

# Conformable bioelectronic interfaces: mapping the road ahead

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**One-sentence summary:** Translating conformable bioelectronic interface research into clinical reality foretells a promising future for an aging society.

Today's technologies hold enormous promise for improving health and well-being. Chronic conditions such as cardiac arrhythmia, deafness, Parkinson's disease, diabetes, or chronic pain, are increasingly assessed and treated with wearable or implantable electronic medical devices. Medical technology is evolving at a rapid pace in response to clinical needs, progress in manufacturing, and research and development conducted within medical device companies. In parallel, bioelectronics research in academic laboratories is fueling innovation in materials, device integration and therapeutic applications to answer the increasing demand for medical devices that can meet the expectations of a growing and aging population, support more personalized health care, and harness large-scale health data. In this Focus article, the seventh in a special series celebrating the 10th anniversary of Science Translational Medicine, we discuss recent progress and ongoing challenges posed by the translation of conformable bioelectronic interfaces.

## REDUCED INVASIVENESS AND IMPROVED BIOINTEGRATION

Within the bioelectronics field, miniaturized devices with high conformability to complex anatomical structures and wireless data transfer capabilities are highly desirable. Although smart (wireless network-connected) medical devices, fueled by high tech companies, have become accepted both by patients and practitioners, their form factor (shape, size, and physical specifications) remains a challenge.

Wearable and implantable devices with better biointegration, bi-directional modalities, and higher spatio-temporal resolution compared to current clinically-approved technology are anticipated to emerge as technology advances. Groundbreaking proof-of-concept work in conformable bioelectronic devices a decade ago triggered exciting opportunities. For example, in 2010, *Viventi et al. (1)* demonstrated a mechanically flexible 288-channel active silicon-based array adhered to the three-dimensional and moving surface of the porcine heart. This flexible array enabled in vivo mapping of cardiac electrophysiology with unmatched spatio-temporal precision. A few months later, *Kim et al. (2)* reported an ultra-thin system that conformally laminates onto the surface of skin to enable intimate human-machine interfaces with high-performance electrophysiological monitoring functionalities.

Since 2010, different materials and technologies have been explored (3–6), yet the general consensus suggests that the next technological breakthroughs will be enabled by the efficient and reliable transfer of microelectronic capabilities onto conformable substrates. Microtechnology offers several advantages. The miniaturization capabilities introduced by lithographic patterning enable fabrication of devices with higher functional density in smaller form factors, therefore reducing the invasiveness of implantation. The batch fabrication techniques of the microelectronics industry permit manufacturing at markedly lower cost compared to today's state-of-the-art electronic medical devices, which are assembled manually by highly skilled personnel. In addition, microelectronic fabrication frameworks offer well-established quality control procedures that can accelerate clinical translation.

In wearable applications, the emerging format is a skin-like patch that hosts thin and/or thinned powering, transmission and transducing devices for imperceptible and ubiquitous physiology monitoring (6). Adhesive solutions for wearable interfaces are a major line of on-going research to bond electronic components together, ensure the bioelectronic devices stay in place and for a long period of time. and offer, if needed, reversibility. The benefits of wearable bioelectronics are the support and continuous tracking of pre-defined biomarkers from people, of any age, in non-clinical environments, such as in the home.

In implantable applications, many designs are driven by the optimization of the mechanical signature of the bioelectronic system. Since mechanics have been shown to play a key role in the onset of foreign body reaction (7), research groups worldwide are developing strategies to make bioelectronics more transparent to the host biology. Numerous solutions are being proposed to mitigate the rejection of implanted devices by the body. The most common perspective in the field is the engineering of mechanical compliance within the implanted devices. This can be achieved by using substrate materials of low Young's modulus (4) or bioresorbable matrices (8); designing reduced stiffness (3, 6), small footprint (5), and radically different form factors such as meshes (9); and advancing wireless, untethered interfaces (6). Other exploratory and complementary solutions include locally administering bioactive molecules to reduce inflammation and promote neural growth (10) or carefully selecting materials enveloping the implanted interfaces based on their surface chemistry (11).

## **TRANSLATING FORM AND FUNCTION**

Conformability in a bioelectronic interface indicates its ability to envelop a surface and maintain functionality under dynamic and multi-axial deformation. This is an essential property for the man-made interface to comply with the convoluted, moving structures that are typical of biology. For example: the skin on the forehead and around the eyes stretches and compresses extensively. The heart beats 60 to 100 times per minute, sustains a total volume variation of about 8% throughout the cardiac cycle (12), and operates at this capacity for a lifetime. When the heart beats, periodic variations in arterial blood pressure result in recurrent, localized motion and deformation of the brain. Such mechanical specifications are

currently unmet by rigid bioelectronic interfaces and significant efforts are deployed towards implementing bioelectronic functions within conformable carrier substrates.

In today's research landscape, there is a trade-off between functionality and conformability: Complex, multi-modal, high channel count systems are typically built on rigid to flexible or bendable substrates, whereas only much simpler devices use soft materials such as elastomers or gels. Advancing conformable bioelectronic interfaces requires the successful combination of these two fronts, with technologies enabling complex functionality on ultra-conformable materials. As new materials and engineering strategies are proposed, considerable research efforts are needed to assess their translational potential, recalibrate expectations, and define a sound way forward to clinical use. Table 1 identifies and summarizes critical challenges associated with the development of bioelectronic interfaces, which once tackled will help to convert technological hype into medical hope. Challenges include: Scaling, hermetic encapsulation, system-level integration and compliance to handling in a typical healthcare use scenario. Wireless telemetry and rechargeable batteries are additional components for which there are currently no proscribed paths forward.

Prototypes of implantable bioelectronic interfaces are often tested in small animal models, and dimensional scaling requires more than simply a linear transformation of the interface geometry. Translation necessitates adjusting the overall dimensions to fit larger anatomical structures, but also re-evaluating the layout and performance of the scaled devices. For example, considering a bioelectronic interface designed to deliver functional electrical stimulation to tissue, the charge injection capacity of a given electrode coating scales down with increasing electrode geometrical surface area. This implies higher current/voltage may be required to deliver equivalent charges per phase to the tissue, or an improved electrode coating may need to be introduced. Compatibility with medical implantable pulse generators, especially in terms of voltage compliance and leads resistive load, should also be anticipated. Iterative design **cycles** are therefore needed to scale the electrical and electrochemical performance of the bioelectronic interface.

## **SURMOUNTING FAILURES AND BYPASSING BOTTLENECKS**

A common failure mechanism of current bioelectronics is the ingress of conductive fluids over time (blood, interstitial fluid, cerebrospinal fluid, but also sweat and water), resulting in loss of insulation between separate conductors. This is particularly challenging for implantable bioelectronics as water permeability of common substrate materials used in conformable bioelectronics (silicones or plastic foils) does not guarantee sufficient insulation over years when implanted in the body. Brittle inorganic layers such as oxides or nitrides offer excellent barrier properties, but at the expense of conformability. A prominent solution that is currently being investigated is the integration of thin multilayer stacks of polymer and inorganic insulators, which promise a combination of conformability and barrier properties. Future embodiments will have to demonstrate reliable material interfaces and integration on soft carrier substrates.

Another current bottleneck for the successful translation of bioelectronic interfaces is the need for reliable integration in standalone, fully implantable systems. Today, most bioelectronic interfaces of any kind must be physically connected to the corresponding driving electronics that relay electrical signals into and out of the body via transdermal connectors or wireless transmission. Wires and cables prevent truly wearable applications. Although electronic boards can be packaged in hermetic implantable capsules, the challenge lies in the interconnection of high channel count devices to such packages with reliable feedthroughs. Current implantable technology enables implanted systems with this type of connection scheme for pacemakers and neuromodulation therapy devices, which use only a small number of channels (<16). Although the approach originally shown by Viventi *et al.* (1) reduced 288 channels to a mere 36 multiplexed channels, new feedthrough solutions are required for devices with higher channel counts to be implanted chronically with minimal invasiveness.

Finally, the ability of devices to perform “as expected” and “on demand” by the user (surgeons, clinicians) in the intended setting (inside and outside of the operating theatre or medical unit) is often overlooked in research prototypes. Rigid devices are relatively easy to implant, position, and manipulate during procedures, but do not provide conformal contact with tissue. Conversely, conformable materials require ad-hoc surgical tools that enable the surgeon to easily place the device where needed and remove it when required. With time, researchers may become accustomed to handling conformable materials, however, it is important to consider and include during the initial design, development, and modification stages all of the tools that will be required for ultimate clinical deployment and use of a device or system by healthcare professionals.

## REGULATION AND THE ROAD AHEAD

From a technical point of view, the inherent design freedom and rapid manufacturability offered by conformable microtechnology pose no obstacles to current methods of surgical planning and device use. However, developments in regulatory compliance for medical devices may tend to favor status quo over innovation, imposing ever stricter validation protocols on medical device producers and clinicians willing to introduce bold changes to medical practice. Such divergence between research directions and the norms regulating innovation in the clinic is another aspect of bioelectronic interface development that warrants careful consideration and ongoing dialogue.

The different ethical facets of current and future research in bioelectronics also require further discussion. Academic work seldom crosses laboratory boundaries to venture into the clinic, and leveraging innovative technology to produce new medical devices for healthcare use is a long and costly challenge. From the academic perspective, considerable effort is required to bring new technology to the clinic, with important validation milestones that must be demonstrated before applying for a first clinical trial. Extensive tests must be conducted in compliance with relevant standards or, in the absence thereof, convincing proof must be provided regarding the fitness and robustness of new candidate devices. In vivo testing using translational animal models plays an important role in demonstrating long-term functionality

of new devices when coupled with existing clinical systems and practices. This process entails heavy investment into development work which, per se, is not sufficiently acknowledged and valued as scientific innovation, and is therefore often difficult to publish in the scientific literature.

From an industrial perspective, regulatory compliance and a widespread conservative approach in medical practice often means that medical technology companies tend to remain anchored to well-established frameworks. As extensive deviation from standard practice entails higher approval barriers, the general trend in the field is to carefully weigh innovation against regulatory requirements. This scenario is in net opposition to the perspective ideological trend of personalized healthcare, which advocates that both technology and therapy must be tailored to the individual needs of each patient, with the aim of improving the therapeutic outcome of treatments. Adaptation of policies should be the subject of discussions among all stakeholders, including clinicians and technologists.

Over the past decade, innovation in conformable bioelectronics has advanced rapidly to the point that it is inconceivable that conformable interfaces will not eventually convert to a standard in healthcare. Although the translational road is arduous and costly, investigators should be encouraged to push their laboratory research towards clinical adoption. Multidisciplinary collaboration and training programs across the life sciences, engineering, and medicine should be fostered, and long-term funding support through public and private partnerships intensified to maximize the impact of technological research and productively, and to bring new conformable bioelectronic technologies to patient care.

- 166 1. J. Viventi, D.-H. Kim, J. D. Moss, Y.-S. Kim, J. A. Blanco, N. Annetta, A. Hicks, J. Xiao, Y. Huang, D. J.  
167 Callans, J. A. Rogers, B. Litt, A Conformal, Bio-Interfaced Class of Silicon Electronics for Mapping Cardiac  
168 Electrophysiology, *Sci. Transl. Med.* **2**, 24ra22-24ra22 (2010).
- 169 2. D.-H. Kim, N. Lu, R. Ma, Y.-S. Kim, R.-H. Kim, S. Wang, J. Wu, S. M. Won, H. Tao, A. Islam, K. J. Yu,  
170 T. Kim, R. Chowdhury, M. Ying, L. Xu, M. Li, H.-J. Chung, H. Keum, M. McCormick, P. Liu, Y.-W. Zhang,  
171 F. G. Omenetto, Y. Huang, T. Coleman, J. A. Rogers, Epidermal electronics, *Science* **333**, 838–843  
172 (2011).
- 173 3. D. Khodagholy, J. N. Gelinas, T. Thesen, W. Doyle, O. Devinsky, G. G. Malliaras, G. Buzsáki,  
174 NeuroGrid: recording action potentials from the surface of the brain, *Nat. Neurosci.* **18**, 310 (2015).
- 175 4. I. R. Mineev, P. Musienko, A. Hirsch, Q. Barraud, N. Wenger, E. M. Moraud, J. Gandar, M. Capogrosso,  
176 T. Milekovic, L. Asboth, R. F. Torres, N. Vachicouras, Q. Liu, N. Pavlova, S. Duis, A. Larmagnac, J. Vörös,  
177 S. Micera, Z. Suo, G. Courtine, S. P. Lacour, Electronic dura mater for long-term multimodal neural  
178 interfaces, *Science* **347**, 159–163 (2015).
- 179 5. S. Guan, J. Wang, X. Gu, Y. Zhao, R. Hou, H. Fan, L. Zou, L. Gao, M. Du, C. Li, Y. Fang,  
180 Elastocapillary self-assembled neurotassels for stable neural activity recordings, *Sci. Adv.* **5**, eaav2842  
181 (2019).
- 182 6. H. U. Chung, B. H. Kim, J. Y. Lee, J. Lee, Z. Xie, E. M. Ibler, K. Lee, A. Banks, J. Y. Jeong, J. Kim, C.  
183 Ogle, D. Grande, Y. Yu, H. Jang, P. Assem, D. Ryu, J. W. Kwak, M. Namkoong, J. B. Park, Y. Lee, D. H.  
184 Kim, A. Ryu, J. Jeong, K. You, B. Ji, Z. Liu, Q. Huo, X. Feng, Y. Deng, Y. Xu, K.-I. Jang, J. Kim, Y. Zhang,  
185 R. Ghaffari, C. M. Rand, M. Schau, A. Hamvas, D. E. Weese-Mayer, Y. Huang, S. M. Lee, C. H. Lee, N.  
186 R. Shanbhag, A. S. Paller, S. Xu, J. A. Rogers, Binodal, wireless epidermal electronic systems with in-  
187 sensor analytics for neonatal intensive care, *Science* **363**, eaau0780 (2019).
- 188 7. D. E. Discher, P. Janmey, Y.-L. Wang, Tissue cells feel and respond to the stiffness of their substrate,  
189 *Science* **310**, 1139–1143 (2005).
- 190 8. D.-H. Kim, J. Viventi, J. J. Amsden, J. Xiao, L. Vigeland, Y.-S. Kim, J. A. Blanco, B. Panilaitis, E. S.  
191 Frechette, D. Contreras, D. L. Kaplan, F. G. Omenetto, Y. Huang, K.-C. Hwang, M. R. Zakin, B. Litt, J. A.  
192 Rogers, Dissolvable films of silk fibroin for ultrathin conformable biointegrated electronics, *Nat. Mater.* **9**,  
193 511–517 (2010).
- 194 9. X. Yang, T. Zhou, T. J. Zwan, G. Hong, Y. Zhao, R. D. Viveros, T.-M. Fu, T. Gao, C. M. Lieber,  
195 Bioinspired neuron-like electronics, *Nat. Mater.* **18**, 510 (2019).
- 196 10. T. D. Y. Kozai, A. S. Jaquins-Gerstl, A. L. Vazquez, A. C. Michael, X. T. Cui, Dexamethasone  
197 retrodialysis attenuates microglial response to implanted probes in vivo, *Biomaterials* **87**, 157–169 (2016).
- 198 11. N. de la Oliva, M. Mueller, T. Stieglitz, X. Navarro, J. del Valle, On the use of Parylene C polymer as  
199 substrate for peripheral nerve electrodes, *Sci. Rep.* **8**, 5965 (2018).
- 200 12. M. Carlsson, P. Cain, C. Holmqvist, F. Stahlberg, S. Lundback, H. Arheden, Total heart volume  
201 variation throughout the cardiac cycle in humans, *Am. J. Physiol.-Heart Circ. Physiol.* **287**, H243–H250  
202 (2004).

209 **Competing interests:**

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Table 1 – Innovative strategies address challenges in developing next-generation conformable and implantable bioelectronic interfaces.

Conformable microfabrication	Hermetic encapsulation	System-level integration	Regulatory adaptation
Manufacturing standards for thin-film devices on conformable carrier substrates	Multilayered stacks of polymer/inorganic barriers	Compact wireless transmission modules	Policy changes for approval of tailor-made medical devices
Hybrid integration of rigid (CMOS)* components and polymer-based transducers	Deposition processes, interface and barrier properties of inorganic films such as silicon carbide (SiC) and hafnium oxide (HfO <sub>2</sub> )	Power management (new battery technology, battery life / heating)	New mechanical norms for conformable devices
Fabrication of soft active** components	Implantable plug-and-play connectors / feedthroughs	Complete kits including tools for clinical use	

\* Complementary metal–oxide–semiconductor

\*\* Active electronics include diodes, transistors, light emitting diodes, and combinations thereof