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Understanding the Bioelectric Aspects of Cytoskeletal Dynamics

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In the third year of the project, my lab developed a set of matrices to quantify and differentiate the capacitive, Faradaic, and thermal outputs from ~30 different Si materials in saline, with the objective of gaining a fundamental understanding of subcellular modulations. We proved light-controlled non-genetic modulations of intracellular calcium dynamics, cytoskeleton-based transport and structures, and cellular excitability. We for the first time discovered the correlation between intracellular transport and intracellular bioelectric activities. During the entire project, we have published several high profile papers, including one on Nature Materials, one Nature Nanotechnology, one Nature Biomedical Engineering.

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FINAL REPORT

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Attention: Dr. Patrick Bradshaw

Understanding the Bioelectric Aspects of Cytoskeletal Dynamics

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I. Overview of the project

In this AFOSR project, I proposed to study the cytoskeletal dynamics from a bioelectric perspective, *i.e.*, by constructing and analyzing hybrid cytoskeleton/silicon networks. Specifically, we synthesized and characterized nanoscale silicon materials that are uniquely suited for interfacing with cytoskeletal components. We then demonstrated microtubule/silicon nanowire interfaces for bioelectric studies. Finally, we explored silicon nanoscale photodiodes as wireless and localized cytoskeleton controllers in single cells.

This work has addressed a wide range of scientific questions in intracellular signaling, cytoskeleton dynamics, and spatiotemporal organization of pathophysiological pathways. Additionally, the bioelectric mechanisms being uncovered in this work suggest new "building blocks" for efforts in the emerging field of synthetic biology – representing a new physical tool for biologists and bioengineers. Alongside the chemical and transcriptional modules found in the tool kit of researchers currently working in this field, the addition of bioelectric signaling modules will allow us to explore the ion flows and endogenous electromagnetic fields (up to ~10^7 V/m) to expand explosively the capabilities of cellular engineering for translational medicine research (*e.g.*, electroceuticals). Finally, the work can potentially enable a bottom-up approach for building new biological cybernetics platform, important for many DoD applications.

II. Brief summary of the achievements made in the entire award period

Silicon-based nanostructured materials have many biophysical and biomedical applications due to their highly tunable electrical and chemical properties, ability to absorb a broad range of wavelengths of light, and biocompatibility. Through this AFOSR YIP grant support, my lab was able to demonstrate non-genetic optical modulation capabilities across multiple length scales, at the interfaces between freestanding Si-based materials and various biological components, and in particular the cytoskeletal systems. Additionally, we performed one of the first dynamic studies of semiconductor nanowire internalization, offering new insights into device design for biomolecule delivery, intracellular sensing, and photoresponsive therapies. My lab developed a robust set of methodologies to study this behavior and quantitatively examine large aspect ratio nanowire-cytoskeleton interactions in a time-dependent manner, on both the single-cell and ensemble levels.

Notably, my lab developed a set of matrices to quantify and differentiate the capacitive, Faradaic, and thermal outputs from ~30 different Si materials in saline, with the objective of gaining a fundamental understanding of subcellular modulations. We proved light-controlled non-genetic modulations of intracellular calcium dynamics, cytoskeleton-based transport and structures, and cellular excitability, highlighting the utility of these new interfaces. We also demonstrated a light-induced neural transmitter release from brain slices, and non-genetic modulation of brain activities in a mouse model.

In three years, our team has produced many high-profile papers, including one in ***Nature Materials***, one in ***Science Advances***, one in ***Nature Nanotechnology***, one in ***Nature Biomedical Engineering***, one in ***Nature Reviews Materials***, and one in ***Nature Communications***.

III. What was accomplished under the goals during the last year?

The project during its last year of support has been very successful, and we have focused on *new Si-based platforms for photoelectrochemical and photothermal modulation of single cells, and the studies of cytoskeletal responses following these stimuli. Critically, we found evidence that intracellular cytoskeleton-based transport is dependent on the bioelectric local environment.* The key advances are listed as follows:

(A) Photoelectrochemical neuromodulation with coaxial Si nanowires

My lab used coaxial p-type/intrinsic/n-type (p-doped cores, intrinsic and n-doped shells) Si nanowires to wirelessly and photoelectrochemically modulate primary rat dorsal root ganglion neuron excitability. Upon light stimulation at a neuron-Si nanowire interface, electrons move towards the n-type shell and holes move to the p-type core; this induces a cathodic process at the n-shell that can locally depolarize a target neuron (**Figure 1**). My lab revealed the presence of atomic gold (Au) on the nanowire surface, likely due to Au diffusion during material growth, leading us to ask how surface Au impacts the photoelectrochemical properties of single nanowires. We used modified quartz pipettes from a patch clamp and recorded sustained cathodic photocurrents from single nanowires. My lab showed that these currents can elicit action potentials in rat DRG neurons through a primarily atomic Au-enhanced photoelectrochemical process. Our work represents the first study of single nanowire-based photoelectrochemical modulation of cellular excitability in a non-invasive, non-genetic, drug-like manner (Figure 1). The Si nanowires can be administered in a drug-like fashion, their length scale allows for high spatial specificity, and their surfaces can be easily modified to allow for high affinity binding to specific cell types. Additionally, atomic Au reduces the kinetic barrier necessary for photoelectrochemical current generation, thereby playing the role that a catalyst would play in traditional photoelectrochemical devices.

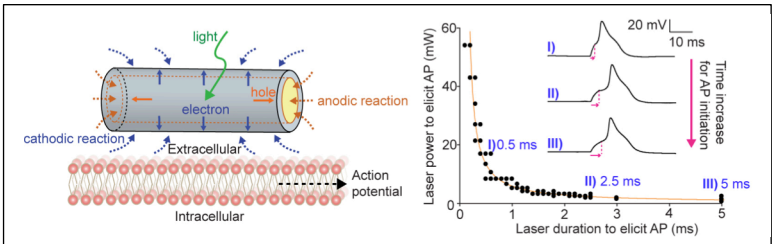

Figure 1. Photoelectrochemical neuromodulation with coaxial Si nanowires.

(B) A rational design for Si-based freestanding stimulation biointerfaces

Silicon displays many size- and doping-dependent physicochemical processes. Si-based materials or devices should be in tight contact with their biological counterparts to efficiently leverage these processes in the context of biointerfaces. Such tight interfaces can be established by van der Waals forces at the organ level, by dynamic cellular focal adhesion at the single-cell and tissue level, and by protein-associated tethering and active motions at the organelle level. My lab has recently identified a biology-guided two-step design principle for establishing tight intra-, inter-, and extracellular Si-based interfaces in which Si and the biological targets have matched mechanical properties and efficient signal transduction (Figure 2). Specifically, my group exploited Si-based materials in the forms of a flexible and distributed mesh (at the organ level), a membrane with rough surfaces (at the cell and tissue level), and a nanowire (at the organelle level), where at least one material dimension can be tuned to promote tight interfaces.

My lab then developed a set of matrices to quantify and differentiate the capacitive, Faradaic, and thermal outputs from ~30 different Si materials in saline, with the objective of gaining a fundamental understanding of biological modulations. We proved light-controlled non-genetic modulations of intracellular calcium dynamics, cytoskeleton-based transport and structures, and cellular excitability, highlighting the utility of these new interfaces. Finally, my lab also demonstrated a light-induced neural transmitter release from brain slices, and non-genetic modulation of brain activities in a mouse model.

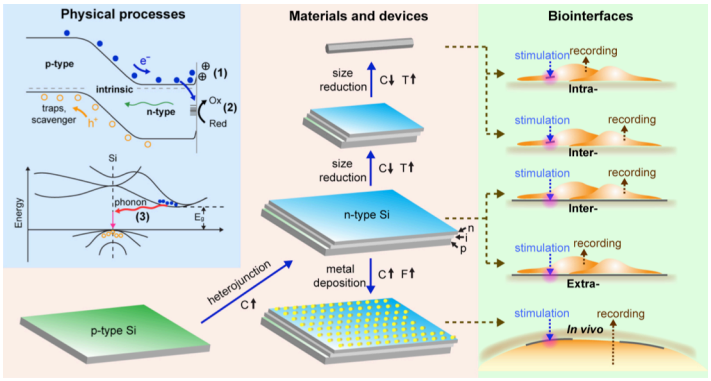

Figure 2. Biology-guided rational design of optical modulation interfaces.

In particular, we have studied several interfaces related to cytoskeletal systems. We first considered Si nanowires for intracellular stimulation biointerfaces because it is an unexplored domain that is beyond the previously studied intracellular sensing or delivery. In a primary culture of neonatal rat dorsal root ganglia (DRG) and associated satellite glia, we noticed a cell-type-specific overlapping of nanocrystalline Si nanowires after ~ 24 hours of coculturing. Statistical analysis of the nanowire-cell colocalization revealed that ~ 87% of total nanowires overlapped with glial cells, ~ 3% with neurons, and ~ 10% stayed in the extracellular space. Perinucleus clustering, rather than random intracellular distributions, of the colocalized nanowires suggests the internalization of these nanowires. Additionally, the presence of bent nanowires following the contours of a few glial cell membranes implies strong mechanical interactions between cells and nanowires. As suggested by a recent study that label-free nanowires can be internalized through a phagocytosis pathway, the fact that glial cells (versus neurons) do have phagocytic activities supports the observed selective glial internalization.

Since Si nanowires can display active transport along microtubules, we next explored the possibility of using nanocrystalline Si nanowires as a dual-role intracellular biophysical tool, *i.e.*, a calcium modulator and a marker for motor protein-microtubule interactions. We simultaneously tracked the location of a single nanowire (*i.e.*, a transport marker) in a glial protrusion and monitored the nearby calcium dynamics, following a remote laser illumination of a different nanowire (*i.e.*, a calcium modulator) to initiate a calcium flux within a network. The dynamics of local calcium concentration and the transverse distance of the nanowire, as well as the overlaid time series for both the calcium wave front and the nanowire center, together suggest a calcium-triggered directional transport of intracellular cargo in the current case. Additionally, mean-squared displacement (MSD) analysis reveals correlated nanowire transport modes with the local calcium dynamics, *i.e.*, from random or restricted diffusions (diffusive exponent, $\alpha \leq 1$) without elevated intracellular calcium, to an active transport (diffusive exponent, $\alpha \sim 2$) after the calcium wave front reached the original nanowire location. The nanowire transport along the glia protrusion is anterograde, *i.e.*, kinesin-based. The motor protein kinetics are typically enhanced by increased adenosine triphosphate (ATP) activities, which may be triggered by the elevation of intracellular calcium concentration.

Besides serving as an intracellular calcium modulator and a transport marker, the photothermal properties of nanocrystalline Si nanowires may be explored to induce a photoacoustic effect for biomechanical manipulation at the subcellular level. To assess this, we chose human umbilical vein endothelial cells (HUVEC), which are active in the phagocytosis of silicon nanowires and have well-studied microtubule networks. Nanocrystalline Si nanowires are trapped in the microtubule meshes after coculturing with HUVEC for ~ 24 hours. When a laser pulse (592 nm, 1 ms, ~ 2.09 mW, ~ 211 nm spot size) was introduced to the nanowire, the surrounding microtubules were rapidly repelled and formed a void space near the nanowire, suggesting a shock-wave generation through a photoacoustic effect. Besides intracellular microtubule networks, Si nanowires can also interface with intercellular conduits, where microtubules form compact bundles. Upon laser illumination of the entangled single nanowire (592 nm, 1 ms, ~ 2.55 mW, ~ 211 nm spot size), the bundled microtubules are broken up immediately, possibly through a shock-wave-mediated, mechanically-induced microtubule depolymerization. The optically-triggered, and nanowire-enabled mechanical manipulation of cytoskeletal structures may serve as a new tool for the study of intra- and intercellular dynamics where a remote structural manipulation of subcellular structures is desired.

Control experiments without nanowires did not yield any of these intra- or intercellular observations. Moreover, the importance of using silicon nanowires instead of other nanostructures (*e.g.*, Au nanoparticles or nanorods) is due to the following: (1) silicon nanowires can be at least partially exposed in cytosol upon phagocytic cellular entrance, (2) silicon has only a moderate photothermal effect (compared to, *e.g.*, that of Au) such that the confocal imaging light source itself will not cause heating from the nanostructures, and (3) the high aspect ratio of silicon nanowires enables their axial alignment with respect to the cytoskeletal filaments.

(C) Uninformed search-based optical training of cardiac cells with a polymer-silicon nanowire mesh

Cells receive stimuli via the engagement of receptors and membrane proteins on their surfaces, often integrating multiple chemical, mechanical, thermal, and electrical signals that are minute, random, and transient in nature, spatially from all over the cell to alter cellular function. This type of stimuli has not been completely recapitulated in existing biological modulation methodologies, such as optogenetics, molecular uncaging and biomaterials based techniques. We develop a freestanding polymer-silicon nanowire mesh for use in optical training of cultured neonatal rat cardiomyocytes (**Figure 3**) as well as adult rat hearts *ex vivo* to beat at a target frequency. We use an uninformed search approach for generating a large set of transient and localized input signals to trigger a single integrated cardiac response. This is enabled by (1) a fast-moving illumination interface via constant changes of either the light source or the sample locations

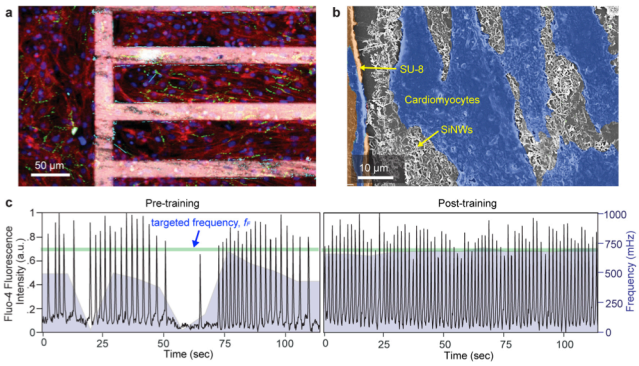

Figure 3. Optical training of cardiomyocytes and isolated hearts.

(Level 1, serial process), and (2) a high density array of Si nanowires that can not only generate light-induced physicochemical outputs but also exhibit waveguiding behavior for additional light intensity modulation (Level 2, parallel process). Integrating these modalities allows for our training approach to mimic physiological stimuli, by spatially engaging whole cells with massive numbers of optical inputs during a short period of time. *We are currently studying the effect of optical training on cytoskeletal dynamics*.

(D) Photothermal modulation of cellular activities with porous silicon nanowires

Engineered silicon-based materials can display photoelectric and photothermal responses under light illumination, which may lead to further innovations at the silicon-biology interfaces. Silicon nanowires have small radial dimensions, promising as highly localized cellular modulators, however the single crystalline form typically has limited photothermal efficacy due to the poor light absorption and fast heat dissipation. In this work, we identified strategies to improve the photothermal response from silicon nanowires by introducing nanoscale textures on the surface and in the bulk. The improved photothermal effect allows high-resolution extracellular modulation of calcium dynamics in a number of mammalian cells including glial cells, neurons and cancer cells. The new materials may be broadly used in probing and modulating electrical and chemical signals at the sub-cellular length scale, currently a challenge in the field of electrophysiology and cellular engineering.

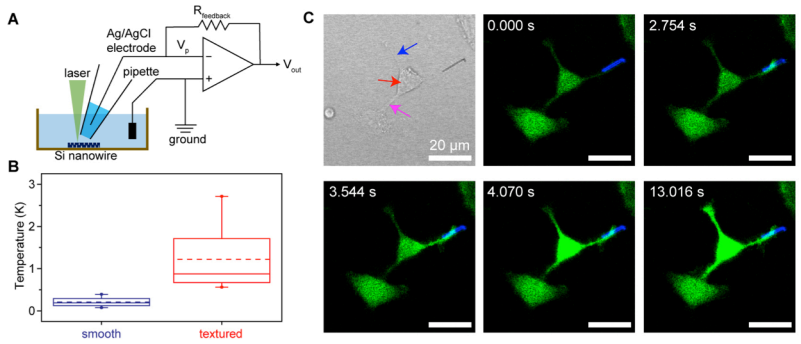

Figure 4. Porous SiNW for cellular modulation. (**A**) Photothermal measurement setup. (**B**) Photothermal response. (**C**) Cellular modulation.

To confirm the potential use of textured i-Si nanowires for freestanding cellular modulation, we first assessed the physicochemical responses of these Si nanowires to laser illumination in saline. Individual photo-responses can then be extrapolated from all the measurements and compared between textured and smooth nanowires (**Figs. 4A, 4B**). From the recorded ionic current dynamics from both textured and smooth Si nanowires, the fitted intercept values of the $\Delta I_{light}(t)$-I_0 curves stay nearly zero throughout the entire illumination period, indicating minimal contributions from the photoelectric effect of i-Si nanowires. On average, the textured i-Si nanowires demonstrate larger photothermal responses (~ 2 °C) than the smooth i-Si nanowires (~ 0.2 °C) over the 1-ms illumination. The porosity in the textured Si nanowires likely contributes to the enhanced thermal output, due to reduced thermal conductivity, heat capacity and enhanced light absorption.

Laser illumination of a textured i-Si nanowires in close contact with a glial cell protrusion elicits rapid calcium surges initiated at the stimulation site, likely related to a series of coupled biophysical processes (**Fig. 4C**). The locally generated calcium concentration gradient can drive

the propagation of the signal inside the cell by going through the cell body and then to other branches of protrusions (**Fig. 4C**). Besides glial cells, Si nanowires can also interface with DRG neurons for direct neuromodulations. Upon laser illumination of the Si/neuron junction, calcium dynamics can be evoked in a similar manner through either voltage or mechano-sensitive calcium channels expressed on the neuron membrane.

IV. What opportunities for training and professional development did the project provide?

Several Tian lab members have been funded on this project. The researchers' development has been enhanced through a program of structured mentoring activities. The goal of the mentoring program is to provide the skills, knowledge and experience to prepare the researchers to excel in their career path. Specific elements of the mentoring plan will include:

- Seminars and workshops on how to write competitive proposals, offered by Chemistry Department or Materials Research Science and Engineering Center (MRSEC) at the University of Chicago.
- Participation in seminars and workshops on teaching and learning, conducted by the Center for Teaching and Learning at the University of Chicago (http://teaching.uchicago.edu/).
- Co-teaching a graduate course (i.e., Materials Chemistry-II, CHEM 391) where written feedback from the students have been provided.
- Training and mentoring in the responsible conduct of research, offered by the PI' annual research meetings. The meeting has been following the online course at citiprogram.org. The topics include research misconduct, data management and sharing, publication practices and responsible authorship, peer review, mentor and trainee responsibilities, conflict of interest, and collaborative research. In particular, the exercises in the online course serve as a starting point to discuss proper research conduct as related to the projects in this proposal.
- Travels to conferences, i.e., 2017 fall Materials Research Society Annual meeting, where the researchers presented a poster and gave a talk at the conference.
- Participation in workshops related to career development such as how to apply for a faculty position, career paths outside of academia, tips for negotiating salary and start-up funds, how to plan an independent research agenda. The workshops have been offered by the Physical Sciences Division at the University of Chicago.
- Participation in the PI' weekly research group meetings, in which the researchers have been presenting their research regularly; feedback and coaching were given to help them develop communication and presentation skills.

V. Publications from this support

Third year:

1. Y. W. Jiang, **B. Z. Tian**, Inorganic semiconductor biointerfaces. *Nature Reviews Materials*, in press.

2. Y. Fang, Y. W. Jiang, H. A. Ledesma, J. Yi, X. Gao, D. E. Weiss, F. Shi, **B. Z. Tian**, Texturing silicon nanowires for highly localized optical modulation of cellular dynamics. *Nano Letters*, **2018**, *18*, 4487-4492.
3. J. F. Zimmerman, **B. Z. Tian**, Nongenetic optical methods for measuring and modulating neuronal response. *ACS Nano*, **2018,** *5*, 4086-4095.
4. M. Y. Rotenberg, **B. Z. Tian**, Talking to cells: semiconductor nanomaterials at the cellular interface. *Advanced Biosystems*, **2018**, https://doi.org/10.1002/adbi.201700242.
5. Y. W. Jiang, X. J. Li, B. Liu, J. Yi, Y. Fang, F. Y. Shi, X. Gao, E. Sudzilovsky, R. Parameswaran, K. Koehler, V. Nair, J. P. Yue, K. H. Guo, Y. Fang, H.-M. Tsai, G. Freyermuth, R. C. S. Wong, C.-M. Kao, C.-T. Chen, A. W. Nicholls, X. Y. Wu, G. M. G. Shepherd, **B. Z. Tian**, Rational design of silicon structures for optically-controlled multiscale biointerfaces, *Nature Biomedical Engineering*, **2018**, 2, 508-521.
6. R. Parameswaran, J. L. Carvalho-de-Souza, Y. W. Jiang, M. Burke, J. F. Zimmerman, K. Koehler, A. Phillips, J. Yi, E. Adams, F. Bezanilla, **B. Z. Tian**, Photoelectrochemical modulation of neuronal activity with free-standing coaxial silicon nanowires, *Nature Nanotechnology*, **2018**, *13*, 260-266.
7. Y. Fang, Y. W. Jiang, M. J. Cherukara, F. Y. Shi, K. Koehler, G. Freyermuth, D. Isheim, B. Narayanan, A. W. Nicholls, D. N. Seidman, S. K. R. S. Sankaranarayanan, **B. Z. Tian**, Alloy-assisted deposition of three-dimensional arrays of atomic gold catalyst for crystal growth studies, *Nature Communications*, **2017**, 8, article number: 2014.

First and second years:

8. J. F. Zimmerman, R. Parameswaran, G. Murray, Y. C. Wang, M. Burke, **B. Z. Tian**, Cellular uptake and dynamics of unlabeled free standing silicon nanowires, *Science Advances*, **2016**, *2*, e16010139.
9. Y. W. Jiang, J. L. Carvalho-de-Souza, R. C. S. Wong, Z. Q. Luo, D. Isheim, X. B. Zuo, A. W. Nicholls, I. W. Jung, J. P. Yue, D.-J. Liu, Y. C. Wang, V. De Andrade, X. H. Xiao, L. Navrazhnykh, D. E. Weiss, X. Y. Wu, D. N. Seidman, F. Bezanilla, **B. Z. Tian**, Heterogeneous silicon mesostructures for lipid-supported bioelectric interfaces, *Nature Materials*, **2016**, *15*, 1023–1030.