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Precision electronic medicine in the brain

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Periodically throughout history developments from adjacent fields of science and technology reach a tipping point where together they produce unparalleled advances, such as the Allen Brain Atlas and the Human Genome Project. Today, research focused at the interface between the nervous system and electronics is not only leading to advances in fundamental neuroscience, but also unlocking the potential of implants capable of cellular-level therapeutic targeting. Ultimately, these personalized electronic therapies will provide new treatment modalities for neurodegenerative and neuropsychiatric illness;Work from our laboratory powerful control of prosthetics for restorative function in degenerative diseases, trauma and amputation; and even augmentation of human cognition. Overall, we believe that emerging advances in tissue-like electronics will enable minimally invasive devices capable of establishing a stable long-term cellular neural interface and providing long-term treatment for chronic neurological conditions.

Neurotechnologies that interface directly with the human nervous system have reached a tipping point—one that could open new applications for electronic implants in neuroscience and medicine. Decades of research and clinical applications of therapeutic electrical stimulation[1–3], as well as the development of neural probes for neuroscientific exploration[4–6], provide a strong foundation for this future. However, despite this positive trajectory, we argue here that current neural interfaces are only a stopgap until basic structural, mechanical and topological mismatches between electrical probes and the cellular networks comprising the brain are resolved[7]. In this Perspective, we highlight the need for truly stable and minimally invasive brain–electronic interfaces that mimic the natural properties of neural tissues and their constitutive cells. Approaches that allow stable mapping and modulation of the same individual neurons and neural circuits over extended periods of time promise to unlock new avenues for delivering personalized therapy to individuals with complex neurological and psychiatric disorders, as well as powerful control of prosthetics for restorative function in degenerative diseases, trauma and amputation—what we term here 'precision electronic medicine'. The key components of precision electronic medicine are as follows: (i) stable recording and tracking of the same individual neurons that comprise neural circuits over time (most current technologies do not have this capability)[8,9]; (ii) stable modulation of the individual neurons in neural circuits based on changes in recorded signals monitored in (i) (current technologies can only modulate regions of the brain comprising thousands of neurons)[1]; (iii) closed-loop feedback and control based on the stable tracking and stable modulation of individual neurons in neural circuits; and ultimately, (4) monitoring and modulation at the level of specific neuron subtypes.

In this Perspective, we suggest that a central component for achieving these breakthroughs will require development and adoption of 'tissue-like' neural technologies capable of producing a stable interface at the cellular to subcellular level in the brain over extended periods of time. We first outline our vision of precision electronic medicine, essential pieces needed for implementation of this vision, and areas where it might influence basic science and therapeutics. Next, we step back to discuss briefly the state of the art in neural implant technologies both for medical and research applications. We highlight substantial advances made in front-end integration where implants connect to the brain and in back-end input/output connectivity and data processing, as well as highlighting fundamental mechanical, structural and biochemical mismatches between implants and cellular networks in neural tissues that ultimately limit the ability to have precise communication with the same neurons over the life of an implant and thus the ability to have more sophisticated biological functionality. We then describe how applying concepts of biomimicry have yielded 'tissue- and neuron-like' electronics with immune-privileged characteristics capable of stably integrating and recording from the brain over long periods of time. Lastly, we discuss developments that could produce a cell-type-specific, bidirectional electrical interface, modification of tissue-like implants to enable cellular development for neural (or tissue) healing, and limitations that must be overcome to realize precision electronic medicine.

Trends in neural recording and neuromodulation

The three key components of neuromodulation and neuroprosthetic systems are sensing, control and processing (Fig. 1). Among the diverse technologies used in these three areas, there are commonalities that can both help assess the advantages and disadvantages of existing and emerging neural devices and provide a framework to contextualize our vision for precision electronic medicine. When referring to sensing, we consider signals of activity recorded directly from the brain (for example, surface or implanted electrode arrays), as well as from devices used to detect, for instance, external visual or audio signals. Signals that provide control are those that can be delivered to a part of the brain or peripheral nervous system via implanted electrodes or to, for example, a prosthetic limb. The last component, the processor, we define as the hardware that transforms sensing signals that are then sent to a control device or nervous tissue. In many commercial implanted stimulators, the processor and control electrodes form an open loop—without direct sensory feedback—although the processor can be adjusted and/or subsequently optimized to maximize effectiveness on the basis of observed patient response. Current and future trends point to closed-loop systems in which feedback signals, especially from the brain or nervous system, are used directly in the processor to optimize the control signals in real time to maximize effectiveness[10,11]. Ultimately, this would allow more precise targeting and control of neural biomarkers directly related to symptom relief, thus improving therapeutic efficacy and reducing unwanted side effects.

To date, most neural devices are unidirectional—capable of recording or stimulating neural activity, but not both. A unidirectional

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recording device, such as a motor prosthetic, can decode motor intention from cortical neural activity and actuate a robotic arm in order to restore movement in a paralyzed individual[12,13]. Similarly, unidirectional stimulation devices, including cochlear implants[14], deep brain stimulation[1], and motor[12] and visual prosthetics[15,16], have yielded successes in modifying and augmenting brain function for therapy or support. Technological and scientific constraints, including the relatively small numbers of electrodes in multisite neural stimulators, a lack of stable neural interfaces making it difficult to stably track neural activity necessary for feedback, limitations in computational processing, and insufficient understanding of the underlying neural code, have limited progress in expanding beyond unidirectional prosthetics, though this is slowly changing[17–19].

Neural stimulation systems. The first account of the clinical application of electrical brain stimulation can be traced to a Roman physician, Scribonius Largus, who in the year 46 detailed the application of a bioelectric fish, *Torpedo ocellata*, to the cranial surface for the treatment of headache and gout[20]. Today, although we have access to more modern technologies, the same open-loop electrical stimulation concept is used in devices implanted on the surface or in deeper tissue of the brain (Fig. 1). These approaches, which include deep brain stimulation (DBS), are being used to treat movement disorders and neurological and neuropsychiatric disorders, including Parkinson's disease, obsessive-compulsive disorder, depression, epilepsy and Alzheimer's disease (for review, see ref. [1]).

These neural stimulation approaches are relatively 'brute force' therapeutic interventions involving widespread modulation of neural activity through implantation of large, low-impedance stimulating electrodes. For example, reduction of motor symptoms such as tremor, bradykinesia and rigidity with bilateral subthalmic nucleus DBS treatment of Parkinson's disease using implantable electrodes is well established, but is prone to the following limitations[21] (see Review by Cagnan et al.[22], this issue): first, DBS electrode sizes and corresponding estimated stimulation volumes encompass large numbers of distinct types of neurons and different functional pathways[23–25], which has the potential for unwanted side effects and precludes therapeutic applications of higher precision; second, stimulation is typically applied without feedback, except for adjustments made post-implantation by the neurologist to optimize effectiveness through iterative and periodic patient observation, limiting the efficiency of therapy; and third, the continuous mode of operation and large implant designs limit the effective lifetime of implants in terms of battery life[26–28] and adverse tissue immune response to the implants[29], respectively.

Several of these limitations are being addressed by efforts focused on improving clinical implants. To provide finer control of the effective stimulation volume, commercial designs that segment the implant and increase the number of addressable electrodes are being implemented[30,31]. However, the typical sizes of these segmented electrodes remain large with respect to individual neurons, and finite element models suggest they may have limited ability to steer therapeutic stimulation currents beyond that provided by the four radial electrodes of common DBS electrode design[32]. Demonstrations of closed-loop stimulation in research studies[17,33] wherein brain activity is monitored through local field potentials (LFPs) have led to the implementation of upgraded DBS systems for clinical evaluation[34,35]. Real-time recordings from DBS electrodes or tandemly placed brain surface electrodes can provide feedback-controlled neural stimulation, adjusting stimulation parameters such as voltage and timing through embedded algorithms[36]. Although advances in closed-loop stimulation delivery have immediate applications for the improved treatment of diseases, such as Parkinson's disease, Tourette's syndrome[37,38] and epilepsy[39], they do not overcome fundamental limitations of selective circuit-to-neuron group pairings necessary in precision electronic medicine. Ultimately, these approaches remain low in resolution, indiscriminately stimulating large numbers of different types of neurons and distinct neuronal pathways; are unable to provide detailed feedback information from neuronal spiking circuit activity; and do not address the intrinsic mismatch of implants with tissue that results in an immune response and ultimately limits electrode stability and lifetime.

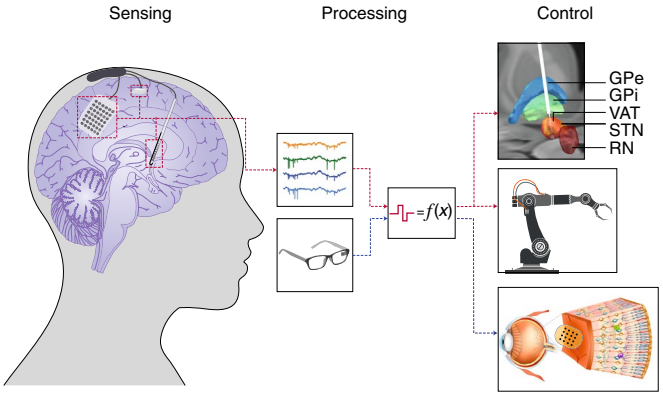

Fig. 1 | Unidirectional and bidirectional neurostimulation approaches. Most commercially available neurostimulation devices are unidirectional, capable of recording or stimulating but not both. For example, unidirectional recording devices (red line), such as motor cortical prosthetics, decode motor intention from motor cortical networks to actuate a robotic arm and restore movement[12,13]. Similarly, unidirectional stimulation devices (blue line), such as retinal prosthetics, map visual-spatial information from cameras to create visual percepts by stimulating retinal receptive fields[15,16]. Bidirectional neurostimulation devices are capable of both sensing and stimulating in a real-time and adaptive manner, thus creating new opportunities leveraging closed-loop approaches. The globus pallidus externus and internus (GPe and GPi, respectively) and the red nucleus (RN) are located in close proximity to the subthalamic nucleus (STN); when the STN is targeted, the imprecise volume-activated tissue (VAT) spills over into neighboring regions, often resulting in side effects.

The development of improved neural interfaces[40,41], including the engineering and manufacture of fully implantable neural recording systems capable of large-scale, high-bandwidth recordings and stimulation, as well as algorithms capable of real-time, closed-loop therapy and prosthetic control[42,43], have also been an emphasis of large research programs worldwide[44–47]. The primary objective of these programs is growth of neurotechnologies that bridge the spatial-temporal gap between the submillisecond functioning of networks with the micrometer-scale connectivity of neurons. For example, these programs have promoted high-density integration (discussed in the next section) and have led to substantial advances in integrated chips for processing between the sensing and control components (Fig. 1). Recently, a fully implanted closed-loop device was produced that was capable of recording LFPs as well as detecting single-unit raw neural signals on device[44,46]. The availability of custom chip design allows configurable recording and stimulation mosaics based on implant location, duration and physiological function[44]. Although these advances represent important milestones in demonstrating proof of principle in technological hardware capable of supporting bidirectional neural applications, these approaches are fundamentally limited by the use of imprecise and relatively rigid neural interfaces that preclude stable interfaces to cellular and subcellular neural elements and, correspondingly, prevent stable monitoring and modulation of the same neurons, which are relevant to precise therapy and prosthetic control.

High-resolution neural interfaces. In parallel with developments in neural stimulation systems, substantial effort has focused on increasing electrode density of neural recording probes (sensing in Fig. 1) to record spiking activity from greater and greater numbers of individual neurons[5,48,49] (see Review by Frank et al.[50], this issue). These efforts have been motivated by earlier contributions to fundamental neuroscience that identified the role of single neurons in behaviors, such as the discovery of simple cells in visual encoding[51], place and grid cells in spatial encoding[52,53], and motor population coding[54]. In addition, advances in the fabrication technology for electronics have allowed the production of devices capable of simultaneously recording on the order of 1,000 neurons. Immediate opportunities to improve brain–machine interfaces for prosthetic control, for example, are possible by increasing the number of simultaneously recorded neurons because larger numbers allow more degrees of freedom for more natural control[13,55,56].

Emerging large-scale electrode technologies[57–59] have enabled the generation of neural recording datasets of unprecedented size across functionally connected networks in different regions of the brain, but not without limitation. Foremost, micromotion and the foreign body response elicited by rigid neural probes makes it difficult to track single neuronal activity over extended periods of times, as would be necessary for a precision therapeutic implant[6]. Many factors contribute to chronic inflammatory response, including the physical size, mechanical properties and biochemical composition of the probe[49,60–62]. For example, activated microglia and reactive astrocytes attempt to sequester the probe, which they recognize as a foreign body, eventually forming a multinucleated dense encapsulation layer between the probe and parenchyma. This barrier reduces probe signal-to-noise ratio, inhibits local axonal growth and results in neural atrophy[4]. The fundamental mismatch of the sizes and mechanical properties of probes and their impact on the foreign body response have been reviewed[8,49] (see Fig. 2 for a summary with respect to the brain and effective probe lifetime). Biomimicry and biocompatibility approaches have been explored with varying degrees of efficacy, including biomolecular coatings to promote neural density and to reduce immunoreactivity near the probe (for comprehensive reviews, see refs. [4–6]). Although these approaches can improve the performance of rigid neural probes, they do not address the fundamental size and mechanical mismatches with host cells and tissues.

Neural probes tailored to the brain architecture

From the perspective of probe function, the different elements that make up nervous tissue span a wide range of sizes: synapses can vary from 20 to 40 nm, whereas neuron cell bodies and glia can span 4 to 100 μm[63]. Microwire and conventional silicon array-based technologies remain larger than the scale of neural elements, particularly in high-density probes[64]. Relative to a probe, neural tissue is soft, and the subcellular structures of neurons, such as axons, are even softer[65,66]. Moreover, neural tissue undergoes periodic motion due to blood flow and periodic pressure changes associated with beating of the heart[67], as well as motion of the brain within the skull during locomotion and head movements[48]. Mechanically, conventional neural probes, such as silicon, carbon or so-called flexible polyimide probes, have bending stiffnesses at least 2 to 3 orders of magnitude greater than that of brain tissue, which is between 10^{-4} to 10^{-1} nN m per unit width for a brain slice 20–100 μm thick[68], with the values for axons being several orders of magnitude smaller[65,66]. The size and mechanical differences between the probe and brain are at the root of chronic inflammatory responses and gliosis, which result in scarring and degradation of the neural interface. Mechanical stiffness mismatch, which readily leads to micromotion, also makes it difficult to track the same individual neurons and neural circuits over time. Finally, the topology of standard probes is different from the interconnected, open 3D structure of the brain, with neurons, astrocytes and glia[69]. Without adopting such a topology, probes not only exclude cells from their occupied volume but also, perhaps more importantly, preclude formation or re-formation of connections across the excluded space and inhibit the free diffusion of molecules that maintain homeostasis[70].

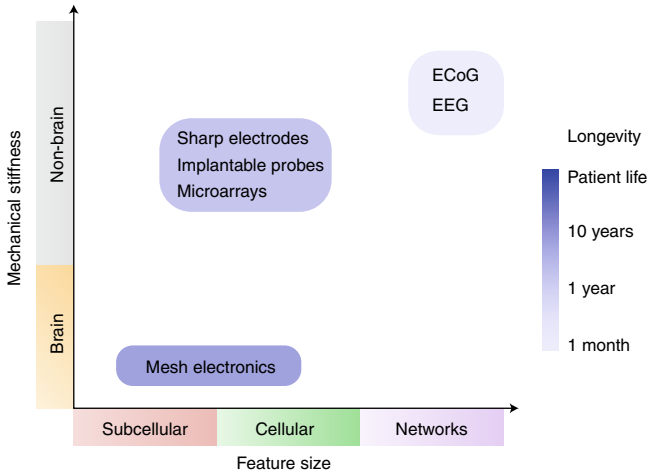

Fig. 2 | Challenges affecting neural interfaces. Mismatches in structural, mechanical and topological features between the brain and interface lead to micromotion and a prolonged chronic immune response limiting the longevity of conventional neural recording probes[6]. Similarly, factors including the physical, chemical and mechanical composition of the electrode influence probe features governing the spatial resolution of the interface, such as diameter, shape, cross-sectional area, and size of recording surfaces[5,84]. Mesh electronics optimize the neural interface design for structural, mechanical and topological similarity between the implant and neural substrate to create an interface that 'looks' and 'feels' like the cellular and subcellular networks comprising the brain[8].

To develop probes that more closely resemble brain properties, our group (C.M.L.)[8,9] has developed mesh electronics, which optimize the neural interface design for structural, mechanical and topological similarity between the implant and neural substrate. The idea is to create an interface that resembles the cellular networks comprising the brain[8,9,49] (Fig. 2). The mesh is fabricated with cellular- to subcellular-sized components within a 2D ultra-flexible scaffold with a bending stiffness comparable to that of neural tissue. This ultra-flexible, macroporous, interconnected arrangement of the mesh allows deep integration and interpenetration of neurons and glia without disruption to the local cytoarchitecture[9,71].

Mesh electronics can be introduced into the brain using a conventional syringe[72], similarly to many biological therapeutics, allowing ease of implantation for less conventional targets, such as the eye[73]. The ultra-flexible 3D structure elicits only a minor foreign body response measured up to 1 year after implantation in mice[74], enabling long-term stable recordings from a set of approximately 200 neurons in a single mouse[71] and stable tracking of the activity of the same neurons and local neural circuits for over 8 months[75]. Despite these promising results, there are areas that must be addressed to enable human translation, including development of a connection to an interface cable or controller chip that is compatible with the constraints of neurosurgery, demonstration of the stability and safety on time scales longer than a year and approaching the projected maximum timescale of patient treatment, and a substantial increase in the number of addressable electrodes similar to the increases being made in high-density silicon probes.

Tissue-like implants enabling precision electronic medicine

New developments in neurotechnology promise to fundamentally shift proof-of-concept studies into applications in basic research

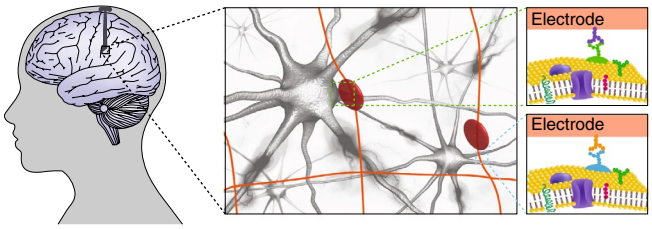

Fig. 3 | Schematic representation of syringe-injectable mesh electronic implant in a human brain. Mesh electronics directly address the structural, mechanical and topological mismatch between probe and host tissue. The mesh is fabricated with subcellular-sized nanowire field-effect transistor detectors that maintain measurement sensitivity and allow highly localized sampling, formation of artificial synapses, and minimally invasive intracellular recordings and single-neuron stimulation (stimulation pad depicted by red circle)[77,85,86,87]. The cellular- and subcellular-sized components are incorporated onto a 3D, ultraflexible scaffold with a bending stiffness similar to that of brain tissue[71], and the macroporous, interconnected arrangement of the mesh allows deep integration and interpenetration of neurons and glia without disruption to the local cytoarchitecture[71]. Schematic representation of mesh electronics implanted in region of heterogenous neuronal subtypes (green and blue dashed squares). Identifying unique cell-surface protein patterns may enable targeted cellular recording and stimulation interfaces through, for example, expression of complementary antibodies or aptamers on the mesh electronics electrode surfaces and/or polymer-encapsulated mesh structure.

and ultimately medical therapy (Fig. 3). For example, the functionalization of neural probes such that individual electrodes promote interactions with specific cell-surface protein markers could allow precise measurement and control of direct and indirect pathway activity. In models of Parkinson's disease, theoretical and computational models have postulated that neural subtypes such as basal ganglia D1 and D2 dopamine receptor subtypes have distinct roles[76]; designing neural probes to interact with these cells may have a beneficial therapeutic effect by promoting selective targeting of underlying neural circuits such as the direct or indirect basal ganglia pathways. Development of neural devices to incorporate both electrophysiological recording and biochemical sensing (for example, of dopamine and/or glutamate) through functionalized field-effect transistors[77,78] may also contribute toward the dynamic application of precision electronic medicine to Parkinson's disease, in which neurotransmitters such as dopamine play an extensive role[79]. For example, the dissociable roles of neural synchronization and dopamine release following electrical stimulation can be used to promote the therapeutic effects on motor symptoms while reducing any unwanted side effects related to excessive dopamine release.

Work from our laboratory (C.M.L.)[9] has shown that cells adhere and migrate along the electronically active scaffold of mesh electronics. It may prove useful to modify neural surfaces to promote interactions with neural progenitor cells and tissue remodeling factors, as this would potentially create an opportunity to build interfaces that address both structural and functional components of neuromodulation. It could also enable an active regenerative therapy in the hippocampus and adjacent cortical regions that are often sites of early neural neurodegeneration in diseases such as Alzheimer's disease[80]. Additionally, emerging evidence suggests that electrical stimulation in the hippocampus induces neurogenesis in the dentate gyrus layer of the hippocampus[76]. In the future, multi-pronged therapeutic strategies could be designed in which temporally interleaved stimulation would induce neurogenesis, allow directed migration and differentiation of new nerve cells on the electronic scaffold, and functionally incorporate these cells into existing neural circuits through electrical stimulation[81,82]. Such approaches would enable exciting applications in precision electronic medicine.

The encouraging prospects for the creation of a long-term stable neural interface, we believe, will result in the enhancement of emerging approaches to neuromodulation therapies, as well as open new approaches previously unconsidered. We envisage future neurotechnologies continuing to blur the mechanical, structural and biochemical dissimilarities between probe and tissue. However, developments are needed in two major areas to realize the full potential of the technology.

First, applying advances in semiconductor fabrication and microscale chip design for signal multiplexing, which have been demonstrated for high-density silicon probes[57], will allow increases in local recording density and volume over larger swaths of the brain and thus should improve capture of the intrinsic network activity observed throughout the human brain over long periods of time. Additional benefits, such as obviating the need for template-based spike sorting, will come with the implementation of more robust signal triangulation methods following attainment of a critical density of recording contacts[83]. Similarly, increases in sensor density will provide high-fidelity control over targeted neurons and circuits through directed exposure to electrical stimulation.

Second, advances in neural implants capable of handling high-density sensing and stimulation will be required to enable next-generation applications of implants that match the brain and are capable of stably recording from populations of neurons over extended periods of time. Challenges relating to mechanical and biocompatibility of high-density connectors, cables and housings, along with issues relating to battery longevity and recharge cycles, will pose substantial barriers to the implementation of precision electronic medicine.

Conclusions

The field of electronic neural implants is poised to usher in a new era of basic research, therapeutic intervention, and other applications in neuroscience. This Perspective outlines some of the constraints on realizing a vision of precision electronic medicine and highlights the importance of a natural tissue–electronics interface for long-term implants that are immune-privileged and free of the foreign body response to enable precise recording and stimulation of the same individual neurons[72] and neural circuits over extended time periods. Given the importance for both fundamental neuroscience research and human translation, we expect to see efforts focused on fabrication of highly flexible probes such as mesh electronics with high densities of recording and stimulation electrodes in the near term. Moreover, we expect that interfacing such ultraflexible implants with mature silicon-based processor chips will see increased emphasis, as it could allow efficient handling of expected large data streams, as well as being central to closed-loop controllers.

With these technology advances emerging, we envisage high-density immune privileged interfaces rapidly expanding our ability to study the brain unlike ever before, building the foundation of understanding necessary to unlock the potential for seamless neural-electronic systems. In the not too distant future, we posit that our level of technological and scientific insight will be sufficient to stably interface with the human brain in a manner that mirrors the organization of the brain itself. This will first arise in the form of enhanced therapeutic approaches to treating some of the most challenging neurodegenerative and neuropsychiatric disease, such as Alzheimer's disease, depression and obsessive-compulsive disorder. Subsequent applications are likely to involve interfacing with the brain in the absence of disease, to enhance or prevent the decline of cognitive capacities, and expanding the exploration of what is possible with such an interface. Given that the brain is the very organ that makes us human, careful consideration of ethical issues will be required, although it is our opinion that the opportunity to develop powerful treatments for neurodegenerative and neuropsychiatric

diseases, as well as enhancing restorative function in trauma and amputation, mandates that these efforts should proceed vigorously.

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Competing interests

C.M.L. is a co-inventor on patents and patent applications relating to the article that have been filed by the authors' institution (Harvard University) as follows: 'Scaffolds comprising nanoelectronic components, tissues, and other applications', inventors C.M.L., J. Liu, B. Tian, T. Dvir, R. S. Langer and D. S. Kohane; US9,457,128 (issued); describes nanoscale transistors for cell recording. 'Systems and methods for injectable devices', inventors C.M.L., J. Liu, Z. Cheng, G. Hong, T.-M. Fu and T. Zhou; 61/975,601 (pending), PCT/US2015/024252 (pending) and 15/301,792 (pending); describes injectable mesh electronics. 'Techniques and systems for injection and/or connection of electrical devices', inventors C.M.L., G. Hong, T.-M. Fu and J. Huang; 62/209,255 (pending), PCT/US2016/045587 (issued) and 15/749,617 (pending); describes injection method of mesh electronics. The authors are not involved in efforts related to commercialization of this intellectual property.

Additional information

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