INVITED PAPER

Reliable Next-Generation Cortical Interfaces for Chronic Brain–Machine Interfaces and Neuroscience

This paper discusses recent advances in neurotechnology developed at Berkeley, including ultrasmall, ultracompliant implantable recording technology, as well as active devices which enable RF coupling, front-end amplification, and transcranial communication.

By Michel M. Maharbiz, *Senior Member IEEE*, Rikky Muller, *Member IEEE*, Elad Alon, *Senior Member IEEE*, Jan M. Rabaey, *Fellow IEEE*, and Jose M. Carmena, *Fellow IEEE*

ABSTRACT | This review focuses on recent directions stemming from work by the authors and collaborators in the emerging field of neurotechnology. Neurotechnology has the potential to provide a greater understanding of the structure and function of the complex neural circuits in the brain, as well as impacting the field of brain–machine interfaces (BMI). We envision ultralow-power wireless neural interface systems that are life-lasting, fully integrated, and that supports bidirectional data flow with high bandwidth. Moreover, we believe in the importance of building neural interface technology that is truly tetherless, has a very small recording footprint, and little to no mechanical coupling between the sensor and the external world. We believe these developments will impact both neuroscience and neurology, revealing fundamental insight about how the nervous system functions in health and disease.

KEYWORDS | Brain–machine interfaces; electrophysiology; neural interfaces; neurotechnology

I. INTRODUCTION

The goal of cortically controlled brain–machine interfaces (BMIs) is to reliably, accurately, and robustly convey enough motor-control intent from the central nervous system (CNS) to drive multi-degree-of-freedom (DOF) prosthetic devices by patients with amputated, paralyzed, or otherwise immobilized limbs for long periods of time (decades). To achieve this goal, two main challenges remain: 1) how to make viable neural interfaces that last a lifetime; and 2) skillful control and dexterity of a multi-DOF prosthetic device comparable to natural movements [1].

The first challenge, which is the one we focus on in this paper, entails having a life-lasting, fully integrated, high-bandwidth, ultralow-power wireless neural interface system that supports bidirectional data flow, for example, reading (recording) and writing (stimulating) from/to the brain at different spatial and temporal scales. Ideally, these systems would be fully implantable in the intracranial space as well as have battery-less operation. They should also be modular enough to allow the measurement of different types of neural signals, such as the extracellularly recorded discharge of individual neurons

Manuscript received January 25, 2016; revised April 22, 2016; accepted May 22, 2016. Date of publication December 15, 2016; date of current version December 20, 2016.
M. M. Maharbiz is with the Department of Electrical Engineering and Computer Sciences and the UCB/UCSF Joint Graduate Program in Bioengineering, University of California Berkeley, Berkeley, CA 94720 USA (e-mail: maharbiz@berkeley.edu).
R. Muller, **E. Alon**, and **J. M. Rabaey** are with the Department of Electrical Engineering and Computer Sciences, University of California Berkeley, Berkeley, CA 94720 USA.
J. M. Carmena is with the Department of Electrical Engineering and Computer Sciences, Helen Wills Neuroscience Institute, and the UCB/UCSF Joint Graduate Program in Bioengineering University of California Berkeley, Berkeley, CA 94720 USA (e-mail: jcarmena@berkeley.edu).
Digital Object Identifier: 10.1109/JPROC.2016.2574938

(typically referred as single-unit and multiple-unit activity), and the field potentials from large numbers of channels sampled at different frequencies, as well as perhaps other physiological parameters such as temperature, blood flow, brain pulsation, etc., that may become important in future generations of this technology.

Moreover, we believe in the importance of building neural interface technology that is truly tetherless, has a very small recording footprint, little to no mechanical coupling between the sensor and the external world, and for which continuous performance tracking and a predictive failure model can be constructed. With such a system, BMI algorithms would track electrode health and predict which channel/single units are best candidates for replacement to maintain unsupervised BMI performance over time.

Moving this vision forward will require high channel count neural recording interfaces that operate within the CNS for appreciable fractions of a primate lifetime. We posit that this technology challenge has four principal thrusts; this review focuses on the first three: 1) the development of a suite of extremely axially compliant implantable recording nodes; 2) the development of active devices which enable RF coupling, front-end amplification, inline electrode health determination, and transcranial communication; 3) the development of completely tetherless interface technologies, and 4) of the refinement or development of materials which allow such implants to survive in the molecularly rich brain environment.

Fig. 1 provides a schematic overview of components and representative variants. The remainder of the paper describes a range of efforts performed at Berkeley to address each of the challenges.

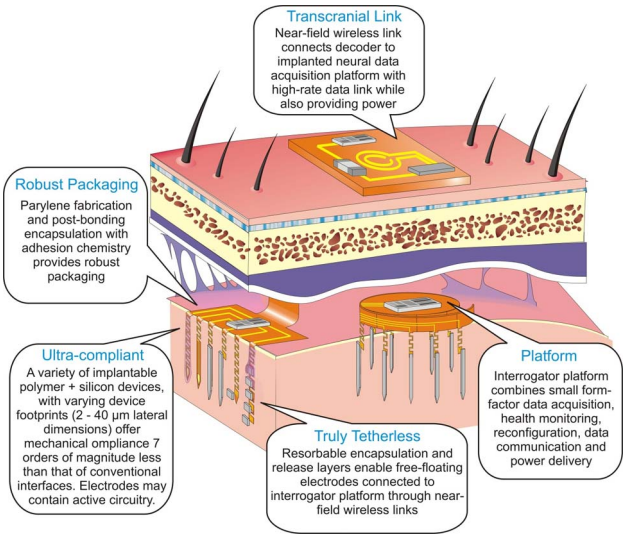

Fig. 1. ***A conceptual view of the various components, scales, and variants in putative CNS interfaces.***

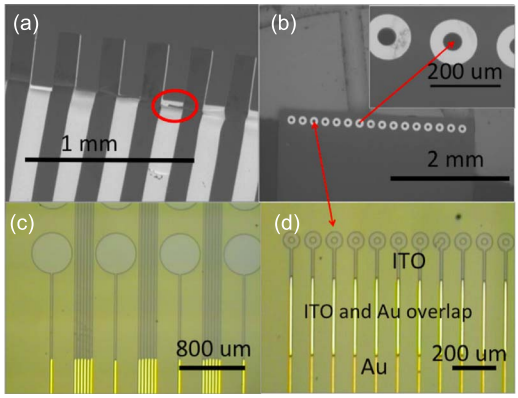

Fig. 2. ***Micrographs and SEM images of the 16-channel and 49-channel devices. (a) Bond pad damage on ITO-only devices. (b) Intact electrodes of a 16-channel ITO device. (c) Electrodes and interconnects of a 49-channel Au-ITO hybrid device. (d) 16-channel hybrid array. The ring-shaped electrodes are made of ITO. The light yellow lines indicate the overlap of Au and ITO. The lower part of the connections consists of Cr/Au. Adapted from [34].***

A. Development of Ultrasmall, Ultracompliant Implantable Recording Nodes

Parylene and polyimide technology has been used to produce a number of extremely thin, flexible components suitable for neural recording [2]–[25]. Recently, for example, the technology has seen a renaissance in the production of high-density microfabricated electrocorticography grids [26]–[30].

As an example, we demonstrated a flexible 256-electrode microfabricated electrocorticography (μECoG) array with an electrode pitch of 500 μm [31]. This μECoG grid was a flexible five-layer parylene MEMS device (two layers of platinum insulated by three layers of parylene) featuring plasma-etched vias and a monolithically integrated parylene cable which is compression-bonded to a fan-out board using anisotropic conductive film (ACF) technology. The devices were characterized by electrochemical impedance spectroscopy in artificial cerebrospinal fluid (aCSF) and initially vetted with recorded acoustic evoked potentials *in vivo* from the rat primary auditory cortex. More recent work by Bouchard and colleagues has made use of this technology to record functionally evoked multiple-unit activity from the cortical surface in three different animal models [32]. This work demonstrates that μECoG-recorded potentials have waveform characteristics similar to multiple-unit activity collected with penetrating electrodes; are evoked by auditory stimuli and are tuned to auditory parameters; and are evoked and manipulated by direct optogenetic intervention. Together, these results demonstrate that μECoG can record localized and functionally meaningful neural output from the cortical surface, increasing its utility as a methodological bridge between basic and clinical neuroscience.

In addition, some preliminary work by Ledochowitsch points to the utility of such high-resolution interfaces for use in BMI tasks. In that work, we investigated if subdural field potentials recorded by microfabricated electrocorticography arrays containing electrodes < 1 mm apart could be decoupled through closed-loop BMI learning [33]. Microfabricated ECoG arrays were chronically implanted subdurally over primary motor cortex (M1) of five male Long-Evans rats who were trained to perform a 1-D center-out task using closed-loop brain control to adjust the pitch of an auditory cursor by differentially modulating high gamma (70–110 Hz) power on pairs of surface microelectrodes that were separated by less than 1 mm. Although the results are preliminary, the animals were able to learn to use pairs of output electrodes quickly and to decouple gamma power on length scales as small as 200 μm. Interestingly, the rats' ability to learn the BMI task appeared to depend on the specific choice of control electrodes.

The basic technology can be further expanded by utilizing novel materials to provide additional or application-specific functionality. For example, a variant of the μECoG above was produced using indium tin oxide (ITO) to produce optically transparent arrays with no photoelectric recording artifacts during optical stimulation [34]. These devices were a 49-channel (μECoG) array with an electrode pitch of 800 μm and a 16-channel linear (μECoG) array with an electrode pitch of 200 μm (Fig. 2). The backing material was Parylene C. Transparent, sputtered indium tin oxide (ITO) with sheet resistances of 40 Ω/square was used in conjunction with e-beam evaporated gold to fabricate the electrodes. The transparent layer demonstrated 90% transmission between 285 and 775 nm.

This technology was subsequently used to demonstrate a large-scale neural interface combining optogenetics and μECoG array technologies in mouse, rat, and nonhuman primate models [35], [36]. This type of interface was bidirectional; it allowed both manipulation and observation of neural activity. In that work, collaborators demonstrated a chronic setup that permitted repeated, daily optogenetic stimulation and large-scale recording from the same sites in NHP cortex. The setup combined optogenetics with a transparent artificial dura (AD) and the high-density microelectrocorticography (μECoG) technology described above. The setup incorporated a 192-channel μECoG array spanning 192 mm^2 into the AD for simultaneous electrophysiological recording during optical stimulation (Fig. 3). The array was chronically implanted over the opsin-expressing areas in M1 and S1 for over two weeks. Optical stimulation was delivered via a fiber optic placed on the surface of the AD. With this setup, reliable evoked activity following light stimulation at several locations was recorded. Similar responses were recorded across tens of days, however a decline in the light-evoked signal amplitude was observed during this period due to the growth of dural tissue over the array.

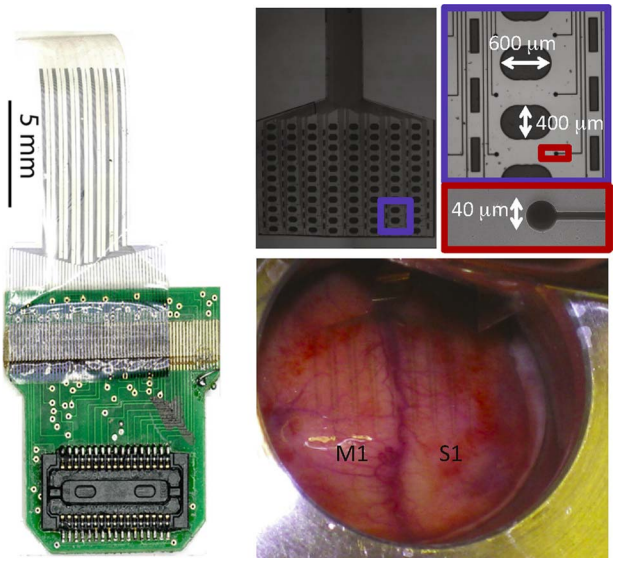

Fig. 3. *An implantable μECoG for use in NHP recordings. Adapted from [35]. (a) Photograph of transparent (μECoG) ACF-bonded to PCB equipped with Zif-Clip compatible Hirose connectors. (b) The large (400 μm $\times$ 600 μm) perforations are designed to allow viral injections and insertion of electrodes or optical fibers for intracortical stimulation and recording. (c) μECoG covering primary motor (M1) and primary somatosensory (S1) cortices in NHP.*

With regards to generalized CNS interfaces, the specific goal of any microfabrication is to produce a variety of implantable node designs which integrate recording electrodes with structural (e.g., silicon shanks) and active computational components (i.e., integrated circuits). A number of approaches have been demonstrated for the crucial (and often under-reported) interconnect between recording grids or shanks and active back-ends [37]–[40]; a notable recent effort focused on monolithic integration of the recording sites with the electronics [41], [42].

Scaling up the number of recording sites for neuronal interfaces while minimizing the impact on brain function presents several engineering challenges. In recent work, we have focused on miniaturizing the probe cable interconnects to minimize tethering forces at the probe–brain interface, allow multiple probes to be implanted in adjacent brain regions, and decrease damage associated with deep brain implants [43]. We fabricated 32- and 64-channel Parylene C cables ranging in length from 7 to 65 mm for use with next-generation silicon probes (nanoprobes). To reduce cable width, 10 μm pitch leads were patterned on two layers sandwiched between three layers of parylene (overall thickness 15 μm). The compliance of the cables was modeled using Timoshenko beam bending theory. Reliability was assessed using accelerated lifetime testing with electrochemical impedance monitoring. These "nanoflex" cables were an order of magnitude smaller and two orders of magnitude more flexible than

existing commercially available devices, a key technology for making viable long term, high-density neuronal recordings in both superficial and deep brain structures.

Ongoing work led by Chamanzar and Blanche has focused on monolithic process integration of high density probes with the polymer interconnect itself [44], [45]. This work focused on the development of high-density neural probes with integrated parylene interconnects for distributed neuronal recording and stimulation. It addressed a long-standing but often overlooked issue in parylene processing to realize reliable multilayer interconnects.

The electrode technologies described above are fully compatible with integrated circuit (IC) technologies and can be seamlessly combined into a compact assembly, as will be described in the next section.

B. Development of Active Devices Which Enable RF Coupling, Front-End Amplification, and Transcranial Communication

The IC is the core of the neural interface microsystem and is the critical component required to acquire the neural signals, in some cases stimulate the neurons to fire, condition the signals and transmit them wirelessly out of the body. This IC should be optimized for both low-power consumption (to minimize the power transmitted by the reader and prolong its battery life) and area occupation. Since the IC is active and often a large rigid component, low area occupation and power consumption are particularly critical. To keep the implant small, efforts to keep the number of external electrical components low are particularly important and demanding innovative power conversion techniques to minimize the use of energy-storage devices. Design techniques in the front-end signal acquisition circuits and in the wireless subunit are key to miniaturization and power efficiency.

1) Miniaturization: While flexible, microfabricated thin-film electrodes enable sensor miniaturization and compatibility with neural tissue, several factors limit the extent of miniaturization of the implant electronics. First, a neural signal recording front-end is required to acquire and digitize the signals from each electrode. To record from multiple sites simultaneously without multiplexing, one front-end is required per active electrode, thus the implanted chip may have hundreds of arrayed data acquisition channels, which dominate the chip area and power in scaled implementations [40], [46]. Future electrode arrays with greater number and density of recording sites will only increase the power and area constraints placed on these front-ends. Second, implantable antennas for neural interfaces have been focused on antenna miniaturization in order to minimize tissue scarring and immune response to the implant. However, this extreme miniaturization has been at the expense of link power efficiency, which drops sharply as the implant size is reduced below a few millimeters [47] limiting the scale at which an implant can receive sufficient power inside the brain.

2) Front-Ends: Highly scaled neural interfaces with large numbers of recording sites require large numbers of neural signal acquisition circuits, making these front-end circuits the most common limiter of the size and power dissipation of the implant IC. A large body of work has been devoted to the efficient realization of these circuits and particularly to their noise/power tradeoff. Table 1 summarizes the performance of the μECoG front-end as compared to state-of-the-art designs from industry and academic researchers [48]–[54]. Limited work has been published on ECoG designs, therefore this work is compared also to EEG front-ends, which have a similar set of specifications. State-of-the-art noise efficiency is achieved, and together with a reduced power supply this work achieves the lowest reported PEF [54] reported, together with three times lower than prior state of the art [48]. The small area enables the highest degree of integration achieved to date in low-frequency high-precision biosignal acquisition with a 64-channel array in only 1.6 mm^2 of active silicon area and no external components required.

One efficient option to address the challenges of low-power low-area neural recording is to exploit the advances in semiconductor technology and its associated reduced feature size combined with innovative architectures to obtain state-of-the-art performance, while simultaneously reducing area and power [55]. A compact solution is obtained by using a system architecture tailored to an advanced process that avoids on-chip passives and takes advantage of high-density logic and aggressive process voltage scaling to reduce power and area. This area-efficient neural signal-acquisition system uses a digitally intensive architecture to reduce system area and enable operation from a 0.5-V supply. The mixed-signal architecture also digitizes both the low-frequency and high-frequency components separately, allowing digitization of the local field potentials (LFPs) and action potentials (APs) separately.

We further expanded this architecture to high-performance recording of low-frequency potentials at the surface of the brain (through ECoG) or at the surface of the scalp (through EEG) [56], [57]. 1/f noise cancellation was employed in a high-resolution capacitive feedback DAC to achieve μV noise levels in only 2.3 μW of power dissipation. This modified mixed-signal architecture enabled a simultaneous $> 20\times$ reduction in size and $> 3\times$ reduction in power efficiency over state of the art. A comparison of the performance is shown in Table 1.

3) Wireless: State-of-the-art work on implantable antennas for neural interfaces has been focused on antenna

TABLE 1 Comparison of Commercial and Research ECoG and EEG Front-Ends [48]–[53], [55]

	Medtronic JSSC '07	IMEC JSSC '08	MIT JSSC '10	UW ESSCIRC '14	Intan RHD2000	Muller JSSC '15
V_{DD} (V)	1.8	3.0	1	1	3.3	**0.5**
Power (μW/ch)	2	33.3	6.5	1.08	100	**2.3**
IRNoise (nV/rtHz)	100	60	130	410	--[c]	**58**
NEF	4.6	4.3	9.37	16.4	--	**4.76**[a]
PEF	38.1	55.5	87.8	269.3	--	**11.3**[a]
Max Input Offset (mV)	+/-50mV	45mV	--		+/-400mV	**+/-50mV**
CMRR (dB)	100	120	60	82	82	**88**
PSRR (dB)	--	--	--	68	75	**67**
THD	0.1% (5mVptp)	1% (1.65Vptp)	--	--	0.1% (4mVptp)	**0.4% (1mVptp)**
Area (mm^2/ch)	0.8	0.5	0.6	0.3	0.5[b]	**0.025**
ADC Resolution	none	11-bit	12-bit	8-bit	16-bit	**15-bit**
# of Channels	1	8	1	1	32	**64**
Crosstalk (dB)	N/A	--	N/A	N/A	-68	**-85**
Technology	0.8μm	0.5μm	0.18μm	65nm	--	**65nm**
Wireless	No	No	No	No	No	**RF Power 1Mbps Tx**
Off-chip components	No	No	Yes	Yes	Yes	**No**

[a] includes ADC
[b] estimated
[c] low-frequency noise not reported

miniaturization in order to minimize tissue scarring and immune response to the implant. This extreme miniaturization has been at the expense of link power efficiency, which drops sharply as the implant size is reduced below a few millimeters [47]. An alternative approach for miniaturization utilizes a larger diameter for the loop antenna but fabricates it on a thin, flexible polymer such that it conforms to the brain surface, keeping the implant rigid components small [58], [59]. Large, rigid structures implanted in the cortex contribute to cortical scarring and result in signal degradation over a timescale of months [60]. Careful modeling of miniaturized implantable antennas showed that extreme miniaturization of 1-mm diameter and below is impractical for powering an implant across the skull [47]. To address this limitation, we recognized that a relatively large diameter of > 5 mm can be utilized if monolithically integrated with the antenna in the same MEMS process as the electrodes [58], [59]. While this increases the total footprint of the implant, it remains thin, flexible, and conformal and therefore does not dramatically increase the invasiveness of the implant. To achieve this form factor, we patterned an antenna onto a polymer thin-film together with the ECoG electrodes described in Section I. The nanoscale thickness of the metallization allows the entire structure to be flexible and conformal. A photograph of the resulting integrated antenna and array is shown in Fig. 5(b).

Minimizing power storage capacitance is another key component to miniaturization by eliminating the need for off-chip passive components. We architected a wireless subsystem for the wireless micro-ECoG implant (discussed in the next section) that utilize electromagnetic field backscattering to transmit data. Backscattering is a well-known communication technique in RFID systems; however, rather than using packet-based communication, our system aims to be constantly powered and transmit a continuous stream of data. Architecting the system in this manner avoids the need for large on-chip power and data storage. We achieved a $20\times$ reduction in the capacitance requirement enabling simple integration of all capacitors on-chip, and we eliminated the need for explicit on-chip memory [56], [57].

While this approach of combining antenna and electrodes onto the same substrate works well for ECoG, scaling it to the dimensions necessary for the acquisition of action potentials poses a formidable challenge, especially if one wants the electrodes to be free-floating and untethered. To explore the limits on what can be accomplished using electromagnetic wireless technologies, a free-floating wireless active action-potential electrode array was developed [61], [62]. The acquisition circuitry for four active channels was combined with wireless powering, data communications and antenna into a 0.125-mm^2 complementary metal–oxide–semiconductor (CMOS) integrated circuit (IC); see Fig. 4. The full

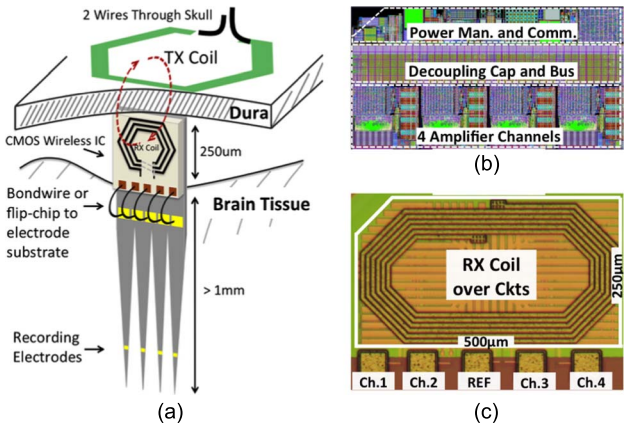

Fig. 4. ***Free-floating wireless active action potential acquisition.***

system, verified with wirelessly powered *in vivo* recordings, consumes 10.5 μW, and operates at 1-mm range with 50-mW transmit power. While this realization served well to demonstrate that free-floating wireless electrodes were indeed feasible, it also pointed out a major dilemma: The tiny $(450\ \mu\text{m} \times 250\ \mu\text{m})$ antenna combined with the high loss of electromagnetic propagation through tissue leads to a truly inefficient solution with a power efficiency of only 0.02%, which is unpractical for real system deployment. This inspired the search for alternative solutions as described later.

II. SYSTEM INTEGRATION

Chronic, high channel count interfaces will require that the active electronics be fully embedded in recording sites and/or polymer platforms to which the electrodes are connected. This also implies that the design of electronics and electrodes is truly synergistic and has to be performed in concert with design of the rest of the system. In order to realize the vision of fully autonomous

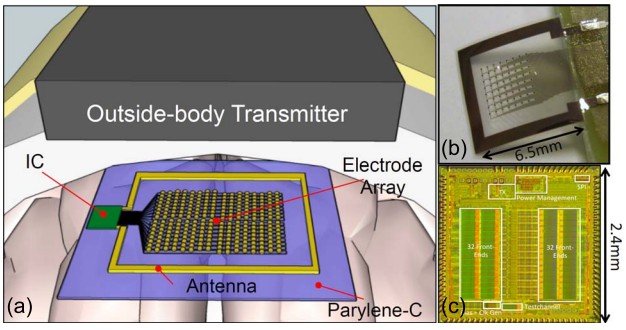

Fig. 5. ***A wireless microelectrocorticography (μECoG) system. (a) μECoG system concept. (b) Photo of microfabricated components [31], [56], [57], [59]. (c) IC microphotograph.***

BMI systems, neural implant devices must not only be effective in their function, but should also meet clinical constraints such as ease of implantation, longevity, safety, and small size. Substantial improvements in neural implant safety, longevity, and form factor are needed to translate existing multisite neural recording systems into technology suitable for long-term use in patients.

To this end, we developed the wireless μECoG device mentioned earlier (Fig. 5). The system has four main components. 1) A microfabricated, submillimeter resolution ECoG grid for neural recordings manufactured using only materials that have been approved by the FDA for chronic implantation; specifically, Parylene-C (a class-IV bioimplantable polymer) and platinum. The 10 μm thin Parylene-C substrate has a Young's modulus $E = 2.75$ GPa, and is comparable in flexibility to 3.5-μm-thin Polyimide $(E = 7.5$ GPa). The grid is sufficiently flexible to conform to the highly folded cortical surface. 2) An IC capable of digitizing the voltage present on the electrodes and that integrates circuitry to receive power and transmit the recorded signals wirelessly across the skull, removing the need for percutaneous plugs and cables. 3) An antenna that is monolithically integrated with the ECoG sensor grid and is used to couple wireless power and transmit data wirelessly across the skull. 4) An external reader that provides power to the implant and receives backscattered signals that are decoded into a data stream.

The wireless μECoG supersedes the current state of the art on three different aspects. 1) The wireless functionality of this system will enable closure of the surgical site, greatly reducing the risk of infection and increasing the stability and longevity of the neural recordings. A wireless, untethered device will restore patient mobility and autonomy allowing patients to be continuously monitored from home and enable a true chronic neural interface for a multitude of applications such as neuroprosthetic control. 2) The use of thin, nonpenetrating ECoG electrodes combined with integrated and miniaturized electronics in this system will substantially reduce the amount of scarring and other forms of tissue immune response, providing stable neural signals for multiple years. 3) The system uses microfabricate electrodes that are spatially 400× denser than current state of the art. These electrodes enable neural signals to be sampled with a spatial resolution comparable to penetrating electrodes, while increasing the longevity by orders of magnitude. The use of a flexible assembly further allows the device to conform to the brain surface.

Similar approaches can be used to develop a miniaturized and low-power neuromodulation interface for the large-scale acquisition of action potentials, while simultaneously performing stimulation on a selected number of channels. In [62] and [63] a 4.8-mm^2 64 channel action-potential neuromodulation IC consuming 417 μW is described (Fig. 6). While similar in many aspects to the ECoG IC described above, it adds two interesting features: 1) it

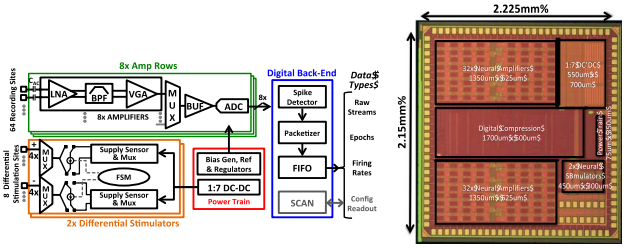

Fig. 6. ***Chip diagram and photograph of neuromodulation IC, supporting action potential acquisition, data compression, and stimulation.***

supports programmable stimulation on eight selectable channels, two of which can be stimulated at the same time; and 2) to reduce the required communication bandwidth, a variety of data compression strategies are included. While supporting raw data transmission, it is also possible to transmit only the epochs around firing events, or only the spike timing. The latter approach reduces the required communication data rate by a factor of 700.

A. Development of Free-Floating Recording Technology

For many applications, the ideal interface would be one which is so small that it effectively "vanishes" inside the nervous system which it is communicating with. Recent work by Seo and colleagues has shown that ultrasonic energy is an extremely attractive option for powering and communicating with extremely small (< 1 mm) implants. A white paper by Seo *et al.* [64] explored the fundamental system design tradeoffs and ultimate size, power, and bandwidth scaling limits of a putative neural recording system built from low-power CMOS circuitry coupled with ultrasonic power delivery and backscatter communication. As an example, a 100-μm scale recording node of so-called *neural dust* embedded 2 mm into cortex and powered via an ultrasonic link would exhibit a best case 7% efficiency power (-11.6 dB), resulting in a received power of ~ 500 μW; this is $> 10^7$ more than EM transmission at similar scale (40 pW). The models used in that study predict that the high efficiency of ultrasonic transmission and ultralow-power CMOS front-ends would enable the scaling of the sensing nodes down to tens of micrometers.

Follow-up work by Seo and colleagues [65] provided experimental verification that the predicted scaling effects follow theory: a $(127\ \text{m})^3$ implant immersed in water 3 cm from an ultrasonic transducer coupled with 0.002% power transfer efficiency and 0.04 ppm backscatter modulation, resulting in a maximum received power of ~ 0.5 μW with1 nW of change in backscatter power with neural activity. The work additionally confirmed the power link scaling trends experimentally for motes ranging in size from ~ 1 mm down to 127 μm.

These initial results open up the possibility of building recording and stimulation devices of extremely small size for both central and peripheral nervous interfaces.

III. CONCLUSION

It is an exciting time to develop systems for neural recording and stimulation, both for central and peripheral nervous system applications. As such, the existing literature is both extensive and rapidly expanding. This review has focused on context and recent directions stemming from work by the authors and collaborators. We believe our developments will impact both neuroscience and neurology, revealing fundamental insight about how the nervous system functions in health and disease. Specifically, neurotechnology has the potential to provide a greater understanding of the structure and function of the complex neural circuits in the brain that facilitate motor learning and control. This will be paramount for the development of neurobiologically informed BMIs designed to aid patients suffering from a large variety of neurological conditions. ■

REFERENCES

[1] J. M. Carmena, "Advances in neuroprosthetic learning and control," *PLoS Biol.*, vol. 11, no. 5, pp. 1–4, 2013.

[2] W. Li *et al.*, "Parylene-based integrated wireless single-channel neurostimulator," *Sens. Actuators A, Phys.*, vol. 166, no. 2, pp. 193–200, 2011.

[3] J. T. W. Kuo *et al.*, "Novel flexible Parylene neural probe with 3D sheath structure for enhancing tissue integration.," *Lab Chip*, vol. 13, no. 4, pp. 554–561, 2013.

[4] Q. He *et al.*, "Parylene Neu Ro-Cages for live neural N Etworks study," in *Proc. 12th Int. Conf. Transducers Solid-State Sens. Actuators Microsyst.*, 2003, vol. 2, pp. 995–998.

[5] A. Tooker, E. Meng, J. Erickson, Y.-C. Tai, and J. Pine, "Biocompatible parylene neurocages," *IEEE Eng. Med. Biol. Mag.*, vol. 24, pp. 30–33, Nov./Dec. 2005.

[6] T. Stieglitz and M. Gross, "Flexible BIOMEMS with electrode arrangements on front and back side as key component in neural prostheses and biohybrid systems," *Sens. Actuators B, Chem.*, vol. 83, no. 1, pp. 8–14, 2002.

[7] T. Stieglitz, "Flexible biomedical microdevices with double-sided electrode arrangements for neural applications," *Sens. Actuators A, Phys.*, vol. 90, no. 3, pp. 203–211, 2001.

[8] C. Hassler, T. Boretius, and T. Stieglitz, "Polymers for neural implants," *J. Polym. Sci. B Polym. Phys.*, vol. 49, no. 1, pp. 18–33, 2011.

[9] F. J. Rodríguez *et al.*, "Polyimide cuff electrodes for peripheral nerve stimulation," *J. Neurosci. Methods*, vol. 98, no. 2, pp. 105–118, 2000.

[10] T. Stieglitz, H. Beutel, M. Schuettler, and J.-U. Meyer, "Micromachined, polyimide-based devices for flexible neural interfaces," *Biomed. Microdevices*, vol. 2, no. 4, pp. 283–294, 2000.

[11] T. Stieglitz, M. Schuettler, and K. P. Koch, "Implantable biomedical microsystems for neural prostheses," *IEEE Eng. Med. Biol. Mag.*, vol. 24, no. 5, pp. 58–65, 2005.

[12] D. Feili *et al.*, "Flexible organic field effect transistors for biomedical microimplants using polyimide and parylene C as substrate and insulator layers," *J. Micromech. Microeng.*, vol. 16, no. 8, pp. 1555–1561, 2006.

[13] D. Farina, K. Yoshida, T. Stieglitz, and K. P. Koch, "Multichannel thin-film electrode for intramuscular electromyographic recordings," *J. Appl. Physiol.*, vol. 104, no. 3, pp. 821–827, 2008.

[14] C. Hassler, R. P. Von Metzen, P. Ruther, and T. Stieglitz, "Characterization of parylene C as an encapsulation material for implanted neural prostheses," *J. Biomed. Mater. Res. B, Appl. Biomater.*, vol. 93, no. 1, pp. 266–274, 2010.

[15] M. Niwayama and T. Yamakawa, "Implantable thin NIRS probe design and sensitivity distribution analysis," *Electron. Lett.*, vol. 50, no. 5, pp. 346–348, 2014.

[16] K. a. Potter *et al.*, "Curcumin-releasing mechanically adaptive intracortical implants improve the proximal neuronal density and blood-brain barrier stability," *Acta Biomater.*, vol. 10, no. 5, pp. 2209–2222, 2014.

[17] J. P. Harris *et al.*, "*In vivo* deployment of mechanically adaptive nanocomposites for intracortical microelectrodes.," *J. Neural Eng.*, vol. 8, no. 4, 2011, Art. no. 046010.

[18] J. K. Nguyen *et al.*, "Mechanically-compliant intracortical implants reduce the neuroinflammatory response.," *J. Neural Eng.*, vol. 11, no. 5, 2014, Art. no. 056014.

[19] M. Jorfi, J. L. Skousen, C. Weder, and J. R. Capadona, "Progress towards biocompatible intracortical microelectrodes for neural interfacing applications," *J. Neural Eng.*, vol. 12, no. 1, 2015, Art. no. 011001.

[20] S. Takeuchi, T. Suzuki, K. Mabuchi, and H. Fujita, "3D flexible multichannel probe array," *J. Micromech. Microeng.*, vol. 14, no. 1, pp. 104–107, 2004.

[21] T. Suzuki, K. Mabuchi, and S. Takeuchi, "A 3D flexible parylene probe array for multichannel neural recording," in *Proc. 1st Int. IEEE EMBS Conf. Neural Eng.*, 2003, pp. 154–156.

[22] D. Ziegler, T. Suzuki, and S. Takeuchi, "Fabrication of flexible neural probes with built-in microfluidic channels by thermal bonding of parylene," *IEEE J. Mmicroelectromech. Syst.*, vol. 15, no. 6, pp. 1477–1482, 2006.

[23] S. Takeuchi, Y. Yoshida, D. Ziegler, K. Mabuchi, and T. Suzuki, "Parylene flexible neural probe with micro fluidic channel," in *17th IEEE Int. Conf. Microelectromech. Syst. Tech. Dig.*, 2004, pp. 208–211.

[24] S. Takeuchi, D. Ziegler, Y. Yoshida, K. Mabuchi, and T. Suzuki, "Parylene flexible neural probes integrated with microfluidic channels," *Lab Chip*, vol. 5, no. 5, pp. 519–523, 2005.

[25] D. C. Rodger *et al.*, "High-density flexible parylene-based multielectrode arrays for retinal and spinal cord stimulation," in *Proc. 4th Int. Conf. Solid-State Sens. Actuators Microsyst.*, 2007, pp. 1385–1388.

[26] S. Thongpang *et al.*, "A micro-electrocorticography platform and deployment strategies for chronic BCI applications," *Clin. EEG Neurosci.*, vol. 42, no. 4, pp. 259–265, Oct. 2011.

[27] M. A. Escabi *et al.*, "A high-density, high-channel count, multiplexed muECoG array for auditory-cortex recordings," *J. Neurophysiol.*, vol. 112, no. 6, pp. 1566–1583, Sep. 2014.

[28] J. Viventi *et al.*, "Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity *in vivo*," *Nature Neurosci.*, vol. 14, no. 12, pp. 1599–1605, 2011.

[29] B. Rubehn, C. Bosman, R. Oostenveld, P. Fries, and T. Stieglitz, "A MEMS-based flexible multichannel ECoG-electrode array," *J. Neural Eng.*, vol. 6, no. 3, p. 36003, 2009.

[30] T. J. Richner *et al.*, "Optogenetic micro-electrocorticography for modulating and localizing cerebral cortex activity," *J. Neural Eng.*, vol. 11, no. 1, p. 16010, 2014.

[31] P. Ledochowitsch *et al.*, "Fabrication and testing of a large area, high density, parylene MEMS μECoG array," in *Proc. IEEE 24th Int. Conf. Microelectromech. Syst.*, 2011, pp. 1031–1034.

[32] K. E. Bouchard *et al.*, "Functionally evoked multi-unit neural activity recorded at the cortical surface with micro-electrocorticography," 2016.

[33] P. Ledochowitsch, A. C. Koralek, D. Moses, J. M. Carmena, and M. M. Maharbiz, "Sub-mm functional decoupling of electrocortical signals through closed-loop BMI learning," in *Proc. 35th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, 2013, pp. 5622–5625.

[34] P. Ledochowitsch, E. Olivero, T. Blanche, and M. M. Maharbiz, "A transparent μECoG array for simultaneous recording and optogenetic stimulation," in *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, 2011, pp. 2937–2940.

[35] P. Ledochowitsch *et al.*, "Strategies for optical control and simultaneous electrical readout of extended cortical circuits.," *J. Neurosci. Methods*, 2015.

[36] A. Yazdan-Shahmorad *et al.*, "Demonstration of a setup for chronic optogenetic stimulation and recording across cortical areas in non-human primates," *SPIE BiOS*, 2015, Art. no. 93052K.

[37] J. F. Hetke, J. L. Lund, K. Najafi, K. D. Wise, and D. J. Anderson, "Silicon ribbon cables for chronically implantable microelectrode arrays," *IEEE Trans. Biomed. Eng.*, vol. 41, no. 4, pp. 314–321, Apr. 1994.

[38] C. Pang *et al.*, "A new multi-site probe array with monolithically integrated parylene flexible cable for neural prostheses," in *Proc. 27th Annu. Int. Conf. Eng. Med. Biol. Soc.*, 2005, pp. 7114–7117.

[39] Q. Bai, K. D. Wise, and D. J. Anderson, "A high-yield microassembly structure for three-dimensional microelectrode arrays," *IEEE Trans. Biomed. Eng.*, vol. 47, no. 3, pp. 281–289, Mar. 2000.

[40] J. N. Y. Aziz *et al.*, "256-channel neural recording and delta compression microsystem with 3D electrodes," *IEEE J. Solid-State Circuits*, vol. 44, no. 3, pp. 995–1005, 2009.

[41] F. Yazicioglu *et al.*, "Ultra-high-density in-vivo neural probes," in *Proc. 36th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, 2014, pp. 2032–2035.

[42] K. Seidl *et al.*, "CMOS-based high-density silicon microprobe arrays for electronic depth control in intracortical neural recording-characterization and application," *J. Microelectromech. Syst.*, vol. 21, no. 6, pp. 1426–1435, 2012.

[43] P. Ledochowitsch, R. F. Tiefenauer, T. J. Blanche, and M. M. Maharbiz, "Nanoflex for neural nanoprobes," *Solid-State Sens.*, pp. 1278–1281, Jun. 2013.

[44] M. Chamanzar, D. J. Denman, T. J. Blanche, and M. M. Maharbiz, "Ultracompact optoflex neural probes for high-resolution electrophysiology and optogenetic stimulation," in *Proc. 28th IEEE Int. Conf. Microelectromech. Syst.*, 2015, pp. 682–685.

[45] M. Chamanzar, M. Borysov, M. M. Maharbiz, and T. J. Blanche, "High-density optrodes for multi-scale electrophysiology and optogenetic stimulation," in *Proc. 36th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, 2014, pp. 6838–6841.

[46] R. R. Harrison *et al.*, "A low-power integrated circuit for a wireless 100-electrode neural recording system," *IEEE J. Solid-State Circuits*, vol. 42, no. 1, pp. 123–133, Jan. 2007.

[47] J. Rabaey, M. Mark, and D. Chen, "Powering and communicating with mm-size implants,"*Autom. Test*, 2011.

[48] T. Denison *et al.*, "A 2 μW 100 nV/rtHz chopper-stabilized instrumentation amplifier for chronic measurement of neural field potentials," *IEEE J. Solid-State Circuits*, vol. 42, no. 12, pp. 2934–2945, 2007.

[49] R. F. Yazicioglu, P. Merken, R. Puers, and C. Van Hoof, "A 200 W eight-channel EEG acquisition ASIC for ambulatory EEG systems," *IEEE J. Solid-State Circuits*, vol. 43, no. 12, pp. 3025–3038, 2008.

[50] F. Zhang, A. Mishra, A. G. Richardson, and B. Otis, "A low-power ECoG/EEG processing IC with integrated multiband energy extractor," *IEEE Trans. Circuits Syst. I, Reg. Papers*, vol. 58, no. 9, pp. 2069–2082, 2011.

[51] N. Verma *et al.*, "A micro-power EEG acquisition SoC with integrated feature extraction processor for a chronic seizure detection system," *IEEE J. Solid-State Circuits*, vol. 45, no. 4, pp. 804–816, 2010.

[52] Intan Technologies, RHD2000.

[53] W. Smith, B. Mogen, E. Fetz, and B. Otis, "A spectrum-equalizing analog front end for low-power electrocorticography recording," in *Proc. 40th Eur. Solid State Circuits Conf.*, 2014, pp. 107–110.

[54] R. Muller, S. Gambini, and J. Rabaey, "A 0.013 mm 2 5 μW DC-coupled neural signal acquisition IC with 0.5 V supply," *IEEE J. Solid-State Circuits*, vol. 47, no. 1, pp. 232–243, 2012.

[55] R. Muller, S. Gambini, and J. M. Rabaey, "A 0.013 mm 2 5 μW DC-coupled neural signal acquisition IC with 0.5 V supply," in *IEEE Int. Solid-State Circuits Conf. Dig. Tech. Papers*, 2011, pp. 302–304.

[56] R. Muller *et al.*, "A minimally invasive 64-channel wireless μECoG implant," *IEEE J. Solid-State Circuits*, vol. 50, no. 1, pp. 344–359, 2015.

[57] R. Muller *et al.*, "A miniaturized 64-channel 225 μW wireless electrocorticographic neural sensor," in *IEEE Int. Solid-State Circuits Conf. Dig. Tech. Papers*, 2014, DOI: 10.1109/ISSCC.2014.6757492.

[58] T. Bjorninen *et al.*, "Antenna design for wireless electrocorticography," in *Proc. IEEE Antennas Propag. Soc. Int. Symp.*, 2012, pp. 1–2.

[59] T. Bjorninen *et al.*, "Design of wireless links to implanted brain–machine interface microelectronic systems," *IEEE Antennas Wirel. Propag. Lett.*, vol. 11, pp. 1663–1666, 2012.

[60] J. Turner, W. Shain, and D. Szarowski, "Cerebral astrocyte response to micromachined silicon implants," *Exp. Neurol.*, vol. 156, no. 1, pp. 33–49, 1999.

[61] D. Yeager, W. Biederman, N. Narevsky, E. Alon, and J. Rabaey, "A fully-integrated

10.5 μW miniaturized (0.125 mm^2) wireless neural sensor," in *Proc. Symp. VLSI Circuits*, Jun. 2012, pp. 72–73.

[62] W. Biederman and D. Yeager, "A fully-integrated, miniaturized (0.125 mm^2) 10.5 μW wireless neural sensor," *Solid-State Circuits*, vol. 48, no. 4, pp. 960–970, 2013.

[63] D. Yeager *et al.*, "A 4.78 mm^2 fully-integrated neuromodulation SoC combining 64 acquisition channels with digital compression and simultaneous dual stimulation," in *Symp. VLSI Circuits Dig. Tech. Papers*, 2014, pp. 1–2.

[64] D. Seo, J. M. Carmena, J. M. Rabaey, E. Alon, and M. M. Maharbiz, "Neural dust: An ultrasonic, low power solution for chronic brain-machine interfaces," 2013, https://arxiv.org/abs/1307.2196

[65] D. Seo, J. M. Carmena, J. M. Rabaey, M. M. Maharbiz, and E. Alon, "Model validation of untethered, ultrasonic neural dust motes for cortical recording," *J. Neurosci. Methods*, vol. 244, pp. 114–122, 2014.

ABOUT THE AUTHORS

Michel M. Maharbiz (Senior Member, IEEE) received the Ph.D. degree from the University of California Berkeley, Berkeley, CA, USA, under Prof. R. T. Howe (EECS) and Prof. J. D. Keasling (ChemE).

Currently, he is a Professor with the Department of Electrical Engineering and Computer Science, University of California Berkeley. His work led to the foundation of Microreactor Technologies, Inc., which was acquired in 2009 by Pall Corporation. From 2003 to 2007, he was an Assistant Professor at the University of Michigan, Ann Arbor, MI, USA. He is the cofounder of Tweedle Technologies, Cortera Neurotech, and served as Vice-President for Product Development at Quswami, Inc., from July 2010 to June 2011. He has been a GE Scholar and an Intel IMAP Fellow. His current research interests include building micro/nano interfaces to cells and organisms and exploring bioderived fabrication methods. His long-term goal is understanding developmental mechanisms as a way to engineer and fabricate machines.

Prof. Maharbiz is a Bakar Fellow and was the recipient of a 2009 National Science Foundation (NSF) Career Award for research into developing microfabricated interfaces for synthetic biology. His group is also known for developing the world's first remotely radio-controlled cyborg beetles. This was named one of the top ten emerging technologies of 2009 by *MIT Technology Review* (TR10) and was in *Time Magazine*'s Top 50 Inventions of 2009.

Rikky Muller (Member, IEEE) received the B.S. and M.S. degrees from the Massachusetts Institute of Technology (MIT), Cambridge, MA, USA and the Ph.D. degree in electrical engineering and computer science from the University of California Berkeley, Berkeley, CA, USA, where she performed research on minimally invasive, wireless neural interfaces.

After her graduate studies, she was a McKenzie Fellow and Lecturer of Electrical and Electronic Engineering at the University of Melbourne, Australia. Currently, she is an Assistant Professor of Electrical Engineering and Computer Science (EECS) at the University of California Berkeley. Her research in implantable neural interfaces led her to cofound Cortera Neurotechnologies, a medical device company, where she held positions as CEO and CTO. Prior to her Ph.D., she worked as an integrated circuit designer at Analog Devices.

Prof. Muller is the recipient of numerous fellowships and awards, and was named one of the top 35 global innovators under the age of 35 (TR35) by the *MIT Technology Review* in 2015.

Elad Alon (Senior Member, IEEE) received the B.S., M.S., and Ph.D. degrees in electrical engineering from Stanford University, Stanford, CA, USA, in 2001, 2002, and 2006, respectively.

In January 2007, he joined the University of California Berkeley, Berkeley, CA, USA, where he is now an Associate Professor of Electrical Engineering and Computer Sciences as well as a Co-Director of the Berkeley Wireless Research Center (BWRC). He has held consulting or visiting positions at Xilinx, Sun Labs, Intel, AMD, Rambus, Hewlett Packard, and IBM Research, where he worked on digital, analog, and mixed-signal integrated circuits for computing, test and measurement, and high-speed communications. His research focuses on energy-efficient integrated systems, including the circuit, device, communications, and optimization techniques used to design them.

Dr. Alon received the IBM Faculty Award in 2008, the 2009 Hellman Family Faculty Fund Award, the 2010 UC Berkeley Electrical Engineering Outstanding Teaching Award, the 2010 ISSCC Jack Raper Award for Outstanding Technology Directions Paper, the 2011 Symposium on VLSI Circuits Best Student Paper Award, and the 2012 Custom Integrated Circuits Conference Best Student Paper Award.

Jan M. Rabaey (Fellow, IEEE) received the Ph.D. degree in applied sciences from the Katholieke Universiteit Leuven, Leuven, Belgium.

In 1987, he joined the faculty of the Electrical Engineering and Computer Science Department, University of California Berkeley, Berkeley, CA, USA, where he now holds the Donald O. Pederson Distinguished Professorship. He has founded and directed a number of influential research labs, including the Berkeley Wireless Research Center (BWRC) and the Berkeley Ubiquitous SwarmLab. He has made major contributions to a number of fields, including advanced wireless systems, ultralow-power design, sensor networks, and configurable ICs. He has been involved in a broad variety of startup ventures. He has authored a number of very widely used textbooks. His current interests include the conception and implementation of next-generation integrated wireless systems over a broad range of applications, as well as exploring the interaction between the cyber and the biological world.

Prof. Rabaey is the recipient of a wide range of major awards, among which are the IEEE CAS Society Mac Van Valkenburg Award, the European Design Automation Association (EDAA) Lifetime Achievement award, and the Semiconductor Industry Association (SIA) University Researcher Award. He is a member of the Royal Flemish Academy of Sciences and Arts of Belgium.

Jose M. Carmena (Fellow, IEEE) received the B.S. degree in electrical engineering from the Polytechnic University of Valencia, Valencia, Spain, in 1995, the M.S. degree in electrical engineering from the University of Valencia, Valencia, Spain, in 1997, and the M.S. degree in artificial intelligence and the Ph.D. degree in robotics from the University of Edinburgh, Edinburgh, Scotland, U.K., in 1998 and 2002, respectively.

Currently, he is a Professor of Electrical Engineering and Neuroscience at the University of California Berkeley, Berkeley, CA, USA, and Co-Director of the Center for Neural Engineering and Prostheses at the University of California Berkeley and the University of California San Francisco. His research program in neural engineering and systems neuroscience is aimed at understanding the neural basis of sensorimotor learning and control, and at building the science and engineering base that will allow the creation of reliable neuroprosthetic systems for the severely disabled. From 2002 to 2005, he was a Postdoctoral Fellow at the Department of Neurobiology and the Center for Neuroengineering at Duke University, Durham, NC, USA.

Prof. Carmena is a member of the Society for Neuroscience and the Neural Control of Movement Society. He has been the recipient of the Bakar Fellowship (2012), the IEEE Engineering in Medicine and Biology Society Early Career Achievement Award (2011), the Aspen Brain Forum Prize in Neurotechnology (2010), the National Science Foundation CAREER Award (2010), the Alfred P. Sloan Research Fellowship (2009), the Okawa Foundation Research Grant Award (2007), the UC Berkeley Hellman Faculty Award (2007), and the Christopher Reeve Paralysis Foundation Postdoctoral Fellowship (2003).