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Recent advances in neural dust: towards a neural interface platform

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The neural dust platform uses ultrasonic power and communication to enable a scalable, wireless, and batteryless system for interfacing with the nervous system. Ultrasound offers several advantages over alternative wireless approaches, including a safe method for powering and communicating with sub mm-sized devices implanted deep in tissue. Early studies demonstrated that neural dust motes could wirelessly transmit high-fidelity electrophysiological data *in vivo*, and that theoretically, this system could be miniaturized well below the mm-scale. Future developments are focused on further minimization of the platform, better encapsulation methods as a path towards truly chronic neural interfaces, improved delivery mechanisms, stimulation capabilities, and finally refinements to enable deployment of neural dust in the central nervous system.

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Introduction

Direct electrical recording and stimulation of the nervous system has been successfully implemented as a therapeutic technology for a diverse range of disorders. Spinal cord stimulation to treat chronic pain [1] and deep brain stimulation for essential tremor [2] are illustrative examples that have seen widespread adoption. A growing understanding of how the nervous system influences diseases of the mind and visceral organ systems has greatly expanded the range of disorders that may someday be treated by interfacing with the brain, spinal cord, and peripheral nerves. For example, the discovery that cholinergic neurons play an important role in the inflammatory cascade has sparked interest in neuromodulatory treatments for rheumatoid arthritis and inflammatory bowel disease [3•]. However, current technologies available for long-term neural recording and stimulation lack several important features that would enable the expansion of bioelectronic therapies into new human disease targets. Current state-of-the-art clinical neurostimulators are bulky, wired systems powered by single-use onboard batteries. Stimulating electrodes are typically designed to activate large regions of brain tissue or entire nerve bundles, which can increase the risk of off-target effects. Finally, most systems are open-loop, meaning that stimulation parameters are adjusted through trial-and-error during clinician visits and cannot adapt to moment-by-moment changes in patient physiology. This is largely due to the fact that chronic recording technologies necessary to detect neural biomarkers and changes in brain state have very limited clinical use, and typically consist of low-channel count brain surface recordings. Key goals for future bioelectronic technologies identified in a recent multi-disciplinary roadmap include moving towards wireless, miniaturized, closed-loop, and fully implantable systems that can selectively interface with parcels of nervous tissue on the sub-mm scale [4•]. Achieving these goals in the near-term will require substantial innovations and novel approaches to overcoming these challenges.

Wireless power and communication are attractive features for next-generation neural interfaces. Eliminating the need for batteries can reduce the size of devices and the need for eventual replacement, as is the case for primary batteries commonly used today. Additionally, replacing wires with wireless links reduces the risk of lead migration which can cause complications or a loss of therapeutic efficacy. Such untethered approaches have also been shown to reduce the foreign body response to implanted electrodes [5]. Electromagnetic (EM) coupling and communication, commonly used in a wide range of consumer electronics, has been demonstrated as a solution for wireless neurosensing and neurostimulation applications [6–10]. However, EM approaches face fundamental limitations which create a lower bound on the size of EM-based devices that can be safely implanted in tissue. First, an antenna (or coil) is required to harvest EM energy, and as the size of the antenna shrinks, the

resonant frequency of the EM wave required to couple to it increases. This can be problematic for small implants: using reasonable assumptions, the propagation loss and attenuation of EM energy in tissue becomes extremely large as frequency increases [11••]. To compound this problem, the long wavelength of EM waves relative to the size of a mm-scale or sub-mm scale device further reduces the efficiency of the antenna. The net effect is that for device sizes smaller than a few millimeters, relying on EM energy transfer would require power levels that would cause unsafe heating of body tissue around the implant [12,13].

To avoid these limitations, we have developed *neural dust*, a scalable neural interface system that uses ultrasound for wireless power and communication. Ultrasound offers an attractive alternative to EM for implantable devices in the sub-mm domain for two primary reasons. First, the attenuation of ultrasonic energy in tissue is far lower than EM energy (Figure 1a) [11••]. Second, the relatively slow speed of sound in water-based materials compared to the speed of light yields smaller wavelengths at similar frequencies, increasing the efficiency of coupling to small-scale devices. This means that, theoretically, devices on the order of tens of microns could be safely powered by ultrasound even when implanted deep in the body [14•].

Wireless, batteryless, scalable neural dust for neural recording

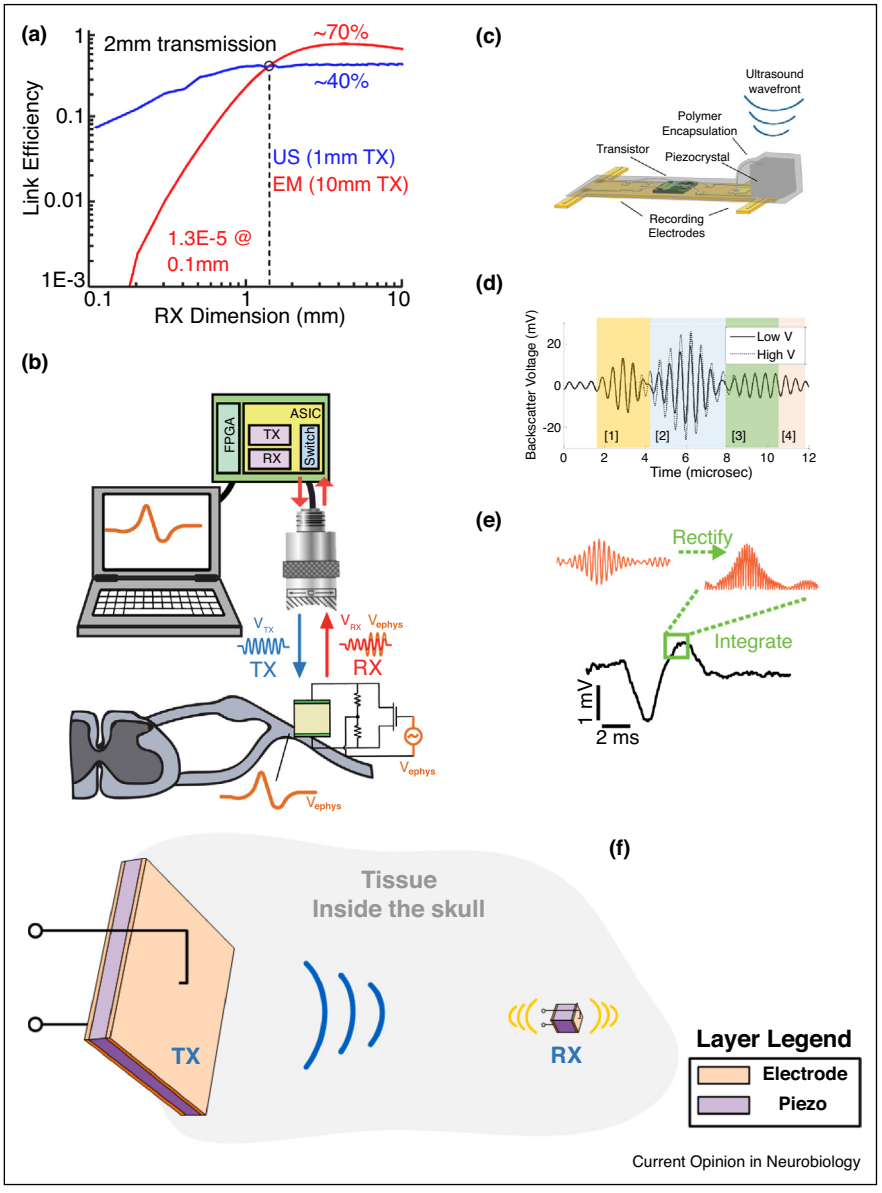
A neural dust sensor achieves untethered sensing of neural signals by operating on the principle of wireless backscatter communication. In a traditional bi-directional wireless link, two devices communicate with each other by each generating a transmission signal to send information out, such as in handheld two-way radios or some recent implantable devices [15]. By contrast, information is wirelessly relayed from a backscatter neural dust by changing the way it reflects ultrasonic waves. These ultrasonic waves are generated by a device called the interrogator, which sits outside the brain and has less stringent size and power constraints. As the dust mote needs only to modulate its reflection parameters rather than generate its own transmission signal, it can be extremely low power, simple in design, and small in size (Figure 1). To detect the change in reflection parameters of the dust mote, the interrogator transmits a signal which reflects off of the backscatter motes and is detected as it arrives back at the interrogator. Processing of this echo signal can then retrieve the neural signal which was modulated onto the reflection at each dust mote. Previous work showed that combining backscatter communication with ultrasound as a carrier domain enables untethered physiological sensors that could scale to a theoretical 50 μm characteristic dimension — small enough to realistically be placed in the brain at high density [11••,16].

Recently, the neural dust concept was demonstrated in an *in vivo* environment [17••]. A neural dust sensor ('mote') was constructed by assembling a piezoelectric crystal — an acoustic-domain analog of a radio antenna — and a custom integrated circuit (IC) into a miniature electronics package with recording electrodes and a thin layer of epoxy encapsulation. This device was surgically affixed to the sciatic nerve of a rat to measure both compound action potentials and electromyograms initiated by proximal stimulation (Figure 2a,b). Pulses of ultrasound were sent from an external interrogation device to the dust mote every 100 μs. For each pulse, the recorded backscatter waveform was processed to extract the changing energy level of the backscattered waveform, with the changes corresponding to electrophysiological information detected by the dust mote (Figure 1d). When calibrated with a scaling factor, this measurement accurately recovered the ground-truth action potential signal with a correlation of 88.5% in the case of saturating stimulation (Figure 2d).

To improve the capabilities of the external interrogator, a beamforming method was developed which uses a linearly constrained minimum variance beamformer to optimally amplify signal from the location in space corresponding to a given mote and suppress signal from other directions [16]. This method shows good promise for suppressing interference from other motes and non-mote scatterers to enable sequential reading from each mote in a large 'cloud' of motes. To empirically investigate this and alternative methods, Seo *et al.*, 2015 implemented delay-and-sum beamforming with a custom ultrasound IC [18] and a custom 7-element ultrasound transducer array. This demonstrated a main lobe full-width-half-maximum of approximately 3.1 mm at 50 mm distance, indicating reasonable spatial discrimination capability even with low element count. In a push towards increased utility for neurophysiology experiments, a 7-element ultrasound interrogator system for neural dust was developed wherein the entire system, including backscatter signal processing and physiological measurement extraction, was contained within a miniaturized rodent-wearable package (Figure 3a) [19].

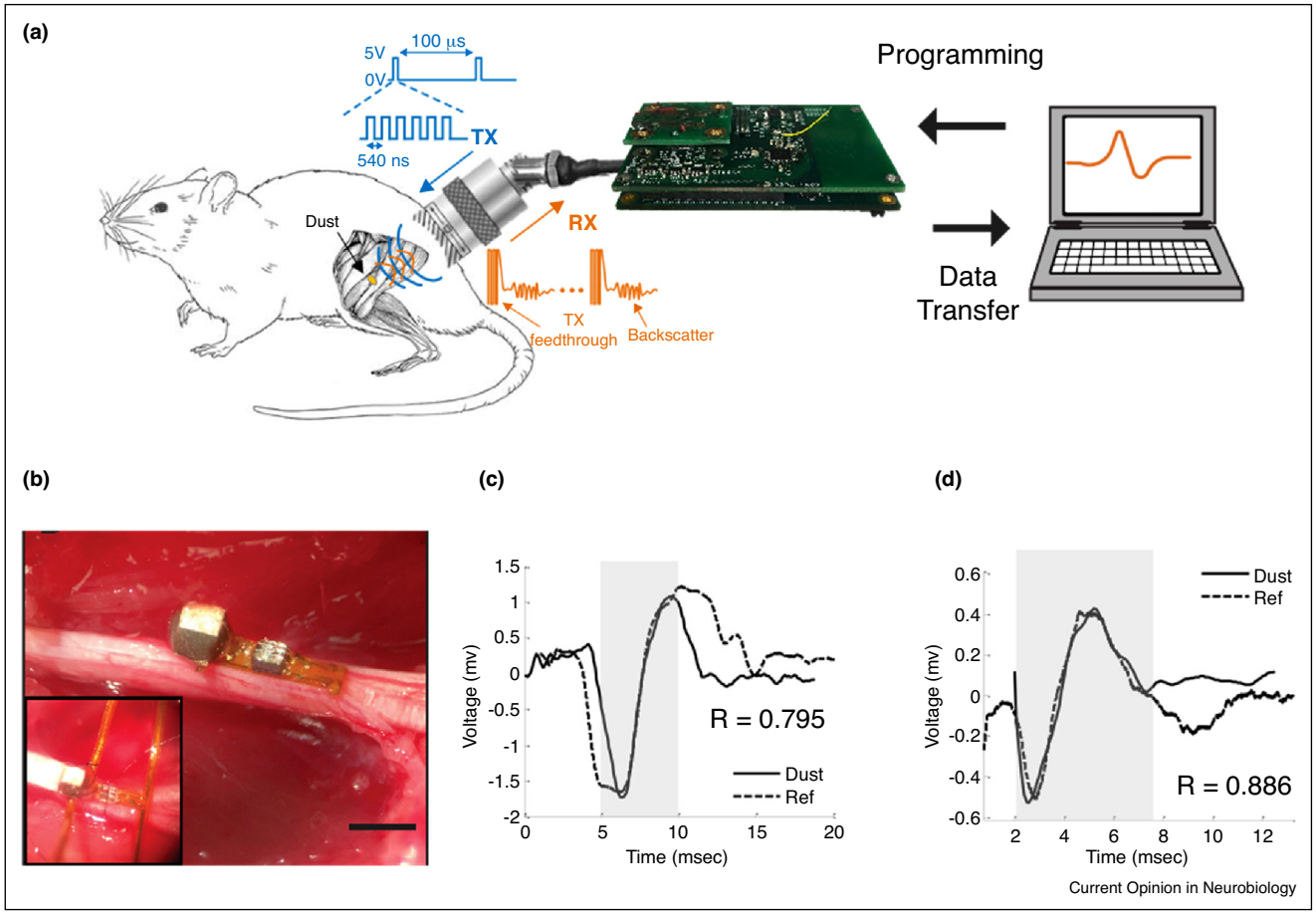
The aforementioned studies tackled a myriad of challenges to demonstrate the neural dust technology in a biological environment. This included development of a miniature dust mote with preliminary encapsulation for acute survival in bodily fluids, a system for generating interrogation ultrasound pulses and digitizing the backscatter waveforms, and a surgical procedure for implanting the dust mote onto peripheral nerves and muscle. The wireless sensor's calculated noise floor of 200 μV enabled the detection of compound action potentials in nerve bundles but should be reduced in future implants to capture action potentials of single neurons. Although this system enables straightforward establishment of an ultrasonic wireless link, it is sensitive to the alignment of the ultrasonic link between the interrogator and dust mote

Figure 1



Neural dust system overview, reproduced from Seo *et al*., 2016. **(a)** Plot of simulated link efficiency for EM and ultrasound in 2 mm of brain tissue indicates that for implants smaller than ~1 mm^2, ultrasonic power transfer outperforms EM significantly (see Seo *et al*., 2013 for simulation details). **(b)** An external transducer powers and communicates with a neural dust mote placed remotely in the body. Driven by a custom transceiver board, the transducer alternates between transmitting a series of pulses that power the device and listening for reflected pulses that are modulated by electrophysiological signals. **(c)** Cross-section of the neural dust mote. **(d)** Example backscatter waveform showing different regions of backscatter. The backscatter waveform is found flanked (in time) by regions which correspond to reflections arising from non-responsive regions; these correspond to reflected pulses from other device components shown in (d). The measurement from the non-responsive regions, which do not encode biological data) can be used as a reference. As a result of taking this differential measurement, any movements of the entire structure relative to the external transducer during the experiment can be subtracted out. **(e)** Received backscattered pulses are filtered, rectified, and the area under the curve is computed in order to produce reconstructed waveforms. Reconstructed waveform is sampled at 10 kHz. Each point of the reconstructed waveform is computed by calculating the area under the curve of the appropriate reflected pulses, received every 100 μs. **(f)** Backscatter communication scheme featuring the transceiver, which alternates between emitting and receiving ultrasonic pulses (TX), and the implanted dust mote (RX) which reflects ultrasound energy in a manner dependent on the recorded physiological signal.

Figure 2



In vivo results, reproduced from Seo *et al.*, 2016. **(a)** *In vivo* experimental setup for EMG recording from gastrocnemius muscle in rats; the neural dust mote was placed on the exposed muscle surface and the wound was closed with surgical suture. The external transducer couples ultrasound to the mote and the wireless data is recorded and displayed on the laptop. **(b)** A neural dust mote anchored to the sciatic nerve in an anesthetized rat. Inset shows neural dust mote with optional testing leads for recording wired reference data. **(c)** Ground truth and reconstruction of ENG signal from the wireless backscatter data at response-saturating stimulation amplitude (100%) matched with $R = 0.886$. **(d)** Ground truth and reconstruction of EMG signal from the wireless backscatter data at response-saturating stimulation amplitude (100%) matched with $R = 0.795$.

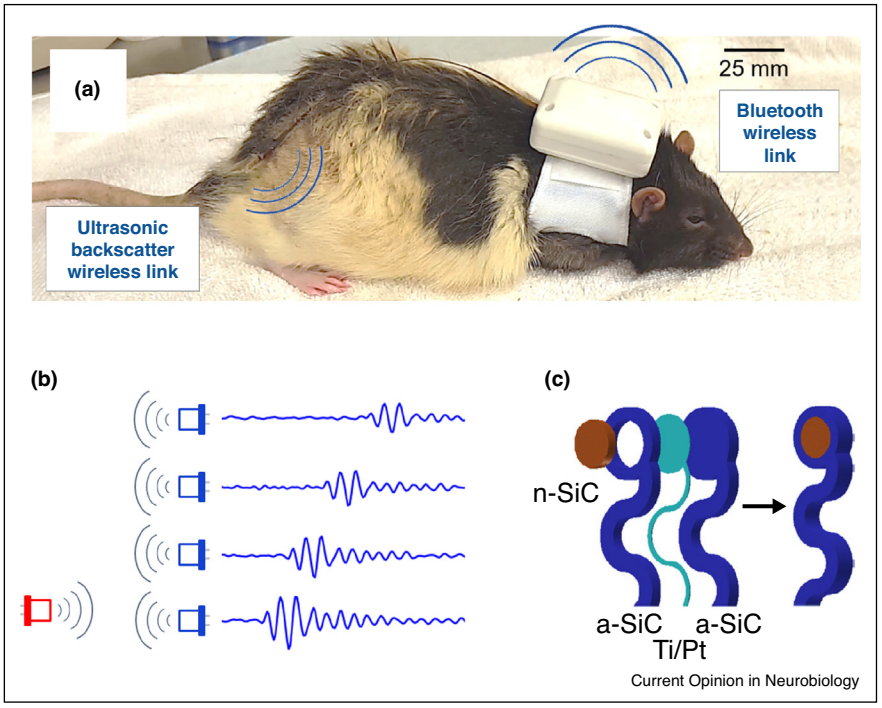
sensor. Further work is needed to make calibration and establishment of a wireless link automatic, and increase robustness in the midst of motion. Finally, while the mote demonstrated in this study was placed *on* tissue, a strategy well-suited for PNS use, developing motes with geometrical characteristics lending themselves to be implanted within nervous tissue is desirable for intracortical and deep-brain recording.

Roadmap and future applications

In order to truly realize the vision of vanishingly small wireless neural interface motes placed in high density across large swaths of the brain, we are pursuing several advances to extend the capabilities of neural dust.

A major goal is the utilization of multiple dust motes implanted in the mammalian cortex to demonstrate neuronal ensemble recording and the feasibility of a neural dust brain–machine interface (BMI). Challenges to overcome include reducing the size of a dust mote, communicating with multiple dust motes, improving signal sensitivity, and developing new delivery techniques. Two of the pressing constraints for size reduction are the size of the piezocrystal and the size added by assembly and packaging steps. The chief limitation to shrinking the piezocrystal is the signal-to-noise ratio of the backscatter link, which can be improved via increasing the sensitivity of the dust mote, and improving the noise performance of the interrogator. In order to improve dust mote assembly and size, microfabrication techniques can be leveraged to improve feature size resolution and enable high-volume parallel fabrication. In addition, design changes to the dust mote will facilitate delivery into cortex with minimal damage and optimize the way ultrasound energy is backscattered to an array of external interrogator elements. Although delivery techniques will differ from standard

Figure 3



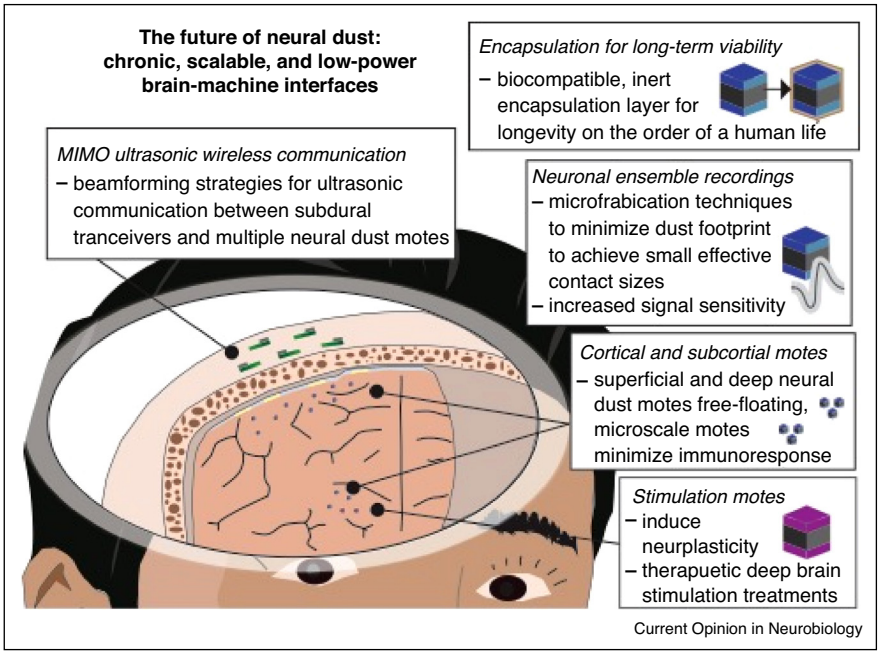
Ongoing work on neural dust. **(a)** Wearable & portable neural dust interrogators enable new neurophysiology experiments. **(b)** Large backscatter datasets acquired by collecting backscatter data (blue waveforms) from a dust mote (red icon) on multiple interrogator transducers (blue icon) can aid improved signal extraction algorithms. **(c)** New encapsulation methods, such as silicon carbide will improve longevity for long-term studies and clinical translation.

microelectrode and microwire array technologies, stereotactic targeting of brain regions can be developed similarly to ensure that motes are implanted in desired cortical targets. Since the motes are asymmetrical, coordinates used should take into consideration the orientation of the mote based on the delivery method.

Another area of active work is the development of new signal processing algorithms operating on backscatter data from a large number of external interrogator elements. These methods take advantage of the inherently multiple-input–multiple-output nature of an array of external transducer elements communicating with a cloud of dust motes in order to resolve signal from the individual motes while interrogating all motes simultaneously rather than sequentially. Implementing machine learning techniques on this data stream may vastly increase the total number and density of motes that can be used in a region of tissue, as well as improve sensitivity [20] (Figure 3b). Furthermore, these approaches are being designed to adapt the backscatter extraction to account for any scattering that occurs at inhomogeneous interfaces in the tissue, such as skin and bone, and automatically align and calibrate to improve motion robustness and do away with the need for careful manual setup. Motion of brain tissue has been shown to consist of both small-displacements due to cardiac and respiratory pulsatility on the order of 10–20 μm, and larger, slow changes of up to 80 μm due to tissue remodeling, pharmacological and other physiological factors [21]. Small motion that is less than the size of a dust mote should not pose a problem for signal extraction, and large, slow drift motion can be calibrated out.

In order to make the dust motes viable in the long-term, the materials used must cause minimal disturbance to the surrounding tissue and resist degradation by the biological environment. In addition, polymeric encapsulation materials common to microscale implants often fail due to water vapor ingress [22]. Diaz-Botia *et al.*, 2017 introduced a new encapsulation method for implantable electrophysiology devices where the entire external surface of a device, including electrodes, is covered with a highly inert and biocompatible layer of silicon carbide (Figure 3c). The exposed electrode surface is fabricated of conductive polycrystalline silicon carbide whereas the rest of the structure is fabricated from insulating amorphous silicon carbide. The extreme stability and biocompatibility of the silicon carbide combined with the lack of any dissimilar material interfaces increases device longevity to at least 8 times the current state-of-the-art [23]. We are currently exploring this technique as part of an overall strategy to achieve encapsulation methods with

Figure 4



Future characteristics of neural dust. Advances in several domains are ongoing for neural dust, and are necessary to realize this novel technology as a solution for clinically viable, wireless, brain–machine interfaces. This includes developing new strategies for ultrasonic multi-mote communication, biocompatible encapsulation, and implantation into cortical and subcortical nuclei. Additionally, motes will be further reduced in size and have a reduced noise floor, enabling single-unit neural recordings. Stimulation motes will be developed for delivering electrical stimulation to neural tissue. All of the properties combined provide a powerful platform for neuroscience studies and neuroprosthetic treatments.

longevity on the order of a human lifetime. As part of this strategy, we are building packages from a variety of biocompatible ceramics (including alumina and SiO_2) which have very low vapor permeabilities [24]. One of the challenges in effective, long-term hermetic packaging of neural dust motes is the need for a piezocrystal in the implant; most such materials have fairly low Curie temperatures (e.g. ~120 °C for PZT). This renders conventional hermetic sealing techniques such as eutectic or thermocompression bonding ineffective due to the temperature required. Furthermore, the acoustic impedance mismatch between ceramic materials and the tissue environment sets requirements for package structure and structure to allow for acoustic power transfer through the package walls. With these material and fabrication challenges in mind, we are currently developing both millimeter scale and microscale hermetic packaging methods.

Closed-loop neural interfaces, which monitor physiology and reactively deliver stimulation in real time, promise exciting developments in the treatment of neurological diseases. Electrical stimulation-based therapies, whose power budgets can be relatively large, pose a major challenge for miniaturized wireless systems. However, the use of ultrasound as an energy and communications carrier allows for scaling down to small sizes with reasonably high-power delivery. This power can be used in a variant of neural dust which delivers stimulating current to modulate neural activity. Still, miniaturization of an untethered stimulating neural dust mote, as well as control of the stimulation intensity in the face of unknown wireless power link efficiency are non-trivial challenges. In a partnership with our collaborators, we are currently working towards bringing stimulation capability to neural dust, which may eventually lead to a closed-loop system consisting entirely of untethered recording and stimulating motes.

The application of ultrasonic power and backscatter communication for wireless neural interface motes opens a wealth of future possibilities. Although there are a number of challenges to solve, this approach yields a clear path towards extreme miniaturization — enabling chronicity and channel count — which may be out of reach for traditional wireless communication approaches.

Conclusion

Neural dust is poised to address many of the major hurdles in the realm of neural interface technology and provide an innovative solution for chronic, scalable, and low-power BMIs. The use of ultrasound for device power and communication enables us to achieve tetherless recordings from extremely miniaturized bioelectronics.

This microscale footprint is necessary to reduce the biological response generated about implanted devices, which is in part responsible for degradation of recording quality in conventional technologies. Neural dust addresses this issue with the additional simultaneous benefit of operating with very low transmit power that is well below FDA limits. This ultrasonic approach is an enticing path towards wireless power and communication for neural recordings, which in turn opens the door for new experimental paradigms in systems neuroscience as well as systems-based neurotherapies.

The future of neuroprosthetics will rely on chronic, stable, and distributed recordings from both cortical and subcortical regions. Leveraging strategies like multi-receiver external transducer topologies and machine learning algorithms will enable the realization of recording from many free-floating motes simultaneously. In addition to cortical recording, dust motes can be placed in subcortical nuclei and interrogated from several centimeters away for chronic deep recording, which is largely impossible today without relying on wired electrode designs. Advanced in these directions will facilitate network-wide recordings from the brain, which is imperative to understanding most neurological disorders which typically affect more than one small area of neural tissue, and for implementing BMI-based treatments. Many established and investigational electrical stimulation neurotherapies for treating neurological and neuropsychiatric disorders rely on stimulation of deep brain targets. Leveraging stimulation-enabled dust motes that can be powered in these deep structures could allow these treatments to be delivered wirelessly and without implanted batteries.

Since future motes will potentially have dimensions on the scale of neuronal cell bodies, neural dust-based electrical stimulation therapies may subsume existing treatments with the potential to induce targeted neuroplasticity as a means to correct pathological activity. The innovations described above will allow for the development of neurobiologically-informed neuroprosthetics with the potential to aid millions of people suffering from devastating neurological and neuropsychiatric conditions (Figure 4). In addition to numerous applications in system neuroscience research, this transformative technology holds strong potential to revolutionize neurotherapeutics in the decades to come.

Conflict of interest statement

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest. RMN is an employee and JMC and MMM are founding members of iota Biosciences, a company that plans to commercialize implantable ultrasonic devices related to the work discussed in this review.

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