ELECTROPHYSIOLOGY

Curving neural nanobioelectronics

Three-dimensional nanowire transistors with curvilinear tips record intracellular signals from neurons.

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Curvature is a hallmark of both soft and hard materials[1]. Skeletons and other biomineral structures, for example, have curved features to cooperatively and homeostatically interface with cells and tissues to promote physiological functions (Fig. 1a). These naturally occurring hard biomaterials have inspired many studies in mathematical biology and biomimetic materials science. Well defined curvatures can be established in inorganic materials through a variety of synthetic or fabrication approaches[2], such as bending the inorganic material around an object; freeform bending through stress relaxation, nanocasting or confined growth in a porous template; or etching against a curvilinear mask. Such curved inorganic nanostructures have been used for studies or applications ranging from three-dimensional (3D) stretchable electronics to catalysis, as well as membrane protein biophysics and enhanced mechanical integration with hydrogels[2].

Writing in *Nature* Nanotechnology, Zhao et al. reveal the promise for curved inorganic nanostructures as neural recording devices[3]. The authors integrate a curvature element into a nanowire-based field-effect transistor (NWFET) and demonstrate that this curved element is critical for neuronal intracellular entry and subsequent electrical recordings. Prior studies have demonstrated that nanostructures can produce responses from curvature-sensing membrane proteins and that nanostructure geometries can affect their internalization dynamics[2].

FET-based intracellular neural recording devices demand several design considerations. A FET requires a pair of electrodes (that is, source and drain electrodes) that connect directly to the semiconductor channel. To enable intracellular device entry, Zhao et al. alter the configuration of the typically head-to-head electrodes by bending the silicon nanowires against lithographically patterned U-shaped trenches[3]. In the resulting assembly, the two nanowire terminals are registered with parallel oriented electrodes, which affords the FET greater access to the cells. To facilitate access and internalization for intracellular recording, the space around the FET channel must be free. The authors achieve this by fabricating the device over a sacrificial nickel layer. Upon nickel removal, residual-stress-enabled upward device bending yields a 3D U-shaped NWFET. The FET channel also has to be short to allow for localized and minimally invasive recording, which is realized by converting part of the curved silicon nanowires into nickel silicide (Fig. 1b). Finally, surface functionalization of the NWFET with a phospholipid bilayer coating induces membrane fusion upon mechanical compression, exposing the FET channels to the cytosol.

With this 3D curved NWFET, the authors report several notable advantages of the device design on electrophysiological recordings[3]. First, they demonstrate successful neural intracellular recording via a direct FET–cytosol interface, with a device nanowire diameter of ~15 nm and channel length of ~50 nm. This is significant because NWFET-based neural recording has been a long-standing challenge.

Second, the proposed device platform is scalable and is designed for multiplexed

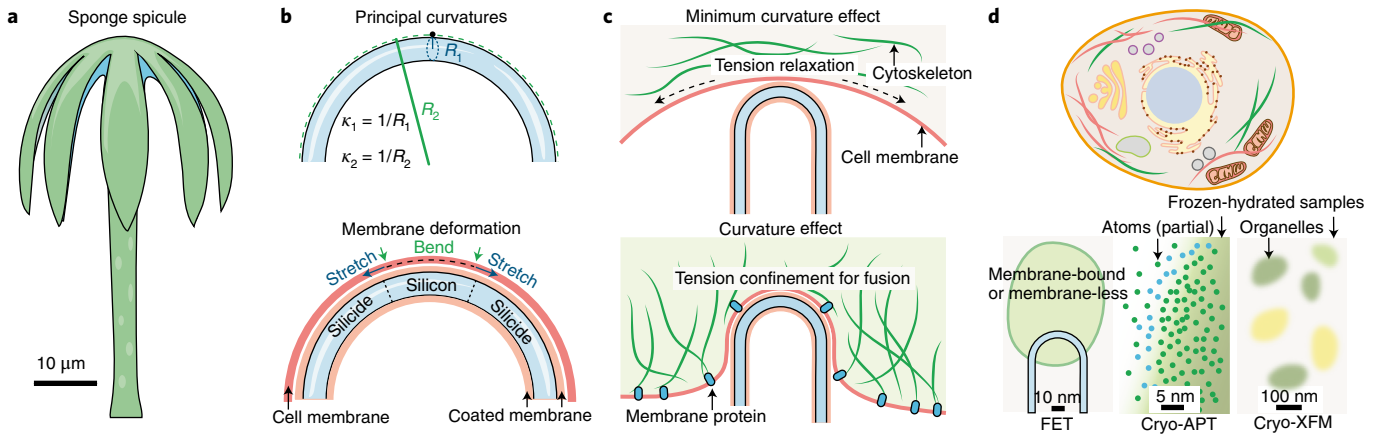

Fig. 1 | Curvature matters in nanobioelectronics. a, A schematic diagram of a part of the amphidisc, a siliceous spicule with a stellate disc at each end. **b**, Two principal curvatures (κ_1, κ_2) at the highest point (black dot) of a bent nanowire are defined by the nanowire radius (R_1) and bending radius (R_2). The lipid-bilayer coated nanowire induces tension in the cell membrane upon tight contact followed by membrane fusion, to deliver the device into the cell (not shown). **c**, The cortical cytoskeleton, together with membrane proteins, restricts the induced membrane tension to a local domain, maximizing the curvature effect from the bent nanowire (lower panel). **d**, There is plenty of room in organelle bioelectrics. The organelles can be either membrane-bound or membrane-less, such as protein/RNA condensates. FET and other tools such as cryogenic atom probe tomography (cryo-APT) and cryogenic X-ray fluorescence microscopy (cryo-XFM) are promising for such studies.

recording from single cells or a cellular network with paired NWFETs. While patch-clamp methods can also be used for multiplexed recording, these methods are ultimately limited in the number of pipettes can that be applied to a single cell. This is less of an issue in the current NWFET platform, given its potential for integration into high-density arrays of recording channels and a soft device backbone.

Third, considering that a 3D object contains two principal curvatures at each point (Fig. 1b), the U-shaped nanowire–cell interface enables precise control of one of these curvatures (related to the bending radius, κ_2) while keeping the second curvature (related to the nanowire radius, κ_1) fixed. The higher bending curvature results in better device entry into the cell. This finding is reasonable, given that higher curvature can yield a larger degree of local membrane stretching and bending (Fig. 1b), assuming a fixed device–cell distance displacement and conformal device–cell contact. The large local deformation produces a large tension in the cell membrane, which triggers membrane fusion as it works to relax the tension.

In relation to membrane tension, the nanowire curvature-dependent intracellular recording supports the recent discovery suggesting that the cortical cytoskeleton provides resistance against external force propagation through the cell membrane[4] (Fig. 1c). The cytoskeleton/membrane protein/lipid bilayer 'composite'[5] generates a highly confined tension and rapid mechanical equilibrium when the cell membrane is locally deformed, without significantly affecting other parts of the cell. This produces a local large tension gradient, which activates mechanosensitive ion channels and vesicle fusion[4]. If the membrane tension could be quickly transmitted to distal regions of the cell membrane (due to membrane elasticity), we can expect that the curvature-dependent membrane fusion and device internalization reported by Zhao et al. would be largely diminished (Fig. 1c, upper panel), assuming the device–cell distance change is constant. Additionally, upon NWFET–cell membrane contact, the local membrane tension and tension gradient may drive molecular diffusion or even phase separation and transition[5]. One could systemically study the device entrance mechanism and the triggered molecular signalling processes by utilizing probes or characterization tools[6] to analyse the tension and dynamics in the cell membrane and cortical cytoskeleton, the viscosity and bending rigidity of the membrane, and the distribution of membrane proteins. Finally, the membrane tension argument also raises the question of how different cytoskeletal structures may affect intracellular recording with NWFETs.

For organelle bioelectrics, it is extremely challenging to study the bioelectric behaviours of individual organelles, given that very few biophysical tools are available to track organelles. However, a number of recent advances have indicated that a much better understanding of organelle bioelectrics is within reach. These advances include the discovery of the correlation between the charge-dependent intracellular diffusivity mapping and the ultrastructure of the actin cytoskeleton[7], the invention of a DNA-based voltmeter for organelles[8], and a novel array of characterization tools such as cryogenic atom probe tomography[9] and cryogenic X-ray fluorescence microscopy[10] (Fig. 1d). In view of their minimally invasive nature and capacity for highly localized recording, NWFETs could expand the intracellular toolset for these studies (Fig. 1d). Nevertheless, organelle targeting will require correlative imaging and careful device surface modification — for example, triphenylphosphinium-conjugated silicon may be used to target mitochondria.

The study by Zhao et al., encompassing device implementation as well as fundamental insights and implications, highlights curvature as an important element in bioelectronics design and represents a step toward the elucidation of membrane tension and organelle bioelectrics. ❐

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