Nano Today xxx (xxxx) xxx

Contents lists available at ScienceDirect

Nano Today

journal homepage: www.elsevier.com/locate/nanotoday

Nanowire probes could drive high-resolution brain-machine interfaces

Anqi Zhang[a], Yunlong Zhao[a,b], Siheng Sean You[a], Charles M. Lieber[a,c,d,*]

[a] Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, USA
[b] Advanced Technology Institute, University of Surrey, Guildford, Surrey GU2 7XH, UK
[c] Center for Brain Science, Harvard University, Cambridge, MA 02138, USA
[d] John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138, USA

ARTICLE INFO

Article history:
Received 25 October 2019
Accepted 27 November 2019
Available online xxx

Keywords:
Nanowires
Intracellular recording
Brain-machine interface
Bioelectronics

ABSTRACT

A central challenge in the field of electrophysiology is to achieve intracellular recording of the complex networks of electrogenic cells in tissues. The historical gold-standard of intracellular recording - patch-clamp electrodes - do have limitations in terms of their invasiveness and difficulty to use in large-scale parallel recording. Recent advances in nanowire-based bioelectronics have demonstrated minimally-invasive intracellular interfaces and highly-scalable parallel recording at the network level. Combined with in vivo recording platforms, these advances can enable investigations of dynamics in the brain and drive the development of new brain-machine interfaces with unprecedented resolution and precision.

© 2019 Elsevier Ltd. All rights reserved.

Main text

Brain-machine interfaces (BMIs) can serve as bidirectional connections that output electrical signals of brain activity or input electrical stimuli to modulate brain activity in concert with external machines, including computer processors and prosthetics, for human enhancement [1,2]. Reading electrical activity from neurons is the foundation of many BMI applications, such as brain mapping, that aims to understand brain functions by decoding the communication between neurons. Reading and processing this activity is also key to neural prosthetics in which brain activity is used to control devices such as artificial limbs. For these BMI applications, most of the in vivo recording tools used today read extracellular neural activity by detecting suprathreshold action potential signals that 'leak' outside of neurons (Fig. 1a (i)), while critical subthreshold events, such as synaptic potentials and dendritic integration, remain hidden [3]. To achieve the most information-rich readings, which could provide more detailed mapping of brain function and the finest control of neural prosthetics, electronic devices need to provide access to intracellular signals from multiple neurons comprising the neuronal circuits and networks of the brain [4].

The most widely used conventional method for intracellular recording is the patch-clamp electrode (Fig. 1a (ii)) [5], although it has limitations in terms of the probe tip size with respect to key subcellular elements such as synapses and ion channels, invasiveness and applicability to large-scale recording. Recent advances in nanowire-based bioelectronics [4], which can reach critical biological length scales of a few tens of nanometers, represent attractive candidates for next-generation cell electrophysiology tools that enable parallel and long-term detection of intracellular activity with high spatial resolution.

The first work describing nanowire-enabled intracellular probes for electrogenic cells was achieved by the synthesis of nonlinear kinked nanowires, with a point-like field-effect transistor (FET) synthetically encoded at the tip [6]. Modification of the surfaces of the kinked nanowire FET probes with phospholipid bilayers yielded spontaneous insertion through the cell membrane of beating cardiomyocytes and subsequent intracellular action potential recording with an average peak amplitude of ~80 mV as expected for these cells. To provide deterministic control over probe–cell interactions, kinked nanowire FETs have also been fabricated on the tip of free-standing probes that can be manipulated in 3D [7]. Significantly, simultaneous nanowire FET and patch-clamp recording from the same beating cardiomyocytes showed that the kinked nanowire probes recorded the same absolute intracellular signals as the standard of electrophysiology without any correction factors, thus opening up new capabilities in terms of spatial resolution and biomimetic cellular targeting. However, the kinked nanowire syn-

* Corresponding author at: Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, USA.
E-mail address: cml@cmliris.harvard.edu (C.M. Lieber).

https://doi.org/10.1016/j.nantod.2019.100821
1748-0132/© 2019 Elsevier Ltd. All rights reserved.

Please cite this article as: A. Zhang, Y. Zhao, S.S. You et al., Nanowire probes could drive high-resolution brain-machine interfaces, Nano Today, https://doi.org/10.1016/j.nantod.2019.100821

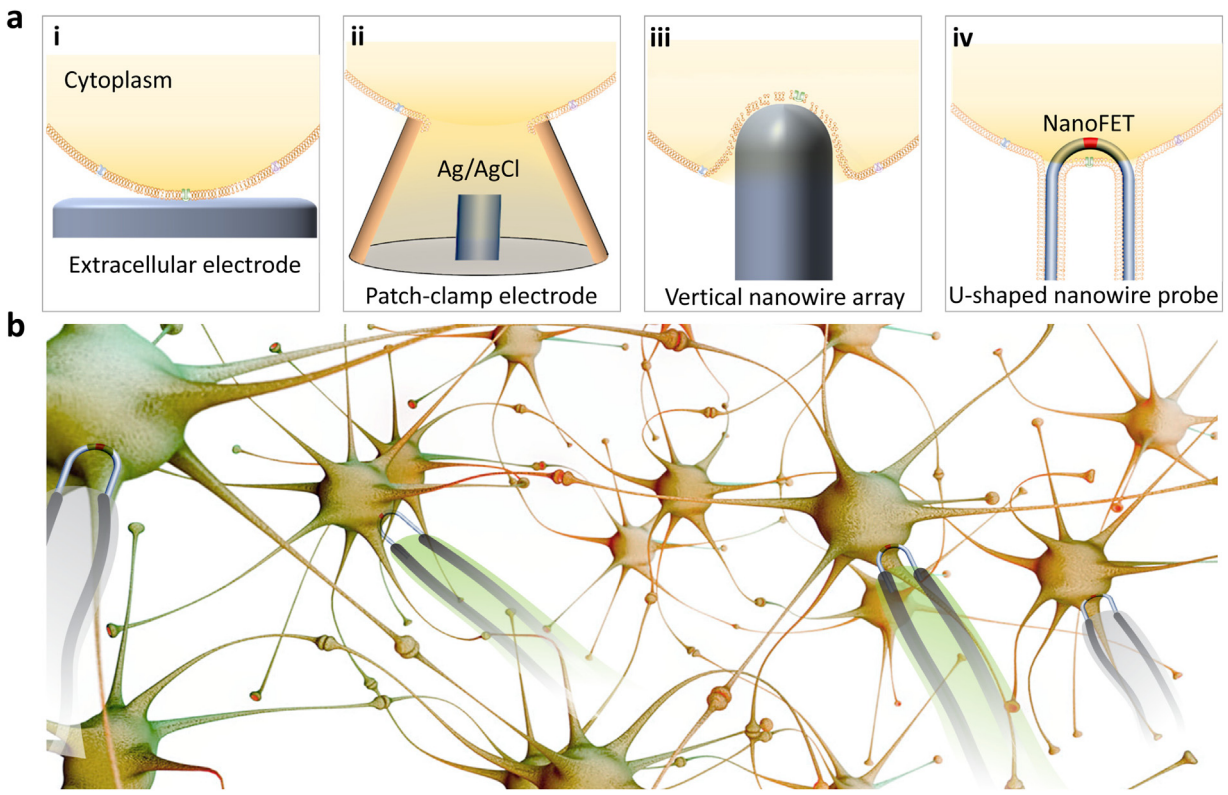

Fig. 1. Nanowire-enabled intracellular recording. a, A comparison between (i) conventional extracellular electrodes, (ii) patch-clamp electrodes, (iii) vertical nanowire arrays, and (iv) ultrasmall U-shaped nanowire probes. Intracellular recording achieved by the ultrasmall U-shaped nanowire transistor probes has demonstrated minimal invasiveness and similar quality to those obtained with the patch-clamp electrodes. b, Nanowire probe arrays could enable network-level parallel recording in vitro or in vivo.

thesis and assembly remains a challenge – they must be located and incorporated into the functional tools one-by-one, a process that is difficult to scale up.

Vertical nanowire electrode arrays (Fig. 1a (iii)) have been developed as a scalable intracellular recording platform of electrogenic cells by several groups [8,9]. These nanowires typically have a height of a few micrometers, a diameter of tens to hundreds of nanometers. When cells are cultured on top of electrode arrays, the plasma membrane deforms and wraps around electrode, creating a tight junction at the interface [10]. Intracellular access can then be achieved by controlled membrane disruption, such as electroporation in which the application of voltage/current pulses at the nanowire tips transiently disrupt the local membrane patch [11,12]. Typically, the measured action potential amplitude is significantly increased immediately following electroporation, and gradually decreases over time as the membrane reseals. The top-down processes used to fabricate vertical nanowire arrays are intrinsically scalable and can be integrated with complementary metal-oxide–semiconductor (CMOS) circuits to enable parallel in vitro recording from thousands of connected cardiomyocytes and neurons [13,14]. Nevertheless, these studies also have limitations, including (i) the intracellular potentials are much lower than the signals expected for true intracellular recording, (ii) the signal-to-noise ratio depends on the electrochemical impedance of the fabricated metal nanowires, and (iii) the positions of the nanowires relative to the cultured cells cannot be manipulated. Additionally, the 2D substrate-based nanowire array platforms are not compatible with minimally-invasive 3D in vivo recording.

To address the limitations of synthesized kinked nanowire devices and fabricated vertical nanowire arrays, we have recently developed a scalable approach to U-shaped silicon nanowire arrays (Fig. 1a (iv)) [15]. The approach combines previous advances in deterministic shape-controlled nanowire transfer [16] with spatially defined semiconductor-to-metal transformation [17] to realize scalable nanowire FET probe arrays with controllable tip geometry and sensor size. Significantly, these new scalable probes enable parallel recording of intracellular action potentials from primary neurons.

The silicon nanowires, with length-to-width ratio of more than 3000, are as flexible as cooked noodles. After bottom-up synthesis, they typically have disordered arrangement and orientations on the growth substrate. To incorporate them into functional device arrays that read intracellular electrical activities, we first patterned a silicon wafer with U-shaped polymer trenches, and then 'comb' the nanowires over the trenches [16]. In addition to removing tangles from the nanowire hair, the combing process forces the nanowires to conform to the designed U-shaped trenches, thus forming an array of 'hairpin'-like U-shaped nanoscale devices. The center of each U-shaped nanowire, which points upward from the wafer surface, is defined as a small FET recorder by controlled semiconductor-to-metal transformation of the nanowire arms [17], and can be inserted into the targeted neurons and cardiac cells for intracellular recording of signals up to or exceeding 100 mV which is comparable to the quality of those obtained with the patch-clamp electrodes. In addition, the cell-membrane mimicking phospholipid bilayer coating on the surfaces of the U-shaped nanowires allowed repeated insertion into multiple cells in parallel without causing damage.

During the development of the nanowire probes, we also compared many different curvatures of the U-shaped nanowire probe tips by varying systematically the top-down fabricated U-shaped trenches as well as different sizes of the FET devices. Importantly, this demonstrated a strong correlation between probes with smaller curvature/FET sizes, ease of internalization and larger

Please cite this article as: A. Zhang, Y. Zhao, S.S. You et al., Nanowire probes could drive high-resolution brain-machine interfaces, Nano Today, https://doi.org/10.1016/j.nantod.2019.100821

recording amplitudes. These findings are consistent with the reported results demonstrating that the cell membrane curvature induced by tight interfacing with smaller nanostructures can induce activation of endocytosis and related biological pathways [18], indicating that using nanoscale topography to enhance device uptake is critical for developing tools that faithfully capture intracellular action potential features.

Taking advantage of the parallel fabrication approach, we also explored different configurations of the device arrays: for example, having multiple nanowire devices on a single probe arm such that it is possible to read from multiple locations in a single cell, as well as ten of the probes that record signals from adjacent cells simultaneously to study signal propagation between cells. These modifications have the potential to make better tools for decoding the communication within and between complex neuron networks (Fig. 1b).

The human brain contains about 86 billion neurons, and they are wired into complex circuits to process information conveyed by electrical signals. To study a large number of neurons in the brain via intracellular recording, the conventional method of patch-clamp electrode is limited by its large micrometer tip size, and it can only read from a few neurons at a time. Recent advances in nanowire intracellular probes have achieved parallel fabrication of nanowire FET arrays, thereby addressing the long-standing challenge of scalable intracellular electrical recording with minimal invasiveness. Looking into the future, this deterministic nanowire-based fabrication strategy could be incorporated into other platforms [19–21], such as syringe-injectable mesh electronics [19], for multi-site 3D in vivo measurements. Two key challenges for the in vivo applications are the difficulty to achieve tight membrane/nanowire interfaces and long-term stability of the intracellular recording. We suggest that future studies exploring either (1) chemical anchoring via surface functionalization with groups that can bind to the actin cytoskeletal [22] or (2) physical anchoring using modulation of nanowire morphology [23] to increase the physical detachment force could improve the stability of the intracellular device configuration. Stable recording and interrogation of the same individual neurons in the neuron networks promises to help decipher complex neurological disorders [2], which develop over time, thus driving advanced BMIs with higher resolution, and perhaps eventually bringing 'cyborgs' to reality.

Acknowledgements

C.M.L. acknowledges support from the Air Force Office of Scientific Research (FA9550-18-1-0469, FA9550-19-1-0246). S.S.Y. acknowledges an NSF Graduate Research Fellowship.

References

[1] M.A. Lebedev, M.A. Nicolelis, Trends Neurosci. 29 (2006) 536.
[2] S.R. Patel, C.M. Lieber, Nat. Biotechnol. 37 (2019) 1007.
[3] D.L. Hunt, C. Lai, R.D. Smith, A.K. Lee, T.D. Harris, M. Barbic, Nat. Biomed. Eng. 3 (2019) 741.
[4] A. Zhang, C.M. Lieber, Chem. Rev. 116 (2016) 215.
[5] A. Molleman, Patch Clamping: An Introductory Guide to Patch Clamp Electrophysiology, John Wiley & Sons, Chichester, England, 2003.
[6] B. Tian, T. Cohen-Karni, Q. Qing, X. Duan, P. Xie, C.M. Lieber, Science 329 (2010) 830.
[7] Q. Qing, Z. Jiang, L. Xu, R. Gao, L. Mai, C.M. Lieber, Nat. Nanotechnol. 9 (2014) 142.
[8] J. Abbott, T. Ye, D. Ham, H. Park, Acc. Chem. Res. 51 (2018) 600.
[9] A.F. McGuire, F. Santoro, B. Cui, Annu. Rev. Anal. Chem. 11 (2018) 101.
[10] F. Santoro, W. Zhao, L.-M. Joubert, L. Duan, J. Schnitker, Y. van de Burgt, et al., ACS Nano 11 (2017) 8320.
[11] J.T. Robinson, M. Jorgolli, A.K. Shalek, M.-H. Yoon, R.S. Gertner, H. Park, Nat. Nanotechnol. 7 (2012) 180.
[12] C. Xie, Z. Lin, L. Hanson, Y. Cui, B. Cui, Nat. Nanotechnol. 7 (2012) 185.
[13] J. Abbott, T. Ye, L. Qin, M. Jorgolli, R.S. Gertner, D. Ham, et al., Nat. Nanotechnol. 12 (2017) 460.
[14] J. Abbott, T. Ye, K. Krenek, R.S. Gertner, S. Ban, Y. Kim, et al., Nat. Biomed. Eng. (2019), http://dx.doi.org/10.1038/s41551-019-0455-7.
[15] Y. Zhao, S.S. You, A. Zhang, J.-H. Lee, J. Huang, C.M. Lieber, Nat. Nanotechnol. 14 (2019) 783.
[16] Y. Zhao, J. Yao, L. Xu, M.N. Mankin, Y. Zhu, H. Wu, et al., Nano Lett. 16 (2016) 2644.
[17] Y. Wu, J. Xiang, C. Yang, W. Lu, C.M. Lieber, Nature 430 (2004) 61.
[18] H.-Y. Lou, W. Zhao, Y. Zeng, B. Cui, Acc. Chem. Res. 51 (2018) 1046.
[19] J. Liu, T.-M. Fu, Z. Cheng, G. Hong, T. Zhou, L. Jin, et al., Nat. Nanotechnol. 10 (2015) 629.
[20] L. Luan, X. Wei, Z. Zhao, J.J. Siegel, O. Potnis, C.A. Tuppen, et al.,Sci. Adv. 3 (2017), e1601966.
[21] S. Guan, J. Wang, X. Gu, Y. Zhao, R. Hou, H. Fan, et al., Sci. Adv. 5 (2019), eaav2842.
[22] J.-H. Lee, A. Zhang, S.S. You, C.M. Lieber, Nano Lett. 16 (2016) 1509.
[23] M. Dipalo, A.F. McGuire, H.-Y. Lou, V. Caprettini, G. Melle, G. Bruno, et al., Nano Lett. 18 (2018) 6100.

Anqi Zhang is currently a Ph.D. student under the supervision of Professor Charles M. Lieber in the Department of Chemistry and Chemical Biology at Harvard University. She received her bachelor's degree in Materials Chemistry from Fudan University in China in 2014. Her research interests include development of flexible nano-/micro-bioelectronic tools and their applications in neurophysiology. She has published 15 peer-reviewed papers and the book "Nanowires: Building Blocks for Nanoscience and Nanotechnology".

Yunlong Zhao is currently Assistant Professor at Advanced Technology Institute, Department of Electrical and Electronic Engineering, University of Surrey with a joint appointment at the National Physical Laboratory (UK) as the Senior Research Scientist. He carried out his postdoctoral and joint doctoral research under the advice of Professor Charles M. Lieber in the Department of Chemistry and Chemical Biology at Harvard University, where he conducted research in nano-semiconductor devices and flexible nano-/micro-electronics for electrophysiology and nano-bio interface. He also received his undergraduate and postgraduate research training at Wuhan University of Technology with focus on electrochemical energy storage and electrochemical probing. His current research interests include bioelectronic devices/sensors, integrated on-chip energy storage, and 3D soft electronic systems.

Siheng Sean You is a postdoctoral associate in the Koch Institute at the Massachusetts Institute of Technology (Cambridge, MA, USA). He received his BA in chemistry and physics from University of Chicago in 2012 and his PhD in Chemical Physics under the supervision of Professor Charles M. Lieber from Harvard University in 2019. His main research interests are in the fields of nanomaterials and bioelectronics with particular application to electrophysiology and ingestible sensing platforms.

Charles M. Lieber is the Joshua and Beth Friedman University Professor, Chair of the Department of Chemistry and Chemical Biology, and faculty member in the Center for Brain Science and Paulson School of Engineering and Applied Sciences at Harvard University. Lieber is an elected member a number of organizations including the National Academy of Sciences, Chinese Academy of Science and National Academy of Medicine. He has received a number of awards, including the Welch Award in Chemistry (2019), Directors Pioneer Award of NIH (2008 & 2017), MRS Von Hippel Award (2016) and Wolf Prize in Chemistry (2012). Lieber has pioneered the field of nanoscience and emerging nanotechnologies, including ground-breaking advances at the boundary between nanoelectronics and medicine as well as the developing the first three-dimensional nanoelectronic arrays that can be seamlessly integrated into the brain. He has published over 400 articles that have been cited more than 105,000 times.

Please cite this article as: A. Zhang, Y. Zhao, S.S. You et al., Nanowire probes could drive high-resolution brain-machine interfaces, Nano Today, https://doi.org/10.1016/j.nantod.2019.100821