frontiers
in Neuroscience

PERSPECTIVE
published: 27 December 2016
doi: 10.3389/fnins.2016.00599

The Pursuit of Chronically Reliable Neural Interfaces: A Materials Perspective

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Brain–computer interfaces represent one of the most astonishing technologies in our era. However, the grand challenge of chronic instability and limited throughput of the electrode–tissue interface has significantly hindered the further development and ultimate deployment of such exciting technologies. A multidisciplinary research workforce has been called upon to respond to this engineering need. In this paper, I briefly review this multidisciplinary pursuit of chronically reliable neural interfaces from a materials perspective by analyzing the problem, abstracting the engineering principles, and summarizing the corresponding engineering strategies. I further draw my future perspectives by extending the proposed engineering principles.

Keywords: stretchable electronics, conducting polymer, neural interface, microelectrode array, biomimicry

Edited by:
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Specialty section:
This article was submitted to Neural Technology, a section of the journal Frontiers in Neuroscience

Received: 29 April 2016
Accepted: 15 December 2016
Published: 27 December 2016

Citation:
Guo L (2016) The Pursuit of Chronically Reliable Neural Interfaces: A Materials Perspective. Front. Neurosci. 10:599. doi: 10.3389/fnins.2016.00599

INTRODUCTION

The fascination of mind-controlled machines often seen in science fiction movies has reflected a recent passionate pursuit of such neurotechnologies by an integrative community of scientists, engineers, and physicians. Collectively, this broad field is named *Neural Prosthetics*, yet its borders are being constantly shaped by fast evolving new technological advances. Although the science fiction has come closer to reality with the demonstration of possibility in humans (Hochberg et al., 2012; Collinger et al., 2013; Bouton et al., 2016), a feasible system for long-term daily use is still far out of reach, primarily due to the discovery of fibrotic encapsulation developing around the implanted neural interface over a short time window of a few months, which physically screens the electrical sensors from accessing to the target neurons (Rousche and Normann, 1998; Jorfi et al., 2015). This hassle has somehow resulted in a brief cooling down of the initial intense enthusiasm in the scientific community and the general public and a halt in the rush to commercialization of such heavily invasive neurotechnologies. Correspondingly, the field's focus has been steered toward scrutinizing this problem of chronic instability of neural interfacing, with an ambition to address it in this decade.

More recently, stimulated by advocations and funding supports on brain-related research across the US, Europe, and Asia, the once electrical-engineering concentrated field starts to bloom, attracting an ever large, and diverse research workforce who brings in invaluable multidisciplinary perspectives and expertise in reforming the field. On the one hand, increasingly more signal channels are being integrated in neural implants to boost the bandwidth of the acquired data in large-scale recording (Berényi et al., 2014; Ruther and Paul, 2015; Shobe et al., 2015), reflecting strong contributions from the traditional community. On the other hand, as the mechanisms of short-term and long-term tissue responses to neural implants are being unveiled (Biran et al., 2005; Polikov et al., 2005; Grill et al., 2009; Kotov et al., 2009; Marin and Fernandez, 2010; Potter et al., 2012; Kozai et al., 2012a, 2014, 2015a,b; Jorfi et al., 2015) materials science and tissue engineering have shown increasing importance as essential add-ons to the research enterprise in developing advanced neural interfaces (Aravamudhan and Bellamkonda, 2011).

In this paper, I will briefly review this multidisciplinary pursuit of chronically reliable neural interfaces from a materials perspective by analyzing the problem, abstracting the engineering principles, and summarizing the corresponding engineering strategies.

THE GRAND CHALLENGE AND THE IDEAL NEURAL INTERFACE

The *grand challenge* to chronically reliable neural interfacing is *instability* and *limited throughput* of the electrode–tissue interface, which is universal to all current implanted neural interfaces. Ideally, a neural prosthesis should function as if it is part of our native body, in terms of both cognitive control and perception. Correspondingly, the *ideal neural interface* needs to be physiologically integrated to the target neural tissue at the tissue and cellular levels with high fidelity over the life span of the host. This high-fidelity physiological integration requires long-term stability in physical integration and long-term stability and sufficient bandwidth in functional integration. I will elucidate these two aspects in details in the following sections.

PHYSICAL INTEGRATION

The engineering challenge to stable physical integration stems from different classes of materials involved at the electrode–tissue interface, with the implanted abiologic materials subject to immune regulation.

Engineering Principles

In order to address the stability issue to physical integration of current neural interfaces, two alternative engineering principles are being explored aiming at making the neural implant either *insensible* or *indistinguishable* to the host tissue environment.

Insensibility

For the insensibility principle, if the host tissue cannot perceive the existence of the implant, there should be no immune response. Although it is impossible to completely make an implant physically insensible, reduction of its footprint down to the micro/nanoscale has proven to dramatically improve the chronic stability of the neural interface (Kozai et al., 2012b; Xie et al., 2015). This engineering principle is straightforward to implement and often applied together with the indistinguishability principle (**Figure 1A**; Kozai et al., 2012b). Its recent manifestation in nanoelectronic neural interfaces shows great promise (**Figure 1B**; Xie et al., 2015).

Indistinguishability

For the indistinguishability principle, alternatively, if the implant materials can be camouflaged so that the cells, particularly the immune cells, would discern minimal differences between the abiologic materials and their native environment, there should be minimal immune response, either. In line with this engineering principle, the ideal neural implant should be able to surpass the immune surveillance by mimicking the host tissue environment both physically and biochemically, thus making itself indistinguishable. In the next section, I will describe two primary biomimicry engineering strategies under this principle, which have been intensively pursued in the field to improve the physical integration of neural interfaces, as related to our own work in the past decade.

Biomimicry Strategies for Stable Physical Integration

Cells reside in their extracellular matrix (ECM) with which they interact physically and biochemically. If the implant materials are made indistinguishable from the ECM, both the immune cells and the target neurons will be fooled, and as a result, neither induction of fibrosis nor expulsion of the neurons should happen. Based on this principle, two representative engineering strategies have been explored from the mechanical and biochemical aspects respectively for biomimicry.

Mechanical Mimicry: From Rigid to Soft Interfaces

The field of neural interfaces has passed a few prominent milestones. The transition from single-needle electrode to multiwire electrodes dramatically increased the information that could be extracted from the nervous system. The introduction of CMOS microfabrication technologies to the fabrication of multichannel neural microelectrode arrays offered unprecedented spatial accuracy and reproducibility to neural interfacing. The renowned Utah Arrays and Michigan Probes are the classic examples of such implantable interfaces. Many excellent reviews are available on these rigid neural interfaces (Cheung, 2007; Heer and Hierlemann, 2007; Ghane-Motlagh and Sawan, 2013; Patil and Thakor, 2016). It is only within the past decade or so that the scientific community started to steer toward making soft versions of these devices, as one prominent approach to reduce the neuro-inflammation response and improve the chronic performance (Grill et al., 2009; Kotov et al., 2009; Nguyen et al., 2014). This is an essential stage for the development of long-term reliable neural prostheses, as contemporary technologies and regulations have advanced sufficient to permit chronic studies. As a result, numerous flexible and stretchable microelectrode arrays have emerged, first as surface interfaces (**Figure 1C**) and later coming up with intracortical probes when a range of insertion mechanisms were developed (Patil and Thakor, 2016). More recently, the concept of regenerative neural interfaces is being revived, combining state-of-the-art stretchable electronics with tissue engineering approaches for a better-integrated electrode-tissue interface (**Figure 1D**; Lacour et al., 2010; Clements et al., 2013; Musick et al., 2015; Srinivasan et al., 2015; Thompson et al., 2016). All these moves manifest the pursuit of a

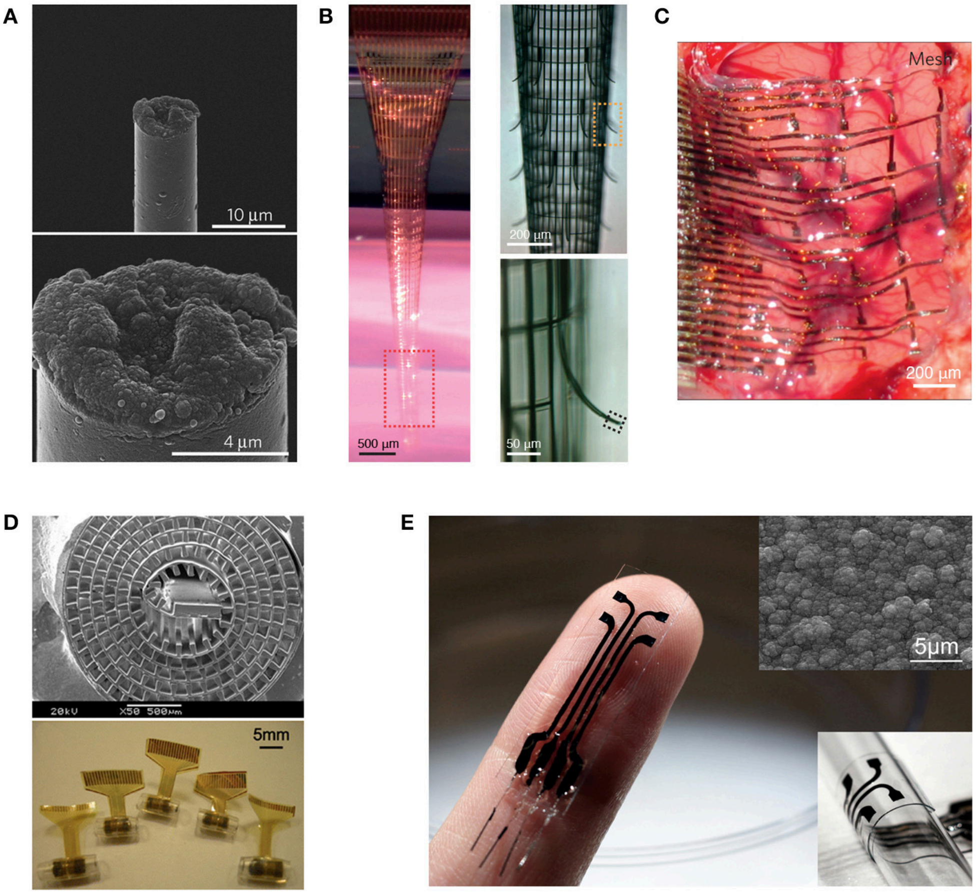

FIGURE 1 | Representative neural interfaces reflecting recent technological evolution. (A) Microthread electrode (Kozai et al., 2012b), **(B)** Macroporous nanoelectrode array (Xie et al., 2015), **(C)** Compliant electrode array for electrocorticography (Kim et al., 2010), **(D)** Regenerative neural electrode array for peripheral nerve interfacing (Lacour et al., 2010), and **(E)** Stretchable polymeric multielectrode array for conformal neural interfacing (Guo et al., 2014). Copyright permissions were obtained from the respective publishers.

biomimicry strategy from the mechanical aspect under the indistinguishability principle. By making neural implants of soft materials that have mechanical moduli closer to those of the host soft tissues, it is intended to minimize the mechanical stiffness mismatch between the implant and surrounding soft tissues, so that the cells feel mechanically more similar to their native environment at the interface and react less wildly, resulting in reduction of both short-term inflammation and long-term fibrotic encapsulation (Kotov et al., 2009; Nguyen et al., 2014).

Biochemical Mimicry: From Metal to Polymer Conductors

Major research efforts have been devoted to biomaterial surface-modification of existing rigid neural interfaces to mimic the ECM, so that the cells feel biochemically similar to their native environment at the interface (Kolarcik et al., 2012; Martin, 2015). Furthermore, if the implant materials can release anti-inflammatory drugs and neurotrophins, while suppressing implantation-induced trauma, the implant can induce target neurons or their axons to grow to the electrode site for an intimate integration. Although the non-conducting parts of a neural implant can be coated with appropriate dielectric polymers to facilitate bio-functionalization, direct bio-functionalization on metal electrodes while preserving their electrical conductivity is difficult. Conducting Polymers (CPs) are unique in accommodating electrical functionality with ECM biomimicry through bio-functionalization and have conventionally been used in electroactive tissue scaffolds (Hardy et al., 2013). They are also capable of releasing anti-inflammatory drugs and neurotrophins in an electrically controlled manner (Svirskis et al., 2010). Therefore, the application of CPs as neural electrode coatings to offer a localized conducive microenvironment for intimate neuron–electrode integration has been extensive investigated in the past decade (Guimard et al., 2007; Green et al., 2008; Ravichandran et al., 2010; Yi and Abidian, 2015).

However, one of the major drawbacks of CP electrode coatings is the delamination issue, making the coating less durable, and the electrical property of the electrode less stable.

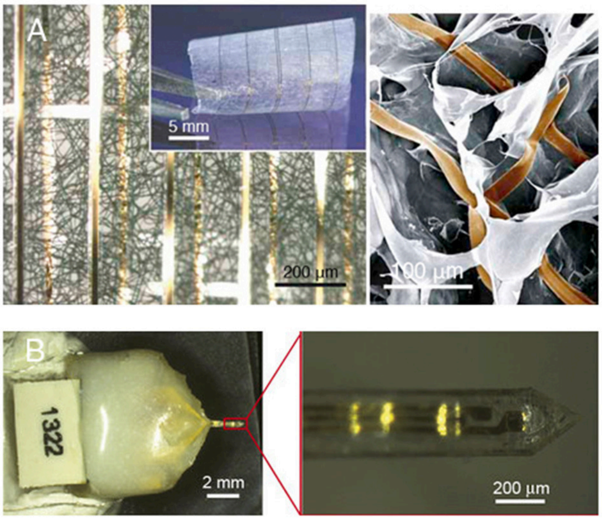

FIGURE 2 | Promising directions for neural interface design. **(A)** Macroporous nanowire electrode array with integrated tissue scaffold (Tian et al., 2012), and **(B)** ECM-based microelectrodes (Shen et al., 2015). Copyright permissions were obtained from the respective publishers.

biologic materials can be used to fabricate the neural interface (Chen and Allen, 2012), as recently demonstrated by fabricating intracortical microelectrodes using an ECM-based substrate material (**Figure 2B**; Shen et al., 2015), waiving the need to camouflage the abiologic material.

Then, one question comes up. What would the neural interface look like if we push the insensibility and indistinguishability principles to the extreme? In such a situation, there will be no abiologic and foreign materials, i.e., the device should be entirely made of autologous materials. As a result, there is no need to camouflage the device materials, as they are autologous and thus indistinguishable to the immune system and target neurons. Therefore, the technological challenges seem to be shifted to implementing the electronic functionalities using autologous materials, which, however, is infeasible in the foreseeable future. I would like to recall that there is no electronics in our body, yet our biologic body can perform sophisticated signal processing functionalities that are unachievable even with our most advanced integrated circuit systems. So, we won't need to build electronics; instead, we just need to implement the desired functionalities using autologous materials, i.e., to build biological circuits and living neural prostheses. Considering a convergence of synthetic biology, tissue engineering and neural prosthetics, such living neural prostheses will not be far from our reach in the foreseeable future.

AUTHOR CONTRIBUTIONS

LG conceived the concept, analyzed the literature, wrote, and revised the manuscript.

ACKNOWLEDGMENTS

This work was supported by startup funds generously provided to LG by the Department of Electrical and Computer Engineering and Department of Neuroscience at The Ohio State University.

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.