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Graphene in the Design and Engineering of Next-Generation Neural Interfaces

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Neural interfaces are becoming a powerful toolkit for clinical interventions requiring stimulation and/or recording of the electrical activity of the nervous system. Active implantable devices offer a promising approach for the treatment of various diseases affecting the central or peripheral nervous systems by electrically stimulating different neuronal structures. All currently used neural interface devices are designed to perform a single function: either record activity or electrically stimulate tissue. Because of their electrical and electrochemical performance and their suitability for integration into flexible devices, graphene-based materials constitute a versatile platform that could help address many of the current challenges in neural interface design. Here, how graphene and other 2D materials possess an array of properties that can enable enhanced functional capabilities for neural interfaces is illustrated. It is emphasized that the technological challenges are similar for all alternative types of materials used in the engineering of neural interface devices, each offering a unique set of advantages and limitations. Graphene and 2D materials can indeed play a commanding role in the efforts toward wider clinical adoption of bioelectronics and electroceuticals.

1. Introduction

Electrically functional neural interfaces are becoming a powerful toolkit for clinical interventions requiring stimulation and/or recording of the electrical activity of the nervous system. Active implantable devices offer a promising approach for the treatment of various diseases affecting the central nervous or peripheral nervous systems by electrically stimulating different neuronal structures.[1] Deep brain stimulation (DBS), based on the electrical stimulation of deep structures within the brain, is clinically used for the symptomatic treatment of motor-related disorders, such as Parkinson's disease, dystonia and tremor, and is under clinical development for other drug-resistant neurological disorders, such as depression, obsessive–compulsive disorder and others.[2] Even more widely used clinically, cochlear implants aim at converting external sound waves recorded by a microphone and transformed into electrical impulses sent along an electrode array that stimulates the cochlea's hearing nerve.[3] Conceptually similar to cochlear implants, eye prostheses (retinal implants) are intended to partially restore vision in blind patients suffering from retinal diseases leading to the loss of photoreceptors.[4] Electrical stimulation of the central (CNS) and peripheral nervous systems (PNS) can also be achieved by implanted neuroprosthetic devices at the spinal cord or peripheral nerves and muscles to restore sensory and motor function in a novel and promising field of therapeutic interventions termed "bioelectronics".[5]

Neural interfaces whose main functionality is to record electrical activity of the brain aim to address clinical needs different to those discussed above. Recording electrodes in the context of basic electrophysiology research have been central to our understanding of action potentials produced by individual neurons, as well as to provide novel insights into cell-to-cell coupling phenomena that eventually lead to the genesis of neural networks.[6] Electrophysiological recordings of brain activity can be performed by positioning electrode arrays in different areas, such as externally onto the scalp, above or under the dura mater and within the cortex. Non-invasive electrodes located on the scalp or close to the dura mater allow recording of the global activity of different areas in the brain, hence provide useful functional information. However, intracranial electrodes are able to record electrical signals with better spatial and time resolution and are the choice for several clinical applications. For example, cortical neural interfaces are employed in the acute clinical setting for diagnostic purposes and/or for pre-interventional brain mapping related to surgery for neurological disorders. More specifically, intracranial neurophysiology is routinely applied in the surgical treatment of epilepsy, brain tumors, pain or even psychiatric conditions.[7]

Taking the concept of brain-activity recording one step further, brain–machine interfaces (BMI) aim at recording the activity of a single or group of neurons using an electrode array, subsequently processing and digitizing the collected signals

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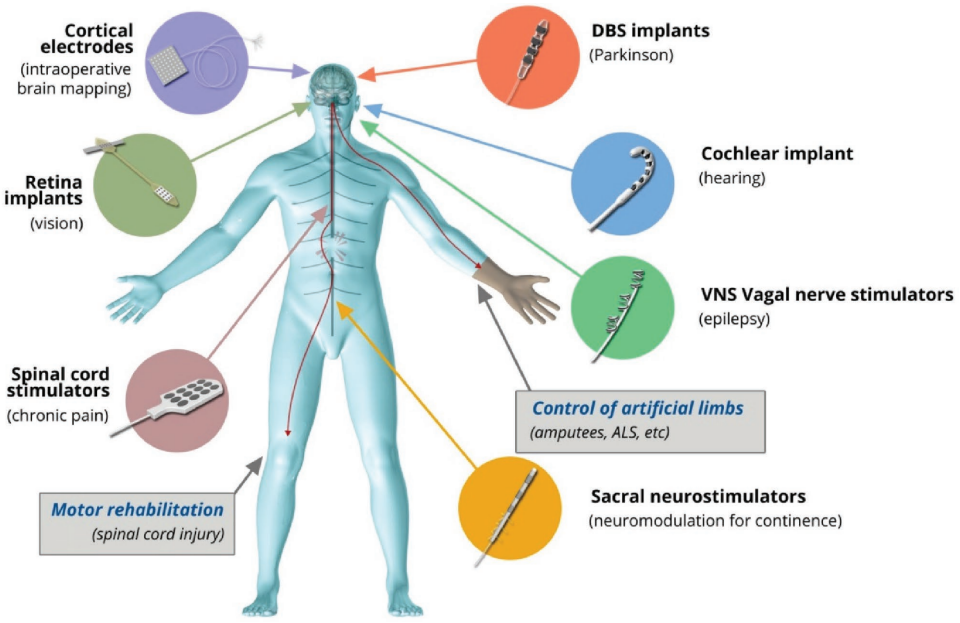

Figure 1. Clinically developed neural interfaces. Schematics of the actual devices are shown (not to scale) along with each disease indication (in parentheses) mainly used or developed for.

that are sent as commands to external devices.[8] Clinically, current effort is directed toward the development of motor BMIs for control of robotic upper limbs.[9] In addition to restoration of motor functionality, cortical BMIs are also employed to enhance communication with patients with severe neurological disorders (e.g., spinal cord injury, amyotrophic lateral sclerosis) using a typing interface[10] or, eventually, a speech prosthesis.[11]

Figure 1 describes the different classes of implantable devices used as neural interfaces for clinical applications as well as novel areas of applications that have not reached broad clinical implantation yet. All these devices have reached different stages of clinical development, but they are all based on the same concept of direct interaction with neural elements in different tissues, connected through wired means to a power source and digital processors. It is important to note that all currently used neural interface devices are designed to perform a single function, either record activity or electrically stimulate tissue. As can be seen from Figure 1, current neural interfaces used in clinical applications are rather elementary designs, mostly based on arrays of few (tens) and large (mm size) metal electrodes. That is in sharp contrast to the potential offered by microelectronic-based designs that include very high integration density as well as on-site signal processing and transmission.

2. Materials for Neural Implants

Due to the complexity of the human nervous system and the intricacy of the anatomical sites where implantation is required, the success of novel clinical implant technologies requires the use of advanced materials and flexible electronic technologies. Any neural interface designed for implantation should be as minimally invasive as possible, allow for a facile surgical procedure, and provide efficient and consistent activity for the duration of its functional lifetime. This can range from several hours for acute experiments (e.g., cortical recording for brain mapping of epileptic lesions) to several years for chronic applications (e.g., cochlear implants or DBS electrodes). Some key requirements to achieve this are: i) biocompatibility with minimal inflammatory (local or systemic) responses from the neural tissue; ii) suitable charge injection capabilities for stimulation applications; iii) adequate signal-to-noise ratio in case of neural recording; and iv) mechanical compliance with neural tissues. The technological challenges required to achieve sufficient levels of efficacy are summed up in the following:

i) Recording capabilities should allow detection of signals of individual neurons (down to few tens of μV) and of assemblies of neurons (inducing field potentials of few hundreds of μV); recording should be possible over large areas (up to few tens of cm^2) and with high spatial resolution (hundreds of μm^2 of the active recording site).
ii) Electrical stimulation requires a minimum level of charge-injection capacity in order to elicit a response in the tissue to be stimulated. Typically, electrode materials should be able to provide on the order of hundreds of $\mu C\ cm^{-2}$ to few $mC\ cm^{-2}$, in pulses between 100 μs and 1 ms. Such a large charge-injection capacity should allow focal stimulation with electrodes with active areas down to hundreds of μm^2.
iii) To minimize foreign-body reaction, electrical neural interfaces should exhibit excellent biocompatibility and mechanical compliance of the neural tissue surrounding the device; long-term stability of the implanted devices can be significantly enhanced by improving the mechanical mismatch between the nervous tissues (Young's modulus ranging between 100 Pa and 10 kPa) and the implantable devices (100 GPa for rigid electronics, 5 GPa for thin polyimide-based devices, and 1 MPa for silicone-based devices).

Table 1. Characteristics of materials (including graphene) used as electrodes in neural interfaces. The values noted are as published in the respective reports.

Type	Material[a)]	Size of the electrode [μm^2]	Charge storage capacity [mC cm^{-2}]	Charge injection limit [mC cm^{-2})	Impedance [kΩ]	Ref.
Metal-based	PtIr	4500	8	0.13	90	[25]
	Porous TiN	2830	5	0.7	55	[54]
	IrOx	4500	0.2			[25]
		177	29	1	113	[55]
	Gold	155	0.4		1500	[56]
	Pt grass	1256		0.3	100	[57]
PEDOT-based	PEDOT:PSS	4500	123	2.9	6	[25]
	PEDOT–CNT	2830	6	1.25	15	[54]
Other carbon materials	Porous diamond	314	10	3	171	[58]
	CNTs	50 000		1,6	2	[59]
Graphene-based	SLG	2500	0.7		3000	[38]
	Doped-SLG	2500	1.9		600	[38]
	rGO foam	625 000		3.1	0.5	[29]
		120 000	62		1	[29]

[a)]PtIr: platinum irdium; TiN: titanium nitride; IrOx: iridium oxide; PEDOT: poly(3,4-ethylenedioxythiophene); PSS: polystyrenesulfonate; CNT: carbon nanotubes; SLG: single-layer graphene; rGO: reduced graphene oxide.

Tremendous effort has been expended over the last decade in the development of novel materials into devices that combine high double layer capacitance (associated to the electrical double layer induced at the electrochemical interface between a conductive electrode and an electrolyte) for both stimulation and recording, biocompatibility toward neural tissue by increased "softness" and flexibility of the substrates. **Table 1** and **2** list characteristics of some of the materials currently used in neural interfaces. Despite the reported performance of those materials and the substrates that have integrated them, their chemical and mechanical stability are still unresolved, posing concerns with regards to their clinical translation. For instance, IrOx is subject to corrosion, CNTs might detach from the electrode substrate and PEDOT substrates can degrade over time in aqueous solutions.[12] In the meantime, flexible implantable scaffolds are being developed to closely conform the cerebral anatomy and to facilitate the insertion of the implant. Radically new implant shapes and structures based on three-dimensional nanoelectronic probes[13] or syringe-injectable mesh-like metal structures,[14] as well as on nanomembranes of crystalline silicon[15] have been recently proposed.

Despite recent advancements, current neural interface materials have not been proved yet to meet all the challenges discussed above, in many cases due to stability issues but also to technology limitations related to these materials. Efforts to develop and integrate new materials that can offer as many options as possible for the design of neural interface devices with multiple capabilities and functionalities are essential for the development of next-generation flexible neural implants.

Table 2. Noise performance of graphene and other materials used in neural interfaces.

Material[a)]	Area [μm^2]	Type	μV_{rms}	$\mu V_{rms}\ \mu m^2$	Ref.
Porous Platinum	113	electrode	2	226	[60]
Porous Diamond	314	electrode	3	942	[58]
TiN	706	electrode	7–10	5000–7000	[61]
Iridium	703	electrode	10	7030	[62]
PEDOT:PSS	100	electrode	8	800	[63]
Doped-SLG	2500	electrode	31	77 500	[38]
Gold	2500	electrode	165	412 500	[38]
SLG	200	transistor	7	1400	[64]

[a)]TiN: titanium nitride; PEDOT: poly(3,4-ethylenedioxythiophene); PSS: polystyrenesulfonate; SLG: single-layer graphene.

3. Graphene Materials for Next-Generation Neural Interfaces

Because of their electrical and electrochemical performance and their suitability for integration into flexible devices, graphene-based materials constitute a versatile platform that could help address many of the current challenges in neural interface design (see Section 2). Different studies have assessed the biocompatibility of graphene with neural cells and its ability to functionally interface with neuronal tissue. Cultures of neural cells on 2D graphene substrates have been found to exhibit enhanced adhesion, good viability as well as improved neurite sprouting and outgrowth.[16–18] The issue of biodegradability of graphene and other 2D materials is also important, but much more challenging to determine in a generalized manner. A few studies have already reported the biodegradation of graphene nanomaterials using enzymes, such as horseradish peroxidase.[19–21] In the design of implantable devices, material degradability will need to be ensured in the event of exfoliation or tear. However, the substrate will need to maintain structural

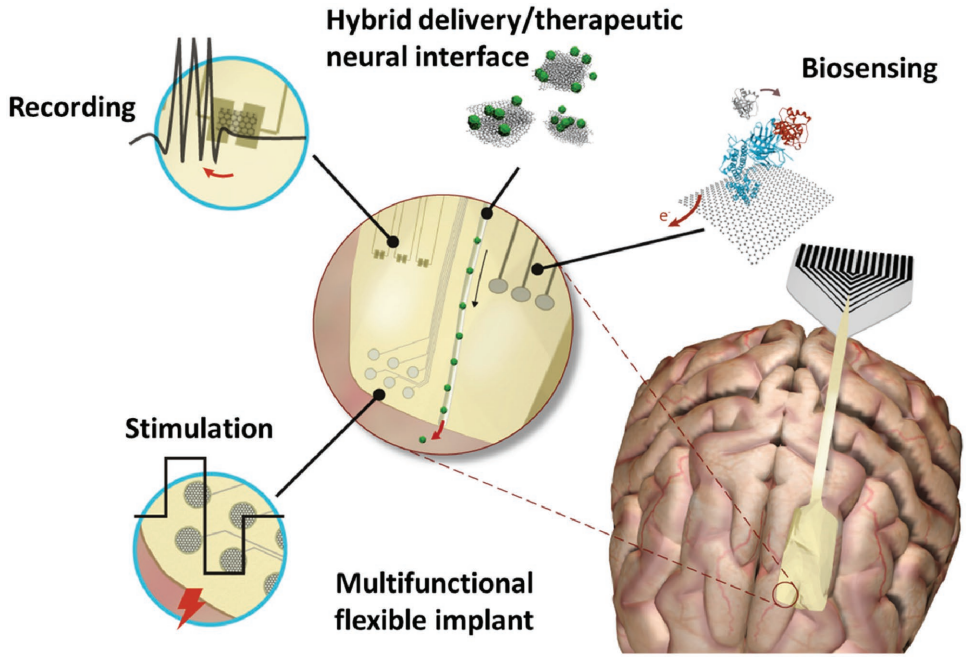

Figure 2. Neural interface functionalities enabled by incorporation of graphene material. By utilising the inherent properties that graphene materials offer, such as large surface area, flexibility, versatility for chemical functionalisation and excellent performance of electronic devices, a variety of functionalities like recording, stimulation, biosensing, and drug delivery at the neural interface could be engineered in various combinations.

stability post-implantation, especially in cases of long-term implants. Longitudinal assessment studies to address the biocompatibility, biodegradation and overall safety of the graphene-based neural devices is warranted and will be imperative.

The conductive properties of CVD graphene planar substrates have been used to electrically stimulate human neural stem cells and hence direct their differentiation toward a neuronal phenotype.[22] Three-dimensional graphene-based scaffolds have also been explored to stimulate adult hippocampal neural stem cells, for instance showing preferred differentiation toward astrocytes and neurons.[23] GO porous hydrogels also allowed the differentiation of embryonic neural progenitor cells to both neuron and glial cells with reasonably high formation of dendrites, axons and synaptic connexions.[24] It has become apparent that the capacity of graphene to interface with neuronal tissue effectively and functionally allows the fabrication of devices for electrical recording and stimulation. In combination with technologies for therapeutic molecule controlled release, the use of graphene-based neural interface implants could achieve optimum integration with the surrounding tissue while minimizing the formation of the fibrotic capsule building around electrodes, as shown in **Figure 2** and further elaborated in the sections that follow.

3.1. Graphene-Based Materials for Neural Stimulation

Effective stimulation of neuronal tissue devoid of damage or adverse (e.g., neuroinflammatory) reaction is required for electrodes used in deep brain, cortical and intra-cortical, or spinal cord stimulation for motor BCIs, cochlear and retinal implants, as well as in peripheral nervous system applications. To elicit a functional response, electrical stimulation requires a minimum level of charge injection to depolarize the membrane of excitable cells in the vicinity of the stimulating electrode, which can typically vary between tens of $\mu C\ cm^{-2}$ and several $mC\ cm^{-2}$ depending on the tissue to be stimulated. The charge injection level provided by the electrode depends on the electrolytic double layer capacitance of the material and on its potential window in water.

Typical reported values for such interfacial capacitance of non-structured CVD grown graphene-based materials are between 5 and 20 $\mu F\ cm^{-2}$ (corresponding to 5 to 20 $\mu C\ cm^{-2}$ for a 1 V potential window in water), slightly lower than standard noble metal electrodes like Pt and Au and well below the tens of $mF\ cm^{-2}$ offered by alternative novel materials proposed for neural stimulation, such as PEDOT–CNT or IrOx.[25] However, recent studies have shown that when used in porous thin-films processed from flakes or introduced in polymer composites,[26,27] graphene-based materials can exhibit dramatically improved performance for neural stimulation. For instance, porous graphene oxide electrodes reduced by laser treatment[28,29] and by the Langmuir–Blodgett method[30] have been reported to be able to stimulate neural tissues with outstanding charge injection values between 1 and 3 $mC\ cm^{-2}$. Furthermore, new promising materials are expected to emerge from the very active research field of the supercapacitors, in which graphene-based materials exhibiting very large active surface area are being developed achieving very high double layer capacitance. For instance, free standing porous graphene grown by CVD has been reported to exhibit double layer capacitance values exceeding tens of $mF\ cm^{-2}$.[31–33] The free standing graphene films are obtained by using a porous sacrificial scaffold or by tuning the growth parameters in order to obtain vertical

growth of graphene walls. More interesting, reduced graphene oxide foams that can be obtained by a variety of procedures show unparalleled values of volumetric charges, which indicates very promising charge injections.[34–36] These materials, however, have not yet been integrated into microelectrodes and thus have to be tested for neural applications. Considering the capacitance and charge injection values given above, structured or 3D films of graphene-based materials, as well as composite films including graphene, show significant potential for stimulation applications.

3.2. Graphene for Electrical Neural Recording

Monitoring electrical brain activity requires recording the signals of individual neurons (down to a few tens of μV) and of assemblies of neurons (inducing potentials of few hundreds of μV or even mV) over large areas that can reach up to few tens of cm^2. In order to achieve this, recoding technologies offering both high spatial resolution and temporal resolution need to be developed. However, when the dimensions of a recording electrode reduce to a few tens of microns, its impedance can become so high that the electrode's intrinsic noise levels can be well above the signal levels of action potentials. In this case, electrode materials with a high double-layer capacitance (i.e., low interfacial impedance) should be used.

Graphene exhibits electrochemical capabilities for neural recording similar to platinum or gold, which have been for long the standard electrode materials for neural recording. Although recent studies have demonstrated the successful recording of local field potentials from the rat cortex using graphene,[37,38] the relatively low double layer capacitance of single layer or few layer graphene results in a high impedance, and thus large thermal noise, which is detrimental to achieve high signal-to-noise ratio with a small microelectrode (diameter below 20 μm). Similarly to the case of neural stimulation, the performance of graphene-based materials for recording applications can greatly improve by using structured or 3D films that increase the specific surface area of the electrode. This has been recently shown[28,29] by recording in vivo brain activity using porous graphene-related materials with a good signal-to-noise ratio.

In contrast to standard metals used in neural interfaces, graphene offers an unique advantage for recording applications: whereas metals only allow for designs based on the electrode configuration, graphene can be used to fabricate sensors based on a field-effect transistor (FET) configuration.[39] In this configuration, the recording mechanism is based on the modulation of the transistor current induced by the electrical activity in the vicinity of the transistor's gate. An important benefit of the transistor recording configuration is its intrinsic signal amplification, which reduces the sensitivity to external noise. In addition, the transistor configuration allows the design of sensor arrays with a level of integration density beyond that offered by electrodes. Due to these advantages, FETs based on various materials (silicon,[40] organic semiconductors,[41] or diamond[42]) have been explored to record neural activity. In the case of graphene, which is suitable for integration with flexible substrates, the exceptional mobility of charge carriers results in graphene FETs exhibiting a high transconductance, a figure of merit for the transistor amplifying capability,[43] that together with the low intrinsic noise of graphene FETs leads to recording capabilities with high signal-to-noise ratio. It has been already demonstrated that arrays of flexible FETs based on CVD graphene with a transconductance over 1 mS V^{-1} can detect action potentials of electrically active cells in vitro,[44] as well as the brain activity in acute in vivo experiments.[45]

3.3. Graphene for Controlled Drug Delivery at the Neural Interface

Graphene and its derivatives are actively being explored in the field of therapeutic agent transport as nanoplatforms able to carry compounds of biological activity to specific cell populations and intracellularly. π–π stacking between GO flakes and the aromatic rings present in various therapeutic compounds (e.g., doxorubicin, camptothecin, heparin) have been described. Other types of non-covalent complexation (e.g., with nucleic acids) is also of great interest in the context of gene therapy applications.[46] In combination with neural interface technologies, graphene flakes can be integrated as nanocarriers able to coat neural electrodes and be released for the in situ delivery of dopamine, microglial inhibitors (such as minocycline or resveratrol) and anti-inflammatory agents such as dexamethasone. There are already various reports describing conjugation and release of dexamethasone from graphene-based polymeric nanocomposites[47] or graphene-coated metal alloys used as dental implants.[48]

The design of electroresponsive graphene-based hydrogels have also been proposed for controlled, stimulation-triggered drug release applications.[49] In these strategies, graphene sheets are incorporated into a hydrogel matrix to enhance mechanical, electrical and thermal properties. In much earlier work following a similar approach, dexamethasone was loaded onto poly(lactic-*co*-glycolic acid) nanoparticles that were subsequently embedded into alginate hydrogels used to coat gold and iridium oxide electrodes for local administration after implantation.[50,51] Overall, such strategies could be employed to engineer smart coatings for neural implants able to release biologically active molecules, to improve surface softness, and enhance neural recruitment and the overall biocompatibility of the implant.

3.4. Graphene for In Situ Biosensing

Beyond the detection of electrical activity in the CNS or PNS, many applications of neural interfaces would hugely benefit from the capability of sensing biomolecules relevant to neurology. In this way, it would be possible to simultaneously map the electrical activity, the biochemistry and metabolic activity of neural tissue. For instance, the detection of neurotransmitters and neuromodulators such as dopamine, serotonin, acetylcholine, choline, or glutamate, or reporter molecules such as H_2O_2 would allow a better understanding of neurological disorders and tissue response to treatment.

Due to its electronic properties and large surface to volume ratio, graphene has been extensively studied in the context of

biosensing applications, and a broad variety of devices exhibiting high sensitivity, low noise, and low detection limits have been reported. Both enzyme and other graphene-based biosensors have been used for the detection of biologically relevant molecules such as glucose, DNA, or cholesterol. More relevant to neural interfaces, enzyme-modified graphene FETs have been used to demonstrate the detection of acethylcholine, a neuromodulator in the CNS and PNS.[52] Functionalized graphene and graphene/polymer composites have also been used for the detection of dopamine, a catecholamine neurotransmitter acting in the CNS.[53] To enable optimal modulation to therapeutic activity and intervention, graphene-based biosensors could be integrated as part of closed-loop system able to adapt the stimulation or therapeutic molecule release according to the level of biosensing readings at the implantation site. The main challenge in most biosensing designs is tailoring specificity of the recognition event. This has to be achieved by a controlled chemical modification of graphene to enable the specific recognition of neurotransmitters, neuromodulators, or other biomarkers.

4. Outlook

In order to fully exploit the potential of neural interfaces, the forthcoming generation of devices is expected to simultaneously offer multiple functionalities, including recording and stimulation of electrical activity, recognition of neurotransmitters, neuromodulators and other neurologically relevant biomolecules, as well as the capability for controlled drug delivery. Given their versatility, which results from a remarkable combination of physico-chemical, structural and electronic properties, graphene-based materials can provide options in several, if not all, of such desired device functionalities.

For instance, microtransistors based on CVD graphene can be at the heart of flexible arrays capable of recording over large areas of the brain with very high spatial resolution. To overcome the limitation introduced by the excessive footprint of the large number of connections associated with the high density recording devices, graphene FETs have the additional advantage of enabling facile multiplexing by using flexible technology based on emerging 2D semiconductors, such as MoS_2.

With respect to neuro-stimulation, three dimensional or structured graphene films exhibiting high porosity (or surface-to-volume ratio), such as CVD foams or rGO porous films, offer charge injection capacitances similar or superior to those of competing materials. Furthermore, graphene-related materials (graphene nanoflakes) can be used in hybrid thin films as a doping material to increase the film conductivity and thus to enhance the charge injection of these films. Graphene can also contribute by providing biosensing functionality on neural interfaces based on the reported high sensitivity of detection of electrical and chemical changes.

Graphene and other 2D materials possess an array of properties (flexibility, electrical mobility, large surface area available for interaction with the neuronal components and amenable to surface modifications) that can enable enhanced functional capabilities for neural interfaces. The technological challenges are similar for the different competing types of materials used in the engineering of such devices. We believe that each material can offer a unique set of advantages and limitations that – depending on the specific indication developed – will ultimately determine efficacious function and eventually clinical adoption.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] N. G. Hatsopoulos, J. P. Donoghue, *Annu. Rev. Neurosci.* **2009**, *32*, 249.
[2] J. S. Perlmutter, J. W. Mink, *Annu. Rev. Neurosci.* **2006**, *29*, 229.
[3] F. A. Spelman, *Audiol. Neurotol.* **2006**, *11*, 77.
[4] S. Picaud, J.-A. Sahel, *C. R. Biol.* **2014**, *337*, 214
[5] D. J. Payne, M. N. Gwynn, D. J. Holmes, D. L. Pompliano, *Nat. Rev. Drug Discovery* **2007**, *6*, 29.
[6] L. Yang, Y. Li, Y. Fang, *Adv. Mater.* **2013**, *25*, 3881.
[7] E. F. Chang, *Neuron* **2015**, *86*, 68.
[8] M. A. Lebedev, M. A. L. Nicolelis, *Trends Neurosci.* **2006**, *29*, 536.
[9] M. Velliste, S. Perel, M. C. Spalding, A. S. Whitford, A. B. Schwartz, *Nat. Lett.* **2008**, *453*, 1098.
[10] A. Vallabhaneni, T. Wang, B. He, *Neural Engineering*, Springer Series in Bioelectric Engineering, Springer, Boston, MA, USA, **2005**, pp. 85–121.
[11] J. S. Brumberg, F. H. Guenther, *Expert Rev. Med. Devices* **2010**, *7*, 667.
[12] E. Vitoratos, S. Sakkopoulos, E. Dalas, N. Paliatsas, D. Karageorgopoulos, F. Petraki, S. Kennou, S.A. Choulis, *Org. Electron.* **2009**, *10*, 61.
[13] X. Dai, W. Zhou, T. Gao, J. Liu, C. M. Lieber, *Nat. Nanotechnol.* **2016**, *11*, 776.
[14] C. Xie, J. Liu, T.M. Fu, X. Dai, W. Zhou, C. M. Lieber, *Nat. Mater.* **2015**, *14*, 1286.
[15] J. A. Rogers, M. G. Lagally, R. G. Nuzzo, *Nature* **2011**, *477*, 45.
[16] N. Li, X. Zhang, Q. Song, R. Su, Q. Zhang, T. Kong, L. Liu, G . Jin, M. Tang, G. Cheng, *Biomaterials* **2011**, *32*, 9374.
[17] D. Sahni, A. Jea, J. A. Mata, D. C. Marcano, *J. Neurosurg. Pediatr.* **2013**, *11*, 575.
[18] A. Bendali, L. H. Hess, M. Seifert, V. Forster, A. F. Stephan, J. A. Garrido, S. Picaud, *Adv. Healthcare Mater.* **2013**, *2*, 929.
[19] G. P. Kotchey, B. L. Allen, H. Vedala, N. Yanamala, A. A. Kapralov, Y. Y. Tyurina, J. Klein-Seetharaman, V. E. Kagan, A. Star, *ACS Nano* **2011**, *5*, 2098.

[20] Y. Li, L. Feng, X. Shi, X. Wang, Y. Yang, K. Yang, T. Liu, G. Yang, Z. Liu, *Small* **2014**, *10*, 1544.
[21] R. Kurapati, J. Russier, M. A. Squillaci, E. Treossi, C. Ménard-Moyon, A. E. Del Rio-Castillo, E. Vazquez, P. Samorì, V. Palermo, A. Bianco, *Small* **2015**, *11*, 3985.
[22] S. Y. Park, J. Park, S. H. Sim, M. G. Sung, K. S. Kim, B. H. Hong, S. Hong, *Adv. Mater.* **2011**, *23*, H263.
[23] N. Li, Q. Zhang, S. Gao, R. Huang, L. Wang, L. Liu, J. Dai, M. Tang, G. Cheng, *Sci. Rep.* **2013**, *3*, 1604.
[24] M. C. Serrano, J. Patiño, C. Garcia-Rama, M. L. Ferrer, J. L. G. Fierro, A. Tamayo, J. E. Collazos-Castro, F. del Monte, M. C. Gutiérrez, *J. Mater. Chem. B* **2014**, *2*, 5698.
[25] S. Venkatraman, J. Hendricks, Z. A. King, A. J. Sereno, S. Richardson-Burns, D. Martin, J. M. Carmena, *IEEE Trans. Neural Syst. Rehabil. Eng.* **2011**, *19*, 307.
[26] W. Yang, Y. Zhao, X. He, Y. Chen, J. Xu, S. Li, Y. Yang, Y. Jiang, *Nanoscale Res. Lett.* **2015**, *10*, 222.
[27] N. Hu, L. Zhang, C. Yang, J. Zhao, Z. Yang, H. Wei, H. Liao, Z. Feng, A. Fisher, Y. Zhang, Z. J. Xu, *Sci. Rep.* **2016**, *6*, 19777.
[28] N. V. Apollo, M. I. Maturana, W. Tong, D. A. X. Nayagam, M. N. Shivdasani, J. Foroughi, G. G. Wallace, S. Prawer, M. R. Ibbotson, D. J. Garrett, *Adv. Funct. Mater.* **2015**, *25*, 3551.
[29] Y. Lu, J. R. Swartz, *Sci. Rep.* **2016**, *6*, 33526.
[30] M. M. Jaafar, G. P. Ciniciato, S. A. Ibrahim, S. M. Phang, K. Yunus, A. C. Fischer, M. Iwamoto, P. Vengadesh, *Langmuir* **2015**, *31*, 10426.
[31] B. G. Choi, M. Yang, W. H. Hong, J. W. Choi, Y. S. Huh, *ACS Nano* **2012**, *6*, 4020.
[32] D. Aradilla, M. Delaunay, S. Sadki, J.-M. Gérard, G. Bidan, *J. Mater. Chem. A* **2015**, *3*, 19254.
[33] S. Drieschner, M. Weber, J. Wohlketzetter, J. Vieten, E. Makrygiannis, B. M. Blaschke, V. Morandi, L. Colombo, F. Bonaccorso, J. A. Garrido, *2D Mater.* **2016**, *3*, 45013.
[34] H. Chen, Z. Song, X. Zhao, X. Li, H. Lin, *RSC Adv.* **2013**, *3*, 2971.
[35] J.-L. Shi, W.-C. Du, Y.-X. Yin, Y.-G. Guo, L.-J. Wan, *J. Mater. Chem. A* **2014**, *2*, 10830.
[36] J. H. Lee, N. B. Schade, J. A. Fan, D. R. Bae, M. M. Mariscal, G. Lee, F. Capasso, S. Sacanna, V. N. Manoharan, G.R. Yi, *ACS Nano* **2013**, *7*, 9366.
[37] D.-W. Park, A. A. Schendel, S. Mikael, S. K. Brodnick, T. J. Richner, J. P. Ness, M. R. Hayat, F. Atry, S. T. Frye, R. Pashaie, S. Thongpang, Z. Ma, J. C. Williams, *Nat. Commun.* **2014**, *5*, 5258.
[38] D. Kuzum, H. Takano, E. Shim, J. C. Reed, H. Juul, A. G. Richardson, J. de Vries, H. Bink, M. A. Dichter, T. H. Lucas, D. A. Coulter, E. Cubukcu, *Nat. Commun.* **2014**, *5*, 5259.
[39] L. H. Hess, M. Jansen, V. Maybeck, M. V. Hauf, M. Seifert, M. Stutzmann, I. D. Sharp, A. Offenhäusser, J. A. Garrido, *Adv. Mater.* **2011**, *23*, 5045.
[40] R. Weis, B. Müller, P. Fromherz, *Phys. Rev. Lett.* **1996**, *76*, 327.
[41] D. Khodagholy, T. Doublet, P. Quilichini, M. Gurfinkel, P. Leleux, A. Ghestem, E. Ismailova, T. Hervé, S. Sanaur, C. Bernard, G. G. Malliaras, *Nat. Commun.* **2013**, *4*, 1575.
[42] M. Dankerl, M. V. Hauf, A. Lippert, L. H. Hess, S. Birner, I. D. Sharp, A. Mahmood, P. Mallet, J.-Y. Veuillen, M. Stutzmann, J. A. Garrido, *Adv. Funct. Mater.* **2010**, *20*, 3117.
[43] C. Mackin, L. H. Hess, A. Hsu, Y. Song, J. Kong, J. A. Garrido, *IEEE Trans. Electron Devices* **2014**, *61*, 3971.
[44] B. M. Blaschke, M. Lottner, S. Drieschner, A. B. Calia, K. Stoiber, L. Rousseau, G. Lissourges, J. A. Garrido, *2D Mater.* **2016**, *3*, 25007.
[45] B. M. Blaschke, N. Tort-Colet, A. Guimerà, J. Weinert, L. Rousseau, A. Heimann, S. Drieschner, O. Kempski, R. Villa, M. V. Sanchez, J. A. Garrido, *2D Mater.* **2017**, *4*, 25040.
[46] M. Vincent, I. de Lázaro, K. Kostarelos, *Gene Ther.* **2017**, *24*, 123.
[47] H. Sun, L. Zhang, W. Xia, L. Chen, Z. Xu, W. Zhang, *Appl. Phys. A* **2016**, *122*, 632.
[48] H. S. Jung, T. Lee, K. Kwon, H. Seop, S. Kwang, C. Soo, *ACS Appl. Mater. Interfaces* **2015**, *7*, 9598.
[49] A. Servant, V. Leon, D. Jasim, L. Methven, P. Limousin, M. Prato, K. Kostarelos, *Adv. Healthcare Mater.* **2014**, *3*, 1334.
[50] D. H. Kim, D. C. Martin, *Biomaterials* **2006**, *27*, 3031.
[51] D.-H. Kim, M. Abidian, D. C. Martin, *J. Biomed. Mater. Res., Part A* **2004**, *71A*, 577.
[52] L. H. Hess, A. Lyuleeva, B. M. Blaschke, M. Sachsenhauser, M. Seifert, J. A. Garrido, F. Deubel, *ACS Appl. Mater. Interfaces* **2014**, *6*, 9705.
[53] B. J. Venton, R. M. Wightman, *Anal. Chem.* **2003**, *75*, 414–A.
[54] R. Gerwig, K. Fuchsberger, B. Schroeppel, G. Steve, G. Heusel, U. Kraushaar, W. Schuhmann, A. Stett, M. Stelzle, *Front. Neuroeng.* **2012**, *5* (8).
[55] S. J. Wilks, S. M. Richardson-Burns, J. L. Hendricks, D. C. Martin, K. J. Otto, *Front. Neuroeng.* **2009**, *2*, 7.
[56] X. Du, L. Wu, S. Huang, Q. Cai, Q. Jin, J. Zhao, *J. Biol. Phys.* **2015**, *41*, 339.
[57] C. Boehler, T. Stieglitz, M. Asplund, *Biomaterials* **2015**, *67*, 346.
[58] G. Piret, C. Hébert, J.-P. Mazellier, L. Rousseau, E. Scorsone, M. Cottance, G. Lissorgues, M. O. Heuschkel, S. Picaud, P. Bergonzo, B. Yvert, *Biomaterials* **2015**, *53*, 173.
[59] K. Wang, H. A. Fishman, H. Dai, J. S. Harris, *Nano Lett.* **2006**, *6*, 2043.
[60] M. Heim, L. Rousseau, S. Reculusa, V. Urbanova, C. Mazzocco, S. Joucla, L. Bouffier, K. Vytras, P. Bartlett, A. Kuhn, B. Yvert, *J. Neural Physiol.* **2012**, *108*, 1793.
[61] T. Ryynänen, V. Kujala, L. Ylä, I. Korhonen, J. M. A. Tanskanen, P. Kauppinen, K. Aalto, J. Hyttinen, E. Kerkelä, S. Narkilahti, J. Lekkala, *Micromachines* **2011**, *2*, 394.
[62] K. J. Otto, M. D. Johnson, D. R. Kipke, *IEEE Trans. Biomed. Eng.* **2006**, *53*, 333.
[63] D. Khodagholy, J. N. Gelinas, T. Thesen, W. Doyle, O. Devinsky, G. G. Malliaras, G. Buzsáki, *Nat. Neurosci.* **2015**, *18*, 310.
[64] L. H. Hess, M. Seifert, J. A. Garrido, *Proc. IEEE* **2013**, *101*, 1780.

