of growing interest, where miniaturized dimensions, anatomically matched geometries, and soft mechanical properties in systems that offer wirelessly controlled, or autonomous, multimodal operation represent some of the most powerful themes in recent research. The constituent materials (Wellman et al., 2018), engineering designs (Rogers et al., 2010), and form factors (Veiseh et al., 2015) are key aspects that determine the levels of invasiveness, the options in functional performance, the types of foreign body reactions, and the degrees of biostability for chronic use. Conventional implants offer broad utility in approved devices for various conditions, but their narrow modes for interfacing to neural tissues limit options. The basic mechanical properties and geometries can also frustrate the formation of persistent, intimate interfaces with the curved, compliant and time-dynamic soft surfaces of neural tissue, especially for an envisioned future that involves scaled integration and multiple interface mechanisms. Device failure and/or biophysical damage can result from micromotions relative to surrounding biological materials (Gilletti and Muthuswamy, 2006; Sridharan et al., 2013) and degradation at the biotic/electrode interface can follow from lack of materials and/or mechanical biocompatibility. Non-ideal surface chemical properties can lead to protein absorption and glial scarring (Christo et al., 2015) onto or adjacent to the device, as forms of foreign body reactions.

Advanced materials, unusual mechanics designs, bio-inspired shapes/morphologies, and biocompatible surface coatings represent some of the most important bioengineering aspects of emerging neural interface technologies. Trends in materials for such systems focus on mimicking biological structures or incorporating living cells, bioactive molecules, and/or biomaterials. Here, surface coatings that promote neuronal growth and attachment can reduce immune responses and associated potential for infections. Negatively charged, hydrophilic surfaces minimize protein absorption and slow the processes of foreign body reaction (Christo et al., 2015). Reviews on surface modifications that minimize immune responses appear elsewhere (Wo et al., 2016; Zhong and Bellamkonda, 2008). At the device level, effective mechanical moduli that match those of neural tissues follow from the use of soft materials, from micro/nanoscale material architectures and/or from hybrid approaches that combine both strategies in deterministically engineered composite matrices. In all cases, curved or articulated geometries add function and improve the fidelity of the soft tissue interfaces in ways that accommodate natural body motions without mechanical constraint.

Figure 3 provides an overview of recently reported design approaches, including platforms that exploit thin, filamentary probes (Figures 3A–3C), soft, conformal sheets (Figures 3D–3F), open-mesh networks (Figures 3G–3I), and distributed particle systems (Figures 3J and 3K), as discussed in the following subsections. In many of these cases, the interfaces exploit aggressive reductions in the cross-sectional dimensions of functional components and/or constituent materials to an extent that yields structures, including those that incorporate high performance inorganic semiconductors such as silicon, with bending stiffnesses that approach those of soft tissues.

Filamentary Probes

As highlighted in Figure 2, filamentary structures facilitate insertion into targeted neural tissue, where thin geometries yield low bending stiffnesses and resulting compliance to the surrounding biology. For electrical interfaces, arrays of tungsten needles, carbon fibers, and platinum (Pt)/iridium (Ir) microwires represent valuable approaches for implantation across large areas and numbers of channels. One example leverages carbon fibers as the basis of neural probes with subcellular cross-sectional dimensions (~7 μm diameter carbon fiber) (Figure 3A) (Kozai et al., 2012). Coatings of poly(p-xylylene) (800 nm thick) and conductive polymer(poly(3,4ethylenedioxythiophene) doped with poly(styrenesulphonate) (PEDOT:PSS) at the tip ends of such platforms

(J) Upconverting nanoparticles that absorb near-infrared light and emit visible light (450 and 475 nm) for optogenetic stimulation (Chen et al., 2018).
(K) Magnetic nanoparticles that transduce alternating magnetic fields to thermal stimuli for the activation of heat-sensitive receptors (Chen et al., 2015).
(L) Coaxial (p-type/intrinsic/n-type) silicon nanowires that photoelectrochemically stimulate neurons upon illumination with visible (532 nm) light (Parameswaran et al., 2018)

serve as dielectric barriers and sites for electrical stimulation, respectively. The small dimensions lead to stiffnesses that are one order of magnitude smaller than those of the smallest silicon probes for research purposes (stiffness of ~4.5 kN/m with diameter of 8.5 μm, compared to ~150 kN/m for silicon probe with cross-section area of 15 × 123 μm^2) and many orders of magnitude smaller than those of commercial electrodes for spinal or brain stimulation (~1 MN/m at a diameter of ~100 μm [Bhunia et al., 2015])

Fabrication schemes adopted from the semiconductor industry allow further miniaturization and scaling of related types of filamentary platforms into highly integrated, large-scale arrays suitable for production and commercialization. An additional recent example is the "Neuralink" array as in Figure 3B, where 96 probes (5–50 μm wide, 4–6 μm thick, 2 cm long) provide thousands of electrodes at distinct locations in the brain, suitable for measuring and stimulating individual neurons (Musk and Neuralink, 2019). A temporary shuttle (tungsten-rhenium wire) provides mechanical stability during insertion of each probe into neural tissue and is then removed, as demonstrated in rat brain cortex. Here, robotic systems track the motion of the brain and the location of vasculature to minimize damage during implantation. Coatings of PEDOT:PSS and iridium oxide (IrO_x) enable low-impedance interfaces (37 ± 5 kΩ for PEDOT:PSS; 56 ± 7 kΩ for IrOx) for neural stimulation and recording across each site area.

As alternatives to temporary shuttles, stimuli-responsive materials can provide structural rigidity during implantation and then soften after insertion. In one case, a polymer with a glass transition temperature near body temperature enables a decrease in modulus of three orders of magnitude after implantation (from ~1 MPa to ~1 kPa) (Ware et al., 2013). In another, liquid metal passed into a microfluidic channel that lies along the shank of a probe yields a mechanism for changing the modulus by two orders of magnitude (from ~950 to ~50 MPa) (Byun et al., 2019; Wen et al., 2019). Similarly, swelling in the constituent materials can also be exploited to achieve filamentary probes with moduli compatible to those of neural tissues (1–100 kPa [Liu et al., 2019b]). As an example, Figure 3C demonstrates hydrogel optical fibers formed by polymerizing alginate-polyacrylamide (PAAm) in a silicone elastomer tubing for optogenetic stimulation, where transitions between rigidity and softness occur via dehydration/hydration (Wang et al., 2018). Specifically, the hydrogel in its dehydrated state offers sufficient rigidity for insertion into neural tissues. Swelling and softening follows from hydration during exposure to biofluids. Fully hydrated fibers exhibit low loss (0.249 dB cm^{-1}) and offer moduli (~60 kPa) that are much lower than those of traditional silica optical fibers (~10 GPa), with the capability to provide optogenetic stimulation even when stretched by 140%. Animal model demonstrations involve delivery of blue light (10 mW) into the hippocampus regions of mice to stimulate ChR2-expressing neurons, with stable operation for 4 weeks.

Soft, Conformal Sheets

Platforms that allow for interfaces across large areas, conformal to the surfaces of neural tissue, rely on thin, flexible sheets where integration occurs non-invasively, without penetration. The resulting capabilities complement those of filamentary probes. The compliant mechanical properties are important because they allow for unconstrained movements of the adjacent soft tissues (e.g., bending, stretching, and twisting, etc.), and they enable geometric conformality to their curved contours. As an example, Figure 3D shows an elastomeric system, referred to as electronic dura mater, that uses a silicone substrate (parylene and poly(dimethylsiloxane) [PDMS], ~120 μm thick) with microcracked gold (Au) interconnects, Pt-silicone composite electrodes, and microfluidic channels as an interface to the spinal cords of rodents (Minev et al., 2015). The effective modulus of this system is only ~1.2 MPa, and it exhibits elastic responses to strains of up to 45%, far larger than those expected in healthy neural tissue. Experimental results show that these platforms can restore locomotion in paralyzed animals via both pharmacological activation (subdural drug delivery of serotonergic replacement therapy) and electrical stimulation over 5 weeks of implantation.

Combining such sheet-like geometries with biocompatible films of silk as temporary substrates can enable intimate integration with neural tissues with superior deformability. An example comprises measurement electrodes embedded in photodefined, ultrathin polyimide mesh, supported by a bioresorbable substrate of silk fibroin (Kim et al., 2010). The silk can be dissolved after implantation into a feline model, yielding conformal contact between the ultrathin electronics and brain surfaces with minimal interface stresses. *In vivo* experiments include stimulation and recordings of neural processes over a month on the visual cortex of a feline model.

Further reductions in the effective modulus to levels that are comparable to those of neural tissue are possible with electrically conductive hydrogel-based systems, as shown in Figure 3E (Liu et al., 2019b). Here, a conductive hydrogel serves as a stimulating electrode and an elastic fluorinated photoresist provides a stretchable encapsulation layer, with an overall modulus of ~30 kPa. Electrode arrays of a nanomembrane of this hydrogel, formed from conductive polymers (PEDOT:PSS) via a solvent exchange and phase separation process, support both electrical and ionic conductivity for stimulation and recording, with stable device characteristics under tensile and compressive strains of up to 20%. The resulting systems in thin film form (30–100 μm thick overall) have charge storage capacity values of ~164 mC/cm^2 for stimulation of peripheral nerves at low voltages (50 mV) in mouse models for 6 weeks. Current efforts focus on large-scale microelectrodes based on these hydrogels and their integration into multifunctional systems for recording and stimulation.

Substrates formed from stimuli-responsive materials provide means for shaping devices to match geometries of complex tissues without external application of force. The system of Figure 3F exploits a climbing-inspired twining stimulation system for peripheral nerves, comprising mesh serpentine Au electrodes embedded in photodefined polyimide films (2 μm thick) on a substrate of flexible shape-memory polymer (SMP, ~100 μm thick) (Zhang et al., 2019c). Shape reconfigurability transforms 2D planar structures into 3D geometries with moduli between ~100 MPa to ~300 kPa, capable of wrapping onto peripheral nerves upon exposure to physiological conditions (in 37°C saline) after implantation. These mechanisms minimize tissue injury during implantation and subsequent use. Studies show capabilities in electrical stimulation with currents of 0.4 mA of the right vagus nerves of rabbit models to reduce their heart rates from

240 to 180 bpm. Advanced 3D geometries, beyond these coil type configurations, create additional opportunities in neural interfaces, as described next.

Open-Mesh Networks

Transformation of flat sheets into 3D, open-mesh architectures further expands options in unusual device architectures. These constructs may result in neural interfaces with superior biocompatibility and deformable properties, with capabilities for spanning across volumes of tissues. Figure 3G illustrates a macroporous flexible-mesh electronic system that consists of 16 recording/stimulating electrodes and Au interconnects embedded in thin photopatterned structures of epoxy at submicron thickness (Fu et al., 2016). The overall design exhibits tissue-like deformable mechanics and low bending stiffnesses (~0.1 nNm), enabling delivery via a syringe injection mechanism, as a floating mesh. Integration with neighboring neurons supports capabilities for evoking stable single-neuron responses to chronic electrical neuromodulation over 8 months in brains of freely behaving mice. Related methods use similar device designs and injection methods to enable recording from retinas in awake mice across 16 interfacing channels with the ability to record from single retinal ganglion cells (Hong et al., 2018). Such platforms also have the potential to support electrical neuromodulation, as with the example in Figure 3G.

Recent concepts allow deterministic transformation of such types of mesh structures from planar layouts of active devices (electronics, semiconductors, dielectrics, etc.) into 3D architectures via compressive forces imparted by an elastomeric substrate. These frameworks afford tissue-like mechanics and they integrate functional elements, including but not limited to electrodes, across 3D spaces, with intimate contact to neural networks and/or individual neurons at various spatial scales. Figure 3H shows a 3D spherical scaffold that incorporates 8 addressable Au electrodes for neural recording/stimulation, embedded by thin polyimide films (7 μm thick) (Yan et al., 2017). Coatings of TiN on these electrodes provide charge injection for electrical stimulation with increased interfacial surface area. Demonstrations show extracellular stimulation and high-fidelity recording from neural networks of rat dorsal root ganglion neurons for 7 days.

Although such 3D scaffolds could conceivably be delivered into fully formed tissues as 2D precursors that subsequently undergo 3D transformation, an alternative scheme involves delivery through vasculature in proximity to but not in direct contact with neural tissues of interest. Endovascular stents can be used in this manner, where stimulation occurs within the wall of a blood vessel. Here, Figure 3I demonstrates an implantable electrode array mounted on a nitinol endovascular stent (which refers to Stentrode) that consists of 6–12 Pt stimulating sites, polyimide encapsulation (~6 μm thick), and an otherwise conventional self-expanding stent (Opie et al., 2018). In demonstration experiments, such stent electrode arrays wind around a stainless steel wire (310 μm diameter) for implantation into cortical blood vessels of sheep through the jugular vein, with minimally invasive procedures. Installed in this manner, these platforms can deliver neuromodulation to stimulate muscular movements in the face and limbs with stimulating threshold currents ranging from 5 to 10 mA after 28 days of implantation. Current work focuses on deployment of such systems into vessels neighboring cortical areas associated with Parkinson's disease and epilepsy.

Distributed Material Elements

Perhaps the ultimate in 3D integration involves material elements in micro/nanostructured forms as transducers distributed across volumes of tissues, where power and control occurs with externalized hardware and wireless schemes. Such types of distributed systems for neuromodulation can address requirements, such as minimally invasive operation across length scales that approach cellular subcellular dimensions, that lie beyond those that are addressable using previously discussed classes of probes. Recent demonstrations, introduced in a prior section and described in greater detail in the following, use nano/microscale particles, tubes, or rods as active materials that respond to magnetic, radio frequency (RF), or IR fields to provide stimulation in the form of electrical, thermal, photonic stimuli, or pharmacological schemes via triggered drug release.

An example in Figure 3J is in DBS via optogenetic effects induced by upconversion of near-infrared (NIR) light from an external source by tissue integrated nanoparticles consisting of core-shell $NaYF_4$ nanocrystals co-doped with $Yb3^+/Tm3^+$ ($NaYF_4$:Yb/Tm) and coated with silica for surface chemical stability. Such nanoparticles exhibit emission at 450 and 475 nm upon excitation at 980 nm, with a conversion yield of ~2.5% (Chen et al., 2018). Animal experiments involve an optical fiber to deliver light from an external laser (980 nm, 13.8 mW/mm^2) to a region located ~4.2 mm below the skull in the mouse brain, to yield upconverted light at intensities of ~0.34 mW/mm^2. Such approaches can provide DBS in the ventral tegmental area for activation of neurons, genetically modified to express ChR2, for one month after implantation without adverse thermal effects. Other examples include use of nanoparticles in the medial septum regions of mouse brains, where NIR irradiation (270–540 mW power, 6–12 Hz, 980 nm) optogenetically engages inhibitory neurons to induce hippocampal oscillations. Challenges are in improving the interactions between upconversion nanoparticles and neural tissues for enhanced interface biocompatibility and long-term stability, where possibilities for toxicity and parasitic thermal effects are primary considerations.

An alternative, but related, approach exploits the transparency of tissue to magnetic fields to induce hysteretic heating of MNPs, as introduced in the discussion of thermal neuromodulation. Figure 3K presents a magnetothermal system of this type for DBS through the use of distributed MNPs (Fe_3O_4 coated in poly(ethylene glycol) shells (Chen et al., 2015). After injection in the ventral tegmental area of the brains of mice, heating associated with the MNPs upon exposure to alternating magnetic fields (15 kA/m amplitude at 500 kHz) enables remote neural excitation through $TRPV1^+$ activation. Animal model studies show capabilities for evoking trains of action potentials in nearby neurons (~250 μm vicinity of the MNPs) and allowing for chronic stimulation for over one month in rat models. Continued work focuses on the development of MNPs with improved energy conversion and reduced latency periods (~5 s in this example [Chen et al., 2015]) between the application of a magnetic field and the onset of neural activity (Lee et al., 2011).

Complex materials systems allow for additional forms of neuromodulation. One example demonstrates photoelectrochemical

stimulation using constructs, shown in Figure 3L, that consist of coaxial p-type/intrinsic/n-type silicon nanowires (SiNWs, 200–250 nm diameter) (Parameswaran et al., 2018). Here, electrons move toward the n-type shell and holes to the p-type core upon exposure to visible light (532 nm, 17 mW), leading to a photocurrent and a cathodic process at the n-type shell capable of depolarizing a target neuron, with minor increases in temperature (0.36 K). This platform allows for stimulation of action potentials in neurons for over a week in the primary rat dorsal root ganglion, limited partly by the slow dissolution of silicon by hydrolysis in the surrounding biofluids. This type of biodegradability can be exploited for applications that demand only temporary neuromodulation, as described in some detail in a subsequent section. In another report, related technology uses organic electrolytic photocapacitors to create open-circuit voltages up to 330 mV upon illumination with light (630–660 nm; intensity of 6 mW/mm^2) (Jakešová et al., 2019). In all cases, an important goal is in the design of these neural systems with various form factors compatible to those of targeted bio-tissues, where biocompatibility is essential at the level of chemistry and mechanics to allow for a stable, minimally invasive operation for neuromodulation *in vivo*. The following section discusses alternative efforts in this direction, emphasizing wireless control systems that match or exceed the performance of the tethered systems described above.

Wireless Interfaces

For all previously discussed examples, fully wireless operation in data transmission, control, and power supply represents an important engineering goal for minimally invasive, chronically stable operation, without restriction on experimental assays, environmental configurations, or behaviors. Experimental demonstrations involve a wide range of animal models (e.g., rodents [Jeong et al., 2015a; Mickle et al., 2019; Park et al., 2015a], fish [Wyart et al., 2009], bird [Arfin et al., 2009], and non-human primates [Capogrosso et al., 2016; Zhou et al., 2019]). Animal studies with miniaturized wireless, battery-free technologies show reduced anxiety-like behaviors and improved social interactions, levels of mobility, and enhanced activity in complex test arenas compared to wired or battery-powered alternatives, with consequences in reliable monitoring of neural processes during naturalistic, ethologically relevant studies (Lu et al., 2018). In a similar way, such approaches offer advantages in clinical use, through reduced surgical trauma, accelerated recovery, minimized infection risks, and improved robustness of operation outside of hospital and laboratory environments, all with costs that can be lower than those of wired and/or externalized systems (Perryman, 2018; Starr, 2018). The interfaces described in the following provide the basis for both communication and/or control and power supply, although the emphasis is on the latter, where the technology challenges are most significant.

As context, batteries represent the standard scheme for supplying power, with numerous examples in commercial platforms (e.g., DBS/VNS/SCS from Medtronic, Abbott, Boston Scientific, Nevro, Sentiva). Certain pre-clinical technologies also use such approaches, particularly for large animal studies. One recent example combines a pulse generator (Activa RC, Medtronic, weight of ~40 g) with flexible stimulating electrodes (Au pads with areas of 2 mm^2, on flexible polyimide films with thicknesses of 40 μm thick and with a 20 μm thick encapsulation layer) that interface to the spinal cord for functional recovery of leg paralysis in a non-human primate (Figure 4A) (Capogrosso et al., 2016). A compliant array of electrodes, distributed along a length of ~50 mm, provides spatially selective stimulation from caudal (activate extension of the leg) to rostral (activate flexion of the leg) compartments of lumbar segments. Here, commands issue from a radio (Bluetooth) user interface to a Bluetooth-to-IR module for transmission to a stimulation programmer (Medtronic), both of which mount on a jacket worn by the animal. The programmer transmits signals to an implanted pulse generator through inductive telemetry. Related schemes can be used in platforms that utilize small-scale, rechargeable polymer lithium cells (0.5–2 g) (Jeong et al., 2015a; Lu et al., 2018; Qazi et al., 2019) on head-mounted units for small animals. In one case, an IR wireless interface provides control over pharmacological and optogenetic manipulation of neuronal circuits through flexible probes inserted into regions of the deep brain of freely moving mice (Figure 4B) (Jeong et al., 2015a).

Although useful in many contexts, batteries pose safety hazards, and their requirements for recharging or replacement represent additional disadvantages. Also, the bulk, size, and weight of batteries often dominate the form factors of the overall systems, thereby limiting miniaturization and constraining options in implantation, of particular concern for use in small animal models (Agrawal et al., 2017; Ferguson and Redish, 2011; Liu et al., 2015). Recent work demonstrates various battery-free, wireless alternatives. Schemes that use power transfer via electromagnetic radiation are attractive due to their demonstrated ability to reliably deliver up to 500 mW (Yu et al., 2019), with many design options. Figures 4C–4H presents a collection of systems of this type, including those based on (Figures 4C and 4D) far-field RF transmission (Figures 4E–4G) near-field resonant coupling, and (Figures 4H) photovoltaics (PVs), each of which can be used to supply power directly or to charge batteries, supercapacitors, or other storage devices.

The first typically involves operation in the ultrahigh frequency (UHF; 300 MHz to 3 GHz) range, where the distance between the transmitting and receiving antennas can be up to meters and more, depending on the power supply requirements and the antenna designs. Figure 4C shows an example that exploits serpentine filaments of copper as structured antennas in an elastomeric polymer matrix (effective modulus of 1.7 MPa) to power soft, thin neuromodulating systems based on optogenetics (optical output of 10 mW/mm^2), with applicability that spans the brain, the spinal cord, and peripheral nerves in mouse models (Park et al., 2015a). These components support stretchable mechanics (strains up to 30%), miniaturized geometries (~16 mm^3), and lightweight construction (~16 mg), to enable reliable operation for more than 6 months in freely behaving animals. Advanced antenna designs with multiple frequency resonances allow independent control over separate μ-ILEDs (Park et al., 2016) and/or other components for neuromodulation, where independent addressability follows from tuning of the frequency of the RF power (1.8 and 2.9 GHz for the combined optogenetic and pharmacologic platform in Figure 4D) (Noh et al., 2018). Disadvantages of far-field power transfer in the UHF range include high sensitivity to the orientations/positions of the antennas, to

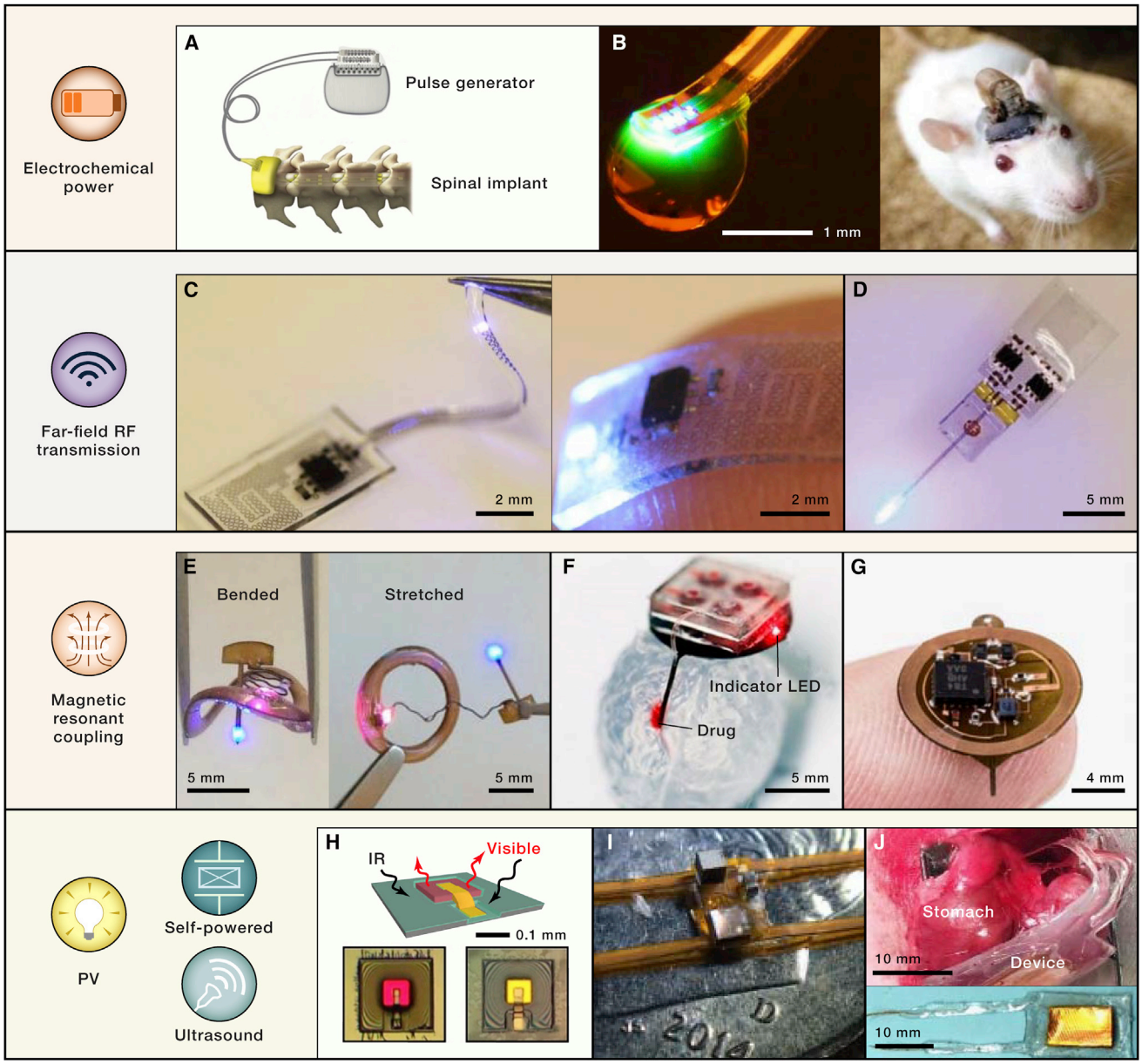

Figure 4. Wireless Interfaces

(A) A spinal cord stimulation system that includes an epidural implant (Au electrodes on flexible polyimide film, thickness 40 μm) and a battery-powered pulse generator (Capogrosso et al., 2016).

(B) Battery powered flexible optofluidic cortical probe that includes microfluidic channels with μ-ILEDs for programmable delivery of pharmacological agents and optical stimulation, respectively (Jeong et al., 2015a).

(C) Far-field RF energy harvester and μ-ILEDs in a soft (effective modulus ~1.7 MPa) stretchable system encapsulated in a silicone elastomer (Park et al., 2015a).

(D) Optofluidic probe with a dual-channel, far-field RF control module in a soft (effective modulus ~1 MPa) platform (Noh et al., 2018).

(E) Optoelectronic probe in a flexible open architecture, powered and controlled by near-field magnetic resonant coupling, for optogenetic stimulation in the deep brain (Shin et al., 2017).

(F) Optofluidic probe with similar wireless interface for programmed delivery of light and pharmacological agents to targeted areas of the brain. LED, light-emitting diode (Zhang et al., 2019a).

(G) Implantable optoelectronic system with integrated circuits and advanced antenna design for improved stability and control in programmable optogenetics (Gutruf et al., 2018).

(H) Implantable microscale optoelectronic device that converts near-infrared to visible light (630 or 590 nm) for optogenetic neuromodulation (Ding et al., 2018).

(I) Implantable electrical nerve stimulator powered by ultrasound (Johnson et al., 2018).

(J) Implantable vagus nerve stimulator powered by triboelectric energy harvested from the motion of the stomach (Yao et al., 2018).

interferences and standing waves that result from interactions with obstacles in the environment, and to absorption by water and biological tissues. As a result, adaptive systems with multiple transmitting and receiving antennas are often necessary for robust operation (Noh et al., 2018; Xie et al., 2019). Even with such approaches, heating associated with tissue absorption (i.e., the specific absorption rate, SAR) impose fundamental limits on the amount of power that can be harvested (Bhat and Kumar, 2013).

Strategies that use near-field magnetic resonant coupling in the low, medium, and high-frequency (LF, MF, HF; 30 kHz to 30 MHz) ranges exhibit greatly reduced sensitivity to environmental obstructions and to details of the antenna designs and orientations. Reliable power transfer (typically a few tens of mW, Zhang et al., 2019a) can be realized with compact antennas, over practical distances of up to one meter (Kurs et al., 2007). The SAR for operation in this frequency range is minimal, due to the relatively low level of water absorption compared to UHF range (Hammer et al., 2016; Qureshi et al., 2016), thereby reducing safety concerns for long-term use even at high-power operation. As a result, such approaches can serve as useful options for a range of neuromodulation devices based on electrical, optogenetic, and pharmacological effects. Figure 4E shows an example of a wirelessly powered optogenetic stimulator (optical output up to 50 mW/mm^2 or more) for use in the deep brain (Shin et al., 2017). The small sizes (diameter of ~9.8 mm, thickness of <1.3 mm) and lightweight (~30 mg) designs allow complete implantation even in small animal models, with mechanical flexibility to conform to the targeted anatomy without significant reductions in power harvesting efficiencies for bending radii down to 6 mm, smaller than that necessary for a typical mouse skull (~7 mm). A bi-layer encapsulation of PDMS ensures good bio-compatibility and long-term stability (more than a year) inside the brain and under the skin.

As with far-field power harvesting, this strategy can also support other modes of operation, such as delivery of pharmacological agents through microfluidic probes (0.35 × 0.1 mm^2, effective modulus of 3 MPa) (Figure 4F) that insert into the deep brain (Zhang et al., 2019a). The small, lightweight designs (0.3 g) enabled by battery-free operation lead to substantially higher baseline locomotor activity with small animal models compared to that associated with otherwise similar, but battery powered, devices (weight of ~2 g) (Jeong et al., 2015a). Here, electrochemical micropumps support low power operation (<1 mW) with minimal heat generation (<0.2°C), as advances over corresponding thermally activated systems (Figures 4B and 4D). Optogenetic stimulation (intensity, 10 mW/mm^2) of the ventral tegmental areas of wild-type mice increases locomotion behavior while infusion of an N-methyl-D-aspartate (NMDA) receptor antagonist blocks this activity. Other examples of wireless power are in devices with single (Figure 4G) or multiple μ-ILEDs on individual probes or across a collection of probes, for targeting spatially distinct sites with programmable frequencies, duty cycles, and emission intensities (Gutruf et al., 2018). These and other advanced features are possible without significant compromises in device size (diameter of 10 mm) or weight (~75 mg) compared to basic systems (Figure 4E), thereby retaining features in minimal invasiveness and full subdermal implantability. The limited range of operation is the most significant disadvantage of these near-field power transfer approaches, although with limited practical consequence when used for charging batteries as opposed to supporting direct operation.

PV technology represents another option in electromagnetic power harvesting. In one example, a pair of PV cells (thickness of 32 μm, areas of ~26 mm^2, and weights of 5 mg) provide power to μ-ILEDs for optogenetic stimulation (Park et al., 2015b). As an advantage over RF power, PV approaches allow reductions in device dimensions to sub-millimeter sizes. Figure 4H shows a thin (thickness of 9 μm), ultraminiaturized (220 × 220 μm^2) system that integrates a PV cell with a visible μ-ILED (e.g., red and yellow) (Ding et al., 2018). Illumination with IR light, which has relatively low absorption in biological tissues, generates PV current that activates the μ-ILED (optical output of >1.1 mW/mm^2). Here, the small size enables neuronal manipulation with high spatial resolution at specific discrete sites. A separate report describes a miniaturized (lateral dimension of 250 × 60 μm, thickness of 330 μm), lightweight (~10 μg), wireless optoelectronic neural interface that integrates complementary metal oxide semiconductor (CMOS) circuits and AlGaAs (aluminium gallium arsenide) photodiodes for neural recording (Lee et al., 2018). The photodiode supports power harvesting, in a PV mode, as well as data transmission, in an NIR LED mode. The CMOS integrated circuit digitizes, encodes, and amplifies the neural signals. Similar schemes can be envisioned for electrical or thermal forms of neuromodulation, although power requirements for these and other PV powered platforms often demand the use of intense light sources, actively directed toward the implant.

Acoustic waves, like electromagnetic waves, can also serve as sources of power. One class of technology uses vibrations of piezoelectric crystals induced by interactions with ultrasound generated by an external transducer and passed through the surrounding tissues, as a means to convert the mechanical power into electrical power (Johnson et al., 2018; Seo et al., 2016). By comparison to PV and far-field RF approaches, ultrasonic harvesting involves comparatively low levels of tissue absorption (1 db/cm for ultrasound at 2 Mhz, 3 db/cm for RF radiation at 2 GHz [Johnson et al., 2018]). In one example, a miniaturized (volume of 6.5 mm^3), lightweight (10 mg) peripheral nerve stimulator utilizes a single piezocrystal (volume of 0.4 mm^3) for both power harvesting and data communication (Figure 4I) (Johnson et al., 2018). Such devices provide electrical currents of up to 400 μA through cuff interfaces to the sciatic nerve. Here, the interface electrode consists of a layer of Au electroplated with PEDOT:PSS to increase the CIC. Related technology uses ultrasound to vibrate a membrane (lateral dimension of 16 cm^2, thickness of 50 μm) that creates electrical power by triboelectric effects, with output voltages and currents that can reach 2.4 V and ~160 μA, respectively (Hinchet et al., 2019). As with far-field RF approaches, the directional propagation of acoustic waves demands careful alignment and/or orientation between the external transducer and the implant, thereby suggesting the need for arrays of transducers and adaptive approaches to maintain adequate coupling. Additionally, parasitic generation of heat by interaction of ultrasound with bone must be considered (Nelson et al., 2009).

These types of piezoelectric and triboelectric effects can also yield power from natural muscle contractions, heart/lung activity, and/or blood flows, thereby avoiding the need for external hardware for power delivery but also eliminating possibilities for use in external communication and/or control. For example, periodic deformation of flexible and conformal piezoelectric devices (500 nm thick lead zirconate titanate [PZT] on 75 μm thick polyimide substrate) affixed to epicardial sites of bovine hearts produce open circuit voltages of ~1 V, which can be further enhanced through multilayer designs (>8 V with 5 layer of PZT) (Dagdeviren et al., 2014). Other work uses flexible triboelectric generators (lateral dimensions of 1 mm^2, thickness of ~1.4 mm) attached on the surfaces of the stomach to produce biphasic electric pulses (peak to peak voltage up to ~0.1 V) that stimulate vagal afferent fibers in response to the peristalsis of the stomach (Figure 4J) (Yao et al., 2018), with envisioned use in the automated control of the hunger sensation. The main disadvantage of harvesting from such types of natural motions is in the relatively low available power (~1–10 μW) (Hinchet et al., 2019) and its intermittency. Future efforts on a combination of power efficient neuromodulation systems and local power storage may lead to solutions that mitigate some of these concerns.

In summary, wireless implantable medical devices are now in widespread use for therapeutic stimulation and for neuroscience research in freely moving subjects. Recent efforts to minimize the critical dimensions and mechanical load of such devices focus on strategies for wireless data transmission and power harvesting to replace traditional, and still mainstream, battery power sources. The results presented here represent some of the most advanced wireless battery-free platforms, with an emphasis on systems with capabilities in electrical, optical, and pharmacological neuromodulation. Associated progress in electrical, biomedical, and material engineering also support impressive measurement performance, resulting in possibilities for automated or closed-loop operation, as discussed in the next section.

Automated, Closed-Loop Operation

Capabilities for adjusting levels of neuromodulation in response to pathologic neuronal activity provide the basis for precise and patient-specific treatments. An example includes real-time control of DBS in response to abnormal neuronal activity (beta frequency band) recorded directly from the stimulating electrode in the subthalamic nucleus of patients with Parkinson's disease (Quinn et al., 2015). Additional demonstrations involve controlling the intensity of SCS according to changes in a patient's body position and modulating focal cortical stimulation in response to abnormalities in electrocorticography signals (Lo and Widge, 2017). Such closed-loop approaches offer energy efficient, consistent treatments, with improved clinical responses (Lo and Widge, 2017; Morrell and Halpern, 2016). FDA-approved platforms (e.g., NeuroPace) are now available to support such combined capabilities in both sensing and neuromodulation, with built-in signal processing, as in responsive stimulation directly at seizure foci for consequent reductions in seizures in adults with intractable partial-onset seizure (Lo and Widge, 2017).

Pre-clinical evidence for conceptually similar conditional or closed-loop operation but with advanced neuromodulation modalities based on optogenetics and with real-time electrophysiological signal and biophysical data processing suggest capabilities in interrupting seizures in freely moving animals (Grosenick et al., 2015). In one example, an array of tungsten wires (diameter of 25 μm) and an optical fiber (diameter of 200 μm) capture cortical electroencephalogram (EEG) data from thalamocortical neurons and optogenetically inhibit their activity (eNpHR3.0 activation at a wavelength of 594 nm), respectively, in injured epileptic cortex (Paz et al., 2013; Yizhar et al., 2011). Real-time EEG recording and consequent calculation of EEG line-length provides the basis for activating a laser light source for optogenetic stimulation in response to onsets of seizures, with stable operation in rodent models for nearly a year. Behavioral analysis, rather than electrophysiology, can also serve as a conditional variable for closed-loop optogenetics, in an otherwise similar fashion. In one example, optical stimulation (ChR2 at wavelength of 473 nm) of single barrels of somatosensory cortex produce perceptions of touch if the stimulation occurs during bouts of whisking (O'Connor et al., 2013). Additional details on closed-loop optogenetic control in behaving animals appear elsewhere (Grosenick et al., 2015).

A frontier direction in the development of closed-loop neuromodulation is to exploit advances described in previous sections for lightweight, miniaturized, battery-free wireless devices for both recording and modulating neural activity in different contexts. A recent publication describes a fully implantable, wireless (resonant magnetic coupling) optoelectronic platform that combines (1) a pair of μ-ILEDs for optogenetic stimulation of peripheral nerves, (2) a soft (effective modulus of 70 kPa) and stretchable sensor for continuous monitoring of organ function, and (3) a wireless power harvesting and control module for bidirectional communication with customized software deployed in a handheld device (Figure 5) (Mickle et al., 2019). Such platforms enable automated neuromodulation with good stability (>1 month) and minimally invasive operation, without requirements for direct contacts to the nerve or incisions in the targeted organs. Figure 5 shows an integrated system with these design features that monitors bladder function using a soft, precision strain gauge as a sensor of voiding frequency and employs computational algorithms to identify pathological behavior. Optogenetic neuromodulation of bladder sensory afferents through a pair of μ-ILEDs normalizes function in the context of acute cystitis, in a closed-loop manner. Identification (>85% accuracy) of overactive voiding triggers automated optogenetic modulation to attenuate voiding, with temporal specificity and active control timed to periods of organ dysfunction. Studies indicate no significant inflammatory responses, changes in gait/weight, or fibrotic responses, owing to the soft mechanics, lightweight construction, and wireless, battery-free operation. The same system architecture has potential for applications beyond the bladder, through use of different sensors (biopotential, biophysical, and biochemical) and different types of neuromodulation (electrical, optical, thermal, pharmacological). Continued work on this technology as a multiuse platform focuses on envisioned applications as interfaces to peripheral nerves for treatments of other conditions,

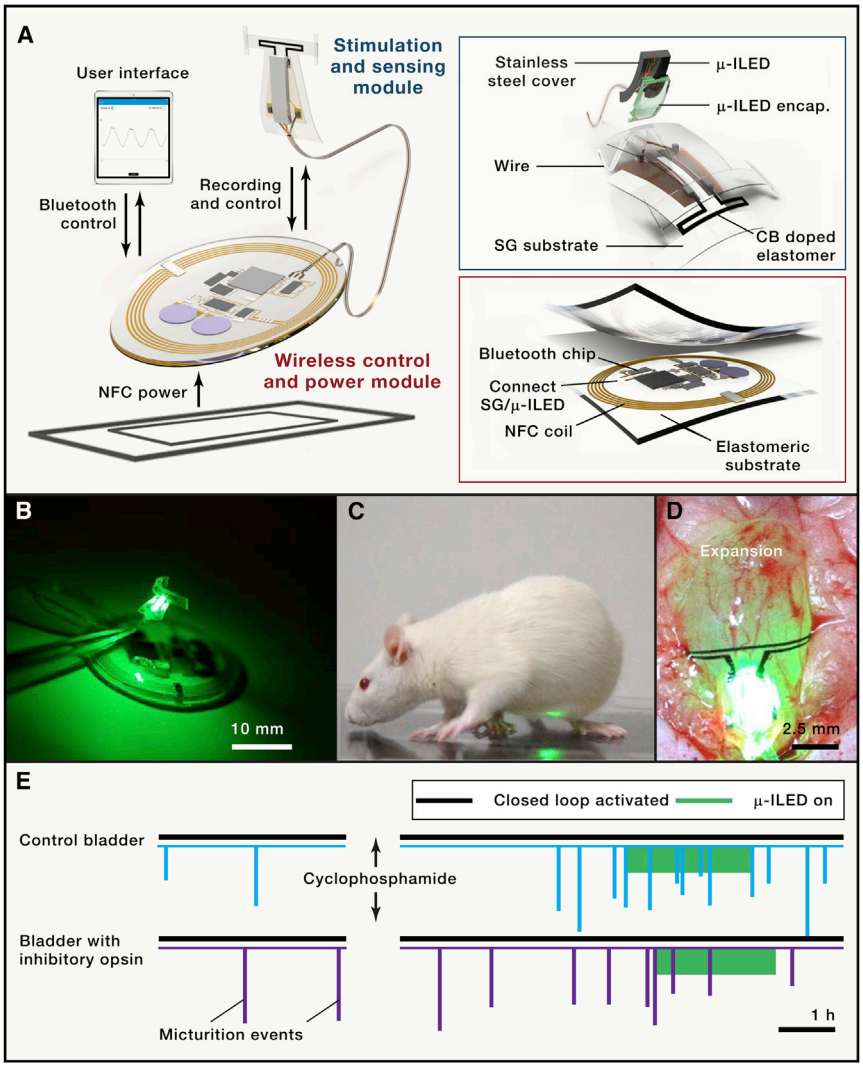

Figure 5. Automated, Closed-Loop System for Neuromodulatory Control of Organ Function

(A) Schematic illustration of a soft, battery-free, wireless, optoelectronic system for automated, closed-loop optogenetic modulation of peripheral nerves in rats. NFC, near-field communication; SG, strain gauge; CB, carbon black; μ-ILED, micro-scale inorganic light-emitting diode.

(B) Optical image of a device that consists of optoelectronic stimulating and sensing module and wireless base station for power harvesting and data communication.

(C) Optical image of a rat implanted with the device.

(D) Optical image of a soft strain gauge (effective modulus of ~70 KPa) and μ-ILED that wraps around the expanded bladder of a rat.

(E) Results of automated activation of μ-ILEDs to modulate sensory neurons that innervate the bladder, in a manner that eliminates bladder voiding event (e.g., micturition event) associated with overactive bladder. Cyclophosphamide causes bladder-specific inflammation and increase voiding event (Mickle et al., 2019)

facilitated by soft, miniaturized form factors and minimally invasive designs.

Bioresorbable Systems

Although the various classes of systems highlighted in the previous sections offer powerful capabilities for neuromodulation, they all have designs oriented toward chronic operation. In many cases, neuromodulation is relevant only for relatively short periods of time, typically defined by a related natural biological process such as a wound healing cascade or an immune response. After this period of need, the devices represent unnecessary loads on the body, with affiliated risks to the patient. Surgical extraction can resolve these issues but only through additional procedures that themselves involve pain, discomfort, additional risks, as well as costs to the healthcare system (Cha et al., 2019; Kang et al., 2018; Won et al., 2018). An emerging area of research in technologies for neuromodulation seeks to address this challenge through materials and device designs that disappear naturally over time frames of interest via processes of bioresorption (sometimes referred to as bioabsorption), typically involving hydrolysis reactions with surrounding biofluids. These systems rely on collections of conductors (e.g., Mg, Mo, W, Ca, Zn, Fe, conductive composite materials, etc.), dielectrics (e.g., SiO_2, MgO, silk fibroin, collagen, poly(lactic-co-glycolic) acid [PLGA], poly(lactic acid.) [PLA], etc.), and semiconductors (e.g., Si, Ge, ZnO, etc.) that dissolve into biologically benign products at rates controlled by the materials combinations and layouts (Cha et al., 2019; Kang et al., 2018; Yu et al., 2018). Optical emission spectrometry indicates complete removal of elemental constituents (e.g., Si and Zn) associated with such types of bioresorbable implants from most organs via excretion through the kidneys at 5–7 weeks after implantation in mice models (Bai et al., 2019; Shin et al., 2019b). Recent demonstrations include bioresorbable devices for electrophysiological (Yu et al., 2016), biophysical (e.g., pressure, temperature, flow, etc.) (Kang et al., 2016), and biochemical (e.g., pH, Ca^{2+}, oxygenation, etc.) (Bai et al., 2019) sensing and for various forms of neuromodulation (e.g., electrical, thermal, chemical). Power supplies include coils and antennas for electromagnetic coupling (Koo et al., 2018), and triboelectric (Liang et al., 2017; Zheng et al., 2016) and piezoelectric (Dagdeviren et al., 2013) components for mechanical energy harvesting. Bioresorbable batteries (Jia et al., 2017; Jia et al., 2016; Yin et al., 2014) and supercapacitors (Lee et al., 2017) are available for energy storage.

Such devices can be combined into complete systems as temporary implants for neuromodulation, with clinically relevant demonstrations in animal models. Figure 6A highlights the use

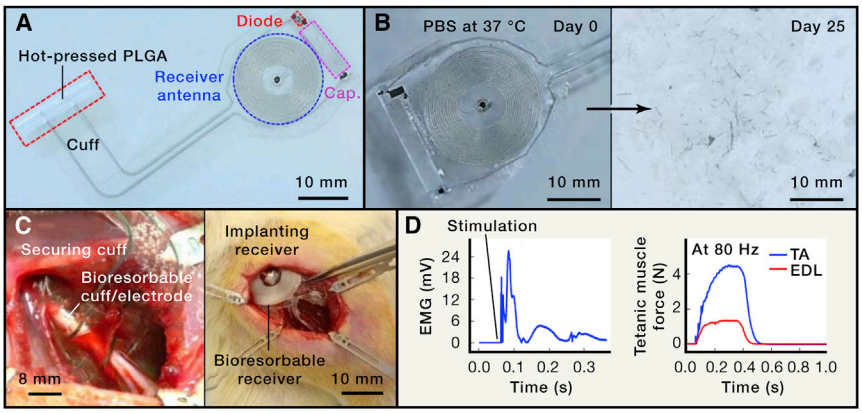

Figure 6. Bioresorbable Systems for Temporary Neuromodulation

(A) Optical image of wireless, fully bioresorbable stimulator designed to interface to damaged peripheral nerves to improve functional recovery and accelerate neurogeneration.

(B) Optical images showing processes of dissolution in phosphate-buffered saline (PBS) at 37°C.

(C) Surgical procedure for implantation of wireless, fully bioresorbable stimulator.

(D) Tetanic and twitch force at tibialis anterior (TA; blue) and extensor digitorum longus (EDL; red) muscles elicited by a monophasic pulse at frequencies of 80 Hz (left) and 0 Hz (right) (Koo et al., 2018).

of bioresorbable materials (Mg, Mo, PLGA, silicon nanomembranes) in electrical stimulators designed to enhance rates of neuroregeneration and functional recovery of injured peripheral nerves (Koo et al., 2018). A bioresorbable stimulator of this type can be implanted into the body as part of an otherwise necessary surgical procedure to treat the nerve, thereby allowing dosed delivery of stimulation at various time points during the recovery and healing process. In this way, such platforms can enhance and extend the known benefits of stimulation delivered with conventional devices during the intraoperative period, where bioresorption eliminates the need for surgical extraction. The complete system (width of 10 mm, length of 40 mm, thickness of 0.2 mm, weight of 150 mg) includes a resonant magnetic coupling antenna (inductor and capacitor made with Mg and SiO_2), a rectifier (diode made with a Si nanomembrane), and a cuff electrode interface (metal strips of Mg or Mo on a thin curved sheet of PLGA), each of which dissolves completely after 25 days in simulated biofluid (e.g., phosphate buffered solution, pH = 7.4 at 37°C). Results indicate that monophasic electrical stimulation using a wireless power delivery and control scheme for 1 h (200 μs pulse duration, 20 Hz frequency) each day over 6 days after implantation leads to improved functional nerve recovery (e.g., muscle reinnervation and axonal regeneration) compared to that achievable with stimulation only for 1 day or for 3 days. Implantation and bioresorption lead to no evidence of axonal damage and no cytotoxic responses.

Other types of bioresorbable devices support programmed release of drugs to deep brain tumor cells through wirelessly triggered thermal actuation (temperature change of ~5°C, by Joule heating) (Lee et al., 2019). The materials and engineering approaches demonstrated in this context can be adapted for neuromodulation using the thermal and chemical pathways described in previous sections, to yield bioresorbable stimulation platforms for manipulating the neuronal activity. These examples of neuromodulation with bioresorbable systems suggest a future in engineered forms of "medicines" that operate and disappear for clinical applications such as those in managed and accelerated wound healing, with examples in peripheral nerve injuries where pharmaceutical approaches have limited efficacy. Opportunities lie in the development of additional bioresorbable materials, particularly those that support combined optical and pharmacological stimulation, for outcomes that lie beyond the scope of either approach individually.

Conclusions and Future Perspectives

Implantable devices for neuromodulation and/or neuroprosthetics are now well established and in widespread use as highly effective treatments for a rapidly expanding patient population and corresponding set of health conditions. Advanced technologies currently deployed in animal models suggest a future where varied modes of neuromodulation, beyond those supported by simple electrical stimulation from small collections of electrodes, offer enhanced functions, expanded applications, improved utility, and reduced invasiveness. Recent progress in materials science, electrical engineering, and design principles in soft mechanics establish the foundations for highly functional, tissue-compliant platforms with such types of sophisticated capabilities in stimulation as well as sensing, some with closed-loop methods of operation and wireless schemes for control, communication, and power delivery. A sub-field in this broader area of engineering science involves temporary neuromodulatory systems constructed entirely with bioresorbable materials, engineered to offer physical lifetimes matched to natural biological processes associated with transient health conditions. Many of these technologies are in advanced stages of animal testing and development for specific envisioned applications in human healthcare. Others are commercially available for animal model studies of fundamental biological processes, most prominently in areas of neuroscience and physiology research.

The emerging systems for neuromodulation highlighted in this review each have immediate uses in fundamental research and academic studies at the level of cell cultures, organoids, and animal models. Although many of the underlying concepts are appealing, critical challenges remain in realizing the full potential of many of these methods for clinical applications, where the most significant areas of work include those in (1) advanced modalities for recording/stimulation and for monitoring/treating neurological disorders, (2) high spatiotemporal resolution and scalability (thousands of active channels) for high-fidelity operation, and (3) chronically stable biocompatibility in materials, surface chemistry, mechanics, and geometry, tailored for specific uses. The first and the second areas emphasize device characteristics in neuromodulation, while the third encompasses issues

related to clinical practice, including important practical concerns such as compatibility with magnetic resonance imaging (MRI) technologies, where high local magnetic fields can affect device operation and connections within the neural networks (Vargas et al., 2018)

Remaining challenges are in realizing chronic operation with flexible, and especially stretchable, mechanics with reliable encapsulation layers and robust neural interfaces, for stable operation over timescales that match or exceed human lifespans. Particularly challenging are complex systems that provide multimodal stimulation capabilities and retain soft mechanical properties. Biocompatible materials for this purpose, in thin film geometries (at submicron thickness) and without defects over areas that can reach scales of square centimeters (such as SiC, SiO_2, SiN_x), are essential for device longevity (Phan et al., 2019). Recent research establishes that thin, transferred layers of SiO_2 derived from thermal growth on silicon wafers offer exceptional characteristics in this context (Song et al., 2019). Ongoing efforts focus on integration of these types of barrier materials with implantable recording/stimulation devices, the results of which may lead to chronic operational stability *in vivo*, with minimal foreign-body immune responses.

Continued efforts in miniaturization of component devices and/or active material structures to cellular and even subcellular dimensions represents a compelling additional focus of research in this field. Soft, shape-conformal mechanics and biocompatible materials will remain essential features for long-term stability as chronic neural interfaces. Device designs and schemes for integration will increasingly blur the boundaries between biotic and abiotic systems. Autonomous closed-loop operation, as an overarching goal, will be facilitated by progress in biophysical, biochemical, and electrophysiological sensing, as a multi-parametric complement to multi-modal neuromodulation. Complete control of neural activity, from individual cells, to tissue constructs and full organ systems defines an aspirational set of goals that will increasingly intersect with technical feasibility and clinical practicality. Realizing this vision will require not only advances in biocompatible microsystems but also improvements in a basic understanding of fundamental biological mechanisms. Here, progress in technology, through the development of sophisticated devices, techniques, and tools, will accelerate the pace of discovery in biology; these discoveries will, in turn, inform further improvements in technology, in a synergistic feedback relationship that follows from cross-disciplinary collaboration. The platforms for sensing and neuromodulation that emerge from this process will be paired with machine-learning techniques that incorporate biological insights, to allow deterministic, efficient, and safe operation. The resulting data and associated medical analytics will yield a corresponding depth of information on human health status and disease progression, with separate, independent value to the healthcare system. The breadth of interesting interdisciplinary topics in applied and basic research, taken together with the potential for outcomes of essential relevance to grand challenges in human health, foreshadows a promising future for continued work in this growing, vibrant field of study.

DECLARATION OF INTERESTS

J.A.R. is a co-founder of a company, NeuroLux, that builds patented wireless neurotechnology for the neuroscience research community.

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