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Bridging the gap — biomimetic design of bioelectronic interfaces

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Applied bioelectronic interfaces have an enormous potential for their application in personalized medicine and brain-machine interfaces. While significant progress has been made in the translational applications, there are still concerns about the safety and compliance of artificial devices interacting with cells and tissues. Applying biomimetic design principles enables developing new devices with improved properties in terms of their signal transduction efficiency and biocompatibility. Learning from the paradigms of biological architecture, we can define four cornerstones of biomimetics, which can guide designing new bioelectronic devices or providing improved solutions to challenging biomedical problems. Recent progress shows how these paradigms were successfully employed, for example, to create neuron-like electronics and assemble electronic materials *in situ* onto the cell membranes using genetic targeting.

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Introduction

Since the earliest days, humans have had a special admiration for Nature. While our understanding of the physical world progressed steadily throughout the ages, biology observed the biggest explosion in the number of discoveries at the end of the last millennia, and today, the funding for life sciences accounts for nearly half of the US federal research spending [1]. Such enormous progress was enabled by the discoveries and development of techniques that enabled the study and understanding of cellular and subcellular processes [2] up to the molecular basis underlying the existence of life. Only now can we truly appreciate the complex yet elegant biological designs present in Nature from which we can learn and adapt its concepts into our own intelligently designed systems.

It is not by accident that our most significant discoveries in biological sciences coincide with the greatest development in human engineering — digital electronics. Without the technologies that enable computer-based processing of information, we would not be able to look into the cells' structure or acquire and understand the significance of the information stored in the genome [3]. The newest advances in data processing and analysis, especially in machine learning, enabled new opportunities in microscopy, computational biology, and translational medicine [4]. This co-dependence of technology and biology will inevitably end with the merging of natural and artificial systems. However, such an endeavor remains a formidable task as our current state of engineering does not allow for the seamless integration between those two naturally dissimilar systems.

It is a major direction in biomedical research, especially in bioelectronics, to achieve seamless biointegration on the subcellular levels. The goal of targeting subcellular components is achieving improved efficiency and high specificity of recording and stimulation. Interfaces formed between large electric elements and tissues generate interactions that are prone to cross-talk between many cells and devices that can interface with only a specific part of the cell membrane maximize the interaction specificity. Additionally, targeting subcellular components can provide new modes of biomodulation, for example, directly affecting energy production through the regulation of the mitochondria network. However, developing such solutions remains challenging and requires new approaches to devices' design.

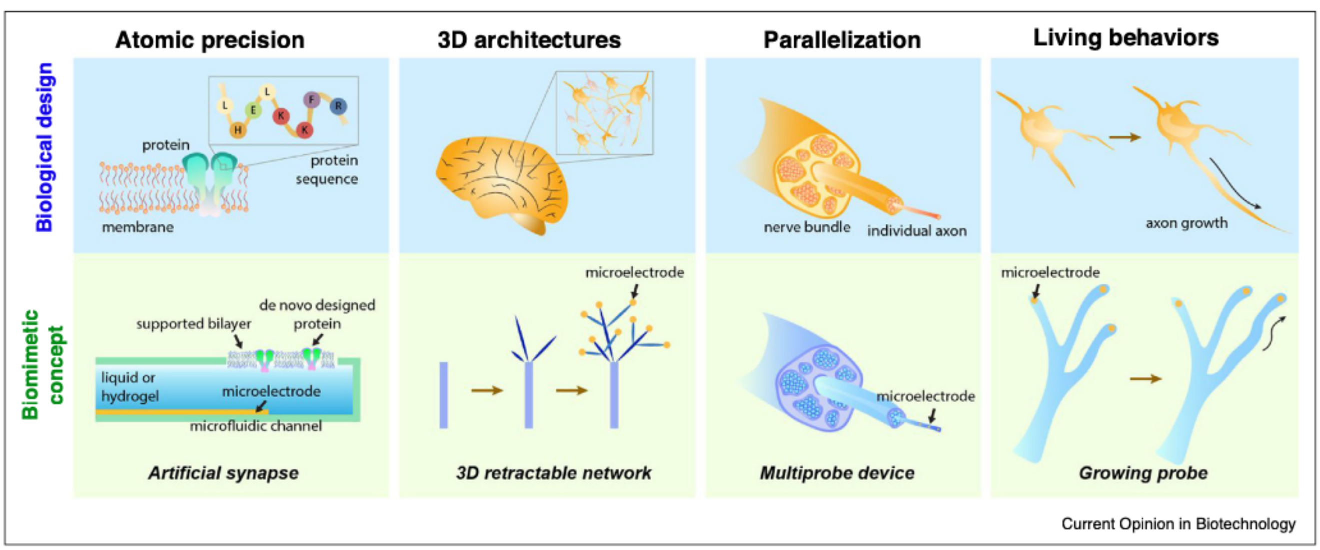
The biological systems evolved over millions of years to specialize in their respective functions, and while our understanding of such processes constantly improves, it does not seem that we would be able to alter or replace biological structures to make them fit our needs in the near future. On the other hand, we can actively strive to make our electronics more nature-like by intentionally introducing biomimetic structures and design paradigms.

Our ultimate goal is to achieve minimally invasive integration through the application of Nature-inspired blueprints and materials. The more similar the structures and less mismatch between their properties — the more biocompatible they become and are less prone to rejection by the biological structure [5]. Proper structural and functional matching would maximize the efficiency of interactions and allow new bioelectronic devices to achieve viability levels that can enable the more delicate and precise study of the physiological process, and which will be adapted to future therapeutical applications as well.

To begin thinking about biomimetic design, we have to consider the specific lessons we can take from Nature on designing and building complex structures (Figure 1). The most important lesson is that biological systems are defined up to an atomic level. Almost every biological structure derives its function from the specific arrangement on the molecular scale. From nucleic acids, through ribosomes, to proteins and protein complexes — a single change can often be introduced that would completely disturb the system. It is, of course, the principle of evolution that the accumulation of changes can enable new functions, but this observation only strengthens the importance of the relationship between the structure and function [6]. Even for the large structures with mineral deposits, such as bone tissue, the material's distribution is precisely controlled, enabling the properties difficult to achieve using heterogeneous materials. Such properties are enabled by the second principle of biological design, which is the formation of complex three-dimensional assemblies. Structures such as the brain cortex or renal pyramids in kidneys can only perform their function thanks to integrating multiple different cells and forming the appropriate spatial arrangement. Further, observing the lower dimensional biological structures, such as nerve bundles, will reveal the next biomimetic design principle — high-density packing and parallelization. For example, research-grade neural recording and stimulation electronics currently enable hundreds of channels [7,8], and translational efforts utilizing multiple shanks can bring the total number of interfacing electrodes to thousands [9]. However, these approaches remain outmatched by biological structures such as the human optical nerves, which are made of more than a million neuron fibers [10]. Therefore, to enable high-throughput and fidelity in biomimetic electronic applications, we must learn to form and scale-up our designs.

For the complete picture of the biological systems, we cannot forget about the plethora of living behaviors that they display. Growth, replication, motility, regeneration, and self-destruction are all processes that can be replicated in the biomimetic design. Many living behaviors are possible thanks to energy transfer mechanisms, for example, adenosine triphosphate (ATP) dissociation can drive organelles' movement within the cell or rotation of flagellum for the entire cell propulsion. Driving such processes requires precise control over progressing chemical

Figure 1



Characteristics of biological design. Atomic-level definition of functions is a primary concept in natural systems. Precise structural definition later translates to the organization at higher levels of hierarchy. The biological structures are, in general, three-dimensional and highly paralleled for increased efficiency. The final indispensable recognition is that biological systems demonstrate 'living behaviors', which creates developmental, functional, and adaptational advantages over inanimate materials and systems. Bottom row shows concepts of artificial biomimetic structures and devices.

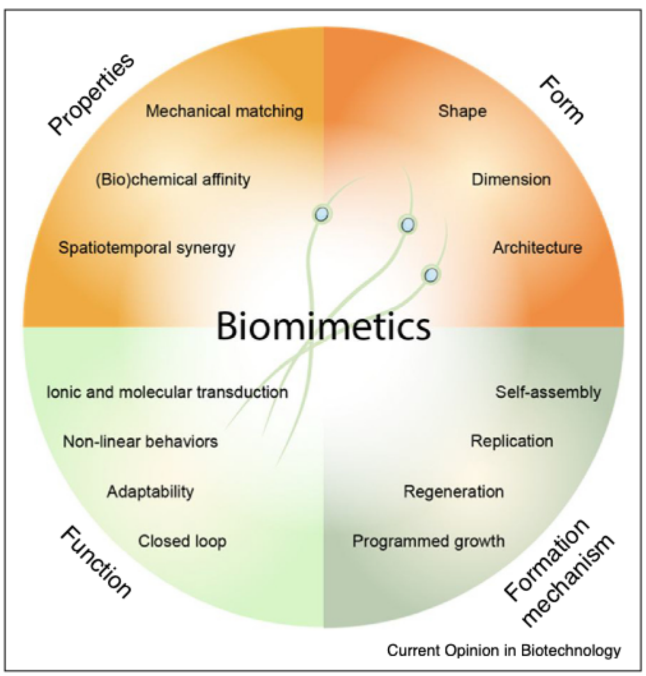
reactions both in time and space. In our biomimetic designs, we are yet to master the creation of structures operating in this far from equilibrium energy landscape.

Applying biomimetic design concepts can make our materials and electronic systems life-like and improve their compatibility with natural structures. This review will summarize current approaches and directions in electronics research inspired by the biological design paradigms. We will discuss current progress in biomimetic electronics, as well as remaining challenges and future directions.

Approaching the biomimetic design

Biological structures can inspire bioelectronic devices design in their physical properties, form, function, and formation mechanism (Figure 2). The most trivial biomimetic devices aim to approach biological structures' properties, especially their mechanical and (bio)chemical behavior. Biological structures show many desirable properties such as high tensile strength with low stiffness compared to classical man-made materials, but they also prefer to form interactions with materials showing such similarity. Mechanical matching and biochemical affinity between tissues and probes have decreased immune response and stabilized their interaction [11•]. Additionally, synergy in both the spatial and temporal scales

Figure 2



The systematic approach helps to identify promising biomimetic approaches. The four corners of biomimetic design: properties, form, function, and formation mechanism allow for planning which aspects of biomimicry can be employed in the system.

between the devices and the biological targets can improve stimulation and recording performance [12•,13–15]. While progress in materials science closes to create perfectly matched materials, the gap can be further bridged when devices take the form of biological structures. On this front, matching the size and shape helps in the device integration.

Another aspect of biomimicry is the functional operation of the devices. While electronic signals are transferred mainly by the movement of electrons, the bioelectronic cues are delivered using ions and small molecules. Additionally, in biological systems, the information is rarely processed with binary logic and linear functions. Especially, the electrical activity of neurons is characterized by a high degree of nonlinearity and complex activation behaviors which can be mimicked with nature-like circuits [16]. It can be expected that in the future, our bioelectronic devices will intrinsically adapt to the cellular forms of communication instead of relying heavily on digital signal processing and delivery, and achieve so through a closed loop system. Finally, we can take inspiration from the way natural structures are formed. Synthesis and assembly of all biological structures are initially encoded in the cell genetic material, but the biological morphogenesis is also driven by self-assembly and directed by other endogenous fields (such as electrical or mechanical cues), which gives rise to order on all scales of the structural hierarchy [17]. The ideal goal of bioelectronics research efforts should be to bring together the advantages of all four corners of the biomimetic design (Figure 2). This would ultimately establish a seamless biointerfaces, as the biomimetic principles are applied to the materials or devices down to the subcellular or even molecular levels blurring the boundary between biology and electronics.

The assembly of the biomimetic devices requires fabrication methods that allow to define the structures with unprecedented precision. Advances in photolithographic fabrication allow to shape materials on the nanoscale and enable fabrication of biomimetic structures, but efforts are still primarily focused on 2D thin-film processes developed for silicon electronics, with limited strategies enabling 3D structures [18]. Recent progress in stereolithography is promising for the fabrication of volumetric biomimetic structures. However, cost and limited scalability remain a challenge. 3D printing methods, especially those enabling printing with multiple functional materials at the same time [19], have the potential to drive forward the effort in the fabrication of biomimetic structures [20]. 3D printing has an important advantage over lithography in such it streamlines the process from design to fabrication, which is advantageous when multiple iterations can be used to evolve initial blueprints. Another technique for large-scale synthesis of thin and flexible electronics is the thermal drawing of multi-material fibers [21]. Assemblies of such fibers that resemble nerve bundles would allow highly multiplexed stimulation and recording while keeping the device's cross-sectional profile small. Finally, the programming of synthesis and assembly of bioelectronic devices in the form of genetic material or other methods would be a culmination of the biomimetic design. While our understanding of developmental biology is still limited and reprogramming the growth and function of organisms remains elusive, the first fundamental demonstrations of *in vivo* assembly of electronic material suggest the considerable potential of this research direction [22••].

Biomimetic design in the current literature

One of the first demonstrations of biomimetic electronics came in the form of materials mimicking extracellular matrix. The cells were grown onto nanoelectronic scaffolds in such approaches, creating systems with similar three-dimensional connectivity and mechanical properties as native tissues [23]. Biomimetic properties were achieved through the integration of nanostructured electronics and flexible polymers. Recently, the nanoelectronics scaffolds enabled complex extracellular recordings from cardiac spheroid organoids [24]. Further investigation into flexible biomimetic electronics allowed the creation of syringe-injectable electronics, expanding to the large volume and filling in internal cavities in an adaptable manner [25,26•]. Eventually, the flexible electronics took upon the form of biological structures, and probes with neuron-like shapes were used for recording and stimulation [27••] (Figure 3a). Thanks to the matching of shape, size, and mechanical properties of subcellular features, unprecedented compatibility with biological structures was achieved with minimal inflammation and no loss in recording quality over the curse of 3 months, demonstrating the advantages of biomimicry in terms of form and properties.

In another recent study, the concept of morphing electronics was introduced to enable the compatibility of devices with growing tissues and organisms [28••]. Stimulation electrodes were made from viscoplastic materials enabling adaptation of electrode shape to the growing sciatic nerve (Figure 3b). The morphing electrode significantly improved integration and had a less negative impact on the nerve growth compared with the stiff cuff electrodes. While bioelectronics devices cannot genuinely grow just yet, this research shows how beneficial is the development of adaptable bioelectronic circuits and the incorporation of living-like behaviors.

An interesting concept in recent research is the creation of living bioelectronics, a subtype of living materials [29], which relies on augmenting normal cells and tissues with classically bioelectronic materials. It was shown that when cells internalize photoresponsive nanodevices [30], the optical stimulation can be used to perform nongenetic electrical interrogation of cells and cellular assemblies with subcellular resolution [31]. In one such study, the cells were merged with semiconductor nanowires forming hybrid composite cells that allowed probing of coupling between myofibroblasts and cardiomyocytes [32•] (Figure 3c). Living bioelectronic systems have the advantage of being part of a cell body that can grow and form junctions with native tissues allowing biocompatible implantation and integration. While *in vivo* demonstrations are yet to be shown, there is a vast potential for studying such hybrid systems, especially if *in situ* synthesis of bioelectric materials and replicating living bioelectronics were achieved.

Genetically targeted assembly of bioelectronics is one of the most intriguing demonstrations shown in recent years [22••]. In this work, the neurons were transfected to express ascorbate peroxidase Apex2 catalytic enzyme, which allowed to deposit electrically conductive polyaniline directly onto cell membranes (Figure 3d). With the application of additional additives, this approach allowed activation or inhibition of specific neuronal cells *in vivo* and altering motor functions of *Caenorhabditis elegans*. Encoding synthesis of bioelectronic materials directly into the genetic code may allow the highest level of biointegration, as well as enable other living behaviors (e.g. growth) and enable access to the final corner of biomimicry — formation mechanism.

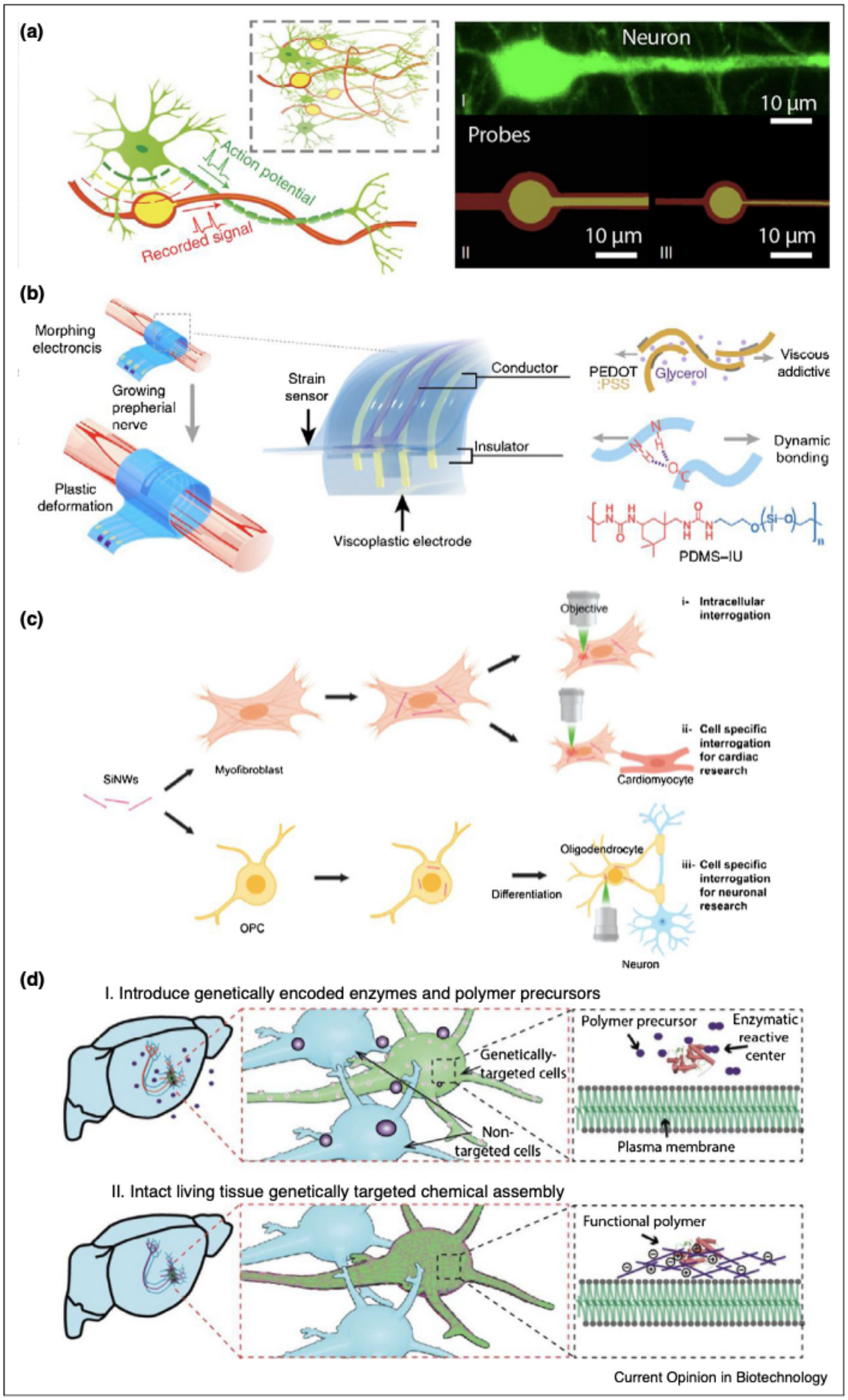
Conclusions

Recent advances demonstrate the enormous potential of biomimetic electronics. Especially the living bioelectronics that can be accomplished through cell hybridization, direct *in vivo* assembly, or a combination thereof, are of particular interest as they can be used for interrogations *in situ* and achieve seamless integration in delicate tissues that are difficult to interface through other means but are highly relevant for developing medical treatments. Notably, neural interfaces have an unparalleled potential to improve the living conditions of patients with certain neurological conditions [33] when such solutions became routinely available in a clinical setting and beyond. With biomimetic and biocompatible design paradigms, we will bridge the gap between natural and artificial systems, creating an opportunity for widespread adaptation of bioelectronics. While technical and ethical concerns of all bioelectronic applications are continued to be addressed, there is no doubt that the rich ecosystem of bioelectronic devices will play an important part in the landscape of future technologies.

Conflict of interest statement

Nothing declared.

Figure 3



Recent examples of biomimetic electronics. **(a)** Neural-like probes were used to interface with brain tissue with improved biocompatibility. Reproduced with permission from Yang *et al.* [27••]. Copyright 2019 Springer Nature. **(b)** Morphing electronics adapted to growing nerves providing reliable function throughout the animals' growth into adolescence. Reproduced with permission from Liu *et al.* [28••]. Copyright 2020 Springer Nature. **(c)** Nanomaterial-bioelectronic hybrid cells demonstrate intercellular integration and modulation. Reproduced with permission from Rotenberg *et al.* [31] Copyright 2020 American Chemical Society. **(d)** Genetically targeted assembly of electronic polymer on the neuronal membranes allows the synthesis of materials within living systems and may enable bottom-up assembly of bioelectronic systems in the future. Reproduced with permission from Liu *et al.* [22••]. Copyright 2020 AAAS.

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