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REVIEW

Technology Roadmap for Flexible Sensors

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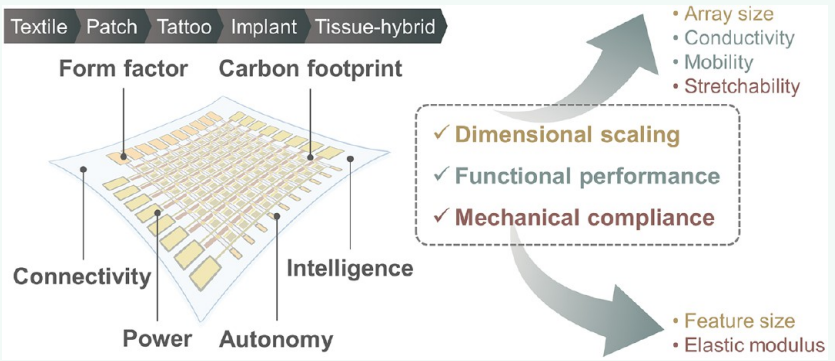

ABSTRACT: **Humans rely increasingly on sensors to address grand challenges and to improve quality of life in the era of digitalization and big data. For ubiquitous sensing, flexible sensors are developed to overcome the limitations of conventional rigid counterparts. Despite rapid advancement in bench-side research over the last decade, the market adoption of flexible sensors remains limited. To ease and to expedite their deployment, here, we identify bottlenecks hindering the maturation of flexible sensors and propose promising solutions. We first analyze**

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challenges in achieving satisfactory sensing performance for real-world applications and then summarize issues in compatible sensor-biology interfaces, followed by brief discussions on powering and connecting sensor networks. Issues en route to commercialization and for sustainable growth of the sector are also analyzed, highlighting environmental concerns and emphasizing nontechnical issues such as business, regulatory, and ethical considerations. Additionally, we look at future intelligent flexible sensors. In proposing a comprehensive roadmap, we hope to steer research efforts towards common goals and to guide coordinated development strategies from disparate communities. Through such collaborative efforts, scientific breakthroughs can be made sooner and capitalized for the betterment of humanity.

KEYWORDS: *soft materials, mechanics engineering, flexible electronics, conformable sensors, bioelectronics, human-machine interfaces, body area sensor networks, technology translation, sustainable electronics*

Living things are equipped with biological sensory systems for light, sound, smell, *etc.* to monitor and to adapt to the environment. In addition to the natural senses, humans use synthetic, fabricated sensors—devices that allow users to measure the values of physical and psychological conditions of interest using the inherent physical properties of the sensors[1]—to augment our natural abilities of perceiving the world, enabling us to interact with the environment and to improve our living conditions.

Amongst the first documented sensors in human history are the thermoscope by Philo of Byzantium in the 3rd century BCE for temperature change detection[2] and the seismoscope by Zhang Heng in 132, used to detect the occurrence of earthquakes and approximate their directions.[3] Sensors in this early era (what we define as Sensors 1.0, Figure 1) convert physical quantities/events to mechanical outputs that are easily observable. Later, with the discovery of electricity and the invention of electric generators, sensors were designed to convert physical parameters to electric signals, enabling control function. For instance, the electric tele-thermoscope invented by Warren Johnson in 1883 could not only monitor temperature, but could also modulate the function of an automatic temperature control system.[4] This marked the era of Sensors 2.0. Moving to Sensors 3.0, the electronics industry promoted the miniaturization and integration of sensors with other electronic components, giving birth to smart devices such as smartphones and smartwatches, where dozens of sensors collectively provide an impressive user experience. In recent years, advances in the Internet of Things (IoT), Industry 4.0, big data, artificial intelligence (AI), robotics, and digital health[5] have prompted sensors to become more connected and intelligent, entering Sensors 4.0. For instance, a large number and variety of sensors are embedded in autonomous vehicles with wireless connectivity for adaptive self-driving, and connected IoT sensors integrated with AI provide effective solutions to energy management of buildings and industrial facilities.[6]

Sensors that translate the physical world into data serve a foundational role in the era of digital transformation. In the digital era, connectivity and decision-making rely heavily on high-quality big data—any data bias or inaccuracy may lead to distorted conclusions and/or incorrect decisions, and the consequences can be catastrophic.[9,10] Therefore, it is critical to develop sensors that can acquire accurate and reliable data at large scales. This capability would potentially expedite solutions to the grand challenges facing humanity,[11] such as aging populations,[12] infectious diseases,[13−15] food security,[16−19] energy crises,[6,20] climate and environment crises,[21−24] and would improve our quality of life. For example, sensors could be employed to test patients for common diseases and even to predict them, to detect bacterial growth in every food package, or to monitor pollution in every lake, stream, and river.

However, conventional sensor technology is usually incapable of such massive-scale ubiquitous monitoring. Being highly integrated and miniaturized, modern sensors serve adequately as the components of smart electronics/machines, but their small and rigid form factors restrict their usage in many applications such as healthcare wearables, interactive robots, smart packaging, and building-integrated electronics, where flexible sensors would enable advances (Table 1). In this Review, we define flexible sensors broadly to include all types of sensors that can withstand mechanical deformation (>10 m^{-1} bending curvature or >1% strain on a device/system) without device failure or significant alteration in sensing performance. We include bendable, rollable, foldable, stretchable, twistable, and conformable sensors.[25] Flexible sensors enable measurements on dynamic and/or shape-changing objects and large-area non-flat surfaces,[26] due to their mechanical flexibility and stretchability, shape adaptability, and fabrication scalability, with which rigid sensors typically struggle. Flexible sensors are lightweight, thanks to the use of organic materials and/or thin-film form factors, benefiting integration, distribution, and application. Furthermore, some flexible sensors can be manufactured using low-cost materials and large-scale processes such as printing,[27,28] making mass deployment economically viable. Importantly, the use of organic materials, the thin-film form factor, and the additive manufacturing of flexible sensors may provide more environmentally sustainable ways of sensor production and disposal, tackling the escalating electronic waste problem.[29]

The above features make flexible sensors well positioned for applications that have demanding requirements in mechanical compliance, integration density and scale, manufacturability, and cost. For example, the physiological parameters that current wearable sensing technologies (*e.g.*, continuous glucose monitors, smartwatches) can measure are limited.[35] Medical-grade measurements of electrocardiogram and sweat metabolites require conformal contact between the sensor and the skin, but this goal is hardly achievable by rigid sensors without causing discomfort due to the surface micro-texture and deformation experienced by the skin.[36] In contrast, soft and stretchable sensors can address these issues, offering disruptive solutions for future healthcare.[37−39] For robots to interact safely with humans,[40] high densities of sensors (>10 sensors per cm^2 to be comparable to human skin[41]) would need to cover the curved robotic surface over large areas (~m^2).[42] In this regard, monolithically manufacturing sensor arrays on flexible substrates is much more efficient than individually placing rigid sensor pixels.[43,44] Furthermore, smart packaging with embedded sensors for product tracking and quality monitoring will be critical to efficient and sustainable supply chains,[45] yet sensor stickers need to be manufactured at costs as low as a few cents to realize this large-scale (and often disposable) application. Likewise, to install sensing maps in industrial facilities such as

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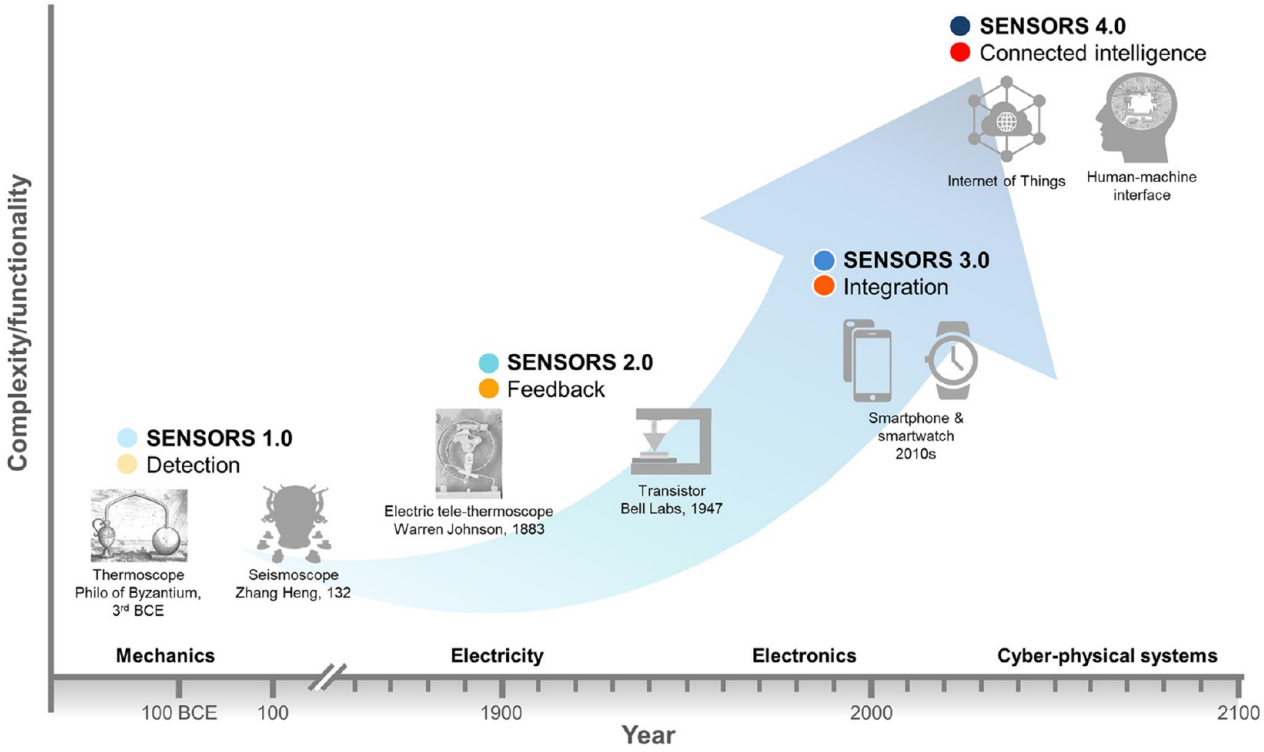

Figure 1. Evolution of sensor technology. Sensors 1.0 only served the function of detection. Sensors 2.0 had the hallmark of electrical feedback. The first transistors achieved sensing as well as the amplification of current.[7,8] Sensors 3.0 are characterized by miniaturization and integration. A smartphone is equipped with pressure sensors, light sensors, sound sensors, temperature sensors, image sensors, motion sensors, location sensors, among many others; smartwatches are likewise equipped with an increasing cohort of diverse sensors. Budding Sensors 4.0 technologies involve sensor networks and advanced algorithms to achieve enhanced perception capabilities and intimate cooperation between humans and machines.

pipes, walls, and floors, low-cost and large-area manufacturability is pivotal. To this end, printed sensors using solution-processable organic/carbon materials provide the most promising solutions. In all, the advantages offered by flexible sensors target the issues of data quantity and quality in the digital era, which will make flexible sensors one of the most valuable players in Sensors 4.0.

Flexible sensors have matured tremendously since the beginning of the 21st century. Starting with pressure sensor arrays on plastic films,[43] flexible sensors now cover a wide range of physical and chemical sensing modalities, including temperature, strain, electrophysiology, ions, biomarkers, metabolites, gases, and many more.[46−55] Substrates are not limited to plastic films but can also be ultra-thin plastic foils,[56] porous polymer mats/meshes,[57] paper,[58,59] elastomers, and hydrogels.[60] From single sensors to sensor arrays, from stand-alone sensors to integrated sensing systems,[28] the development has been astonishing, and fascinating applications including sweat-based stress monitoring[54,61,62] and remote robotic control through skin sensor-enriched virtual reality[63] have been demonstrated.

Despite significant research achievements, the adoption of and market for flexible sensors often falls short of predicted levels.[27] Some flexible sensors still have a long way to go to meet the stringent demands posed by real-world problems. It is therefore timely to identify the bottlenecks hindering flexible sensor deployment, not only technical challenges, but also cultural and regulatory hurdles (Figure 2, left). Here, we summarize promising on-going efforts to address these challenges and propose further plausible solutions. In doing so, we hope to steer and to accelerate research efforts towards faster translation of laboratory innovations and prototypes into widely used products. Additionally, we anticipate long-term issues facing future sensor deployment (Figure 2, right). Early awareness of these issues will prompt crafting and development of effective solutions. We conclude by predicting what future intelligent flexible sensors will do. These challenges and prospects are summarized into a comprehensive roadmap, in the hope of guiding collective and cooperative development strategies towards common goals by the research community and beyond.

SENSING PERFORMANCE

Sensing performance is of paramount importance for any sensor. Performance of flexible sensors encompasses the basic metrics that apply to both rigid and flexible sensors, including the classical 3S's (stability, selectivity, and sensitivity), as well as aspects unique to flexible sensors, including tolerance to mechanical deformation and monolithic integration into large-area sensing arrays. We identify key issues in these three aspects: basic metrics, mechanical performance, and array performance (Figure 3), and provide detailed discussions on existing solutions and research gaps.

Basic Performance Metrics Comparable to Rigid Sensors. Stability, selectivity, and sensitivity are primary metrics used to assess sensor performance. Because of the materials, manufacturing techniques, and sensing mechanisms used in flexible sensors, their performance often falls short of rigid sensors, even when no mechanical deformation is involved. Here, we discuss some most prominent issues in the 3S's—stability being the most challenging and pressing problem for

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real-world applications, particularly when trying to achieve long-term sensing. We also briefly discuss considerations other than the 3S's, including the dynamic responses of mechanical sensors and sensing capabilities enabled by wearable biosensors. We summarize sensor performance by emphasizing holistic approaches to sensor accuracy and fundamental correlation-establishing studies.

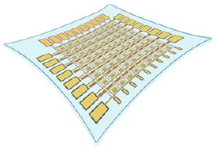
Stability in Harsh Environments Despite the Use of Unstable Materials. Stability is essential for deployable sensors because it ensures repeatable and reliable usage in changing environments, especially for long-term monitoring. Here two dimensions are considered: time and stress (*e.g.*, temperature, humidity).[64] The challenge of stability for flexible sensors often stems from the use of organic and polymeric materials in their fabrication, which tend to degrade over time and whose properties are easily altered by environmental factors. Furthermore, wearable biosensors incorporating biological receptors face additional bio-instability. The challenge is exacerbated by the degradative environments flexile sensors are exposed to, such as *in vivo* tissues and biofluids, the deep sea, and high altitudes, where extreme physicochemical stresses are present.

The most straightforward approach to tackling the stability challenge is to improve the environmental stability of sensor materials. Engineering conventional rigid sensor materials into flexible and stretchable form factors is one effective approach, but the fabrication complexity can limit scalability and cost effectiveness. A special case of this strategy is the recently discovered giant magnetoelastic effect in soft systems for pressure sensing, where inorganic magnetic particles are embedded in elastomers to induce changes in magnetic fields under deformation.[65] The sensing materials and mechanism employed are intrinsically waterproof and environmentally stable.[65−68] While materials synthesis and modification towards environmentally stable organics[69−71] and other emerging materials (*e.g.*, perovskites)[72,73] are a constant pursuit, this strategy is fundamentally challenging, governed by the physicochemical nature of these materials.

Therefore, when no direct contact between the stimulus and the sensing material is required (in mechanical, temperature, and light sensors, for example), a more viable approach is to apply protective layers to sensitive materials and the entire device.[74] To this end, high-performance humidity and oxygen barrier materials are in great demand. However, flexible materials themselves usually have poor barrier properties (Figure 4) due to the intrinsic free volume in polymers and defects in inorganics,[74] and barrier properties degrade with repeated mechanical deformation. Such issues are most severe for the elastic packaging of mechanical sensors and other stretchable sensors, when both elasticity and barrier properties are required.[75] Adding thin-film coatings[76] and filler additives to packaging materials are two frequently employed strategies,[77] but there remains a lack of effective methods to improve the barrier properties of elastic substrates and packaging layers.[60] In addition to specialized barrier layers, effective sealing is also critical for devices made of fluidic or liquid-containing materials (*e.g.*, liquid metal, electrolyte, hydrogel) and devices used in liquid environments (*e.g.*, *in vivo* biological tissues,[76] seawater[78]).

Encapsulation, and packaging in general, are of paramount importance to flexible sensors, especially wearable sensors. Proper packaging enables users to wear devices over extended periods with minimal noise or signal drift. This issue is often ignored by the academic community and is more typically considered by industry. However, packaging must be addressed in order to obtain meaningful on-body data in population studies.

Table 1. Comparison of Conventional Rigid Sensors and Emerging Flexible Sensors

Form factor/ appearance		
	Rigid sensors	Flexible sensors
Performance		
Stretchability	< 1%[a,30]	Up to 1000%[31,32]
Young's modulus[b,33]	1−200 GPa	10 kPa−200 GPa
Conformability on non-flat surfaces	No	Yes
Measurement during mechanical deformation	No	Yes
Manufacturing		
Methods	MEMS[c] techniques	Printing, MEMS techniques, *etc.*
Scale[27]	0.01−0.1 m^2 (wafer)	Up to 1−100 m^2 (web)[28]
Single-step throughput[27]	0.001^{-1} m^2 min^{-1}	Up to 10−1000 m^2 min^{-1}[d]
Potential cost per unit area[34]	High	Low
Carbon footprint	High	Low
Applications		
	Smartphones, autonomous vehicles, industrial robots, *etc.*	Conformal skin patches, smart textiles, sticker sensors for industrial IoT, supply chain, food, *etc.*

[a]Stretchability of rigid sensors is approximated as the fracture strains of conventional electronic materials. However, the real stretchability would be smaller taking performance alteration in consideration. [b]Ranges cover the Young's moduli of common materials (packaging materials included) used in rigid and flexible sensors. [c]MEMS, microelectromechanical systems. [d]Assuming 1 m wide web on a roll-to-roll platform.

Temperature is an environmental stress affecting almost all flexible sensors because most sensing materials, including rigid ones, are sensitive to temperature changes.[79] This problem cannot be solved simply through material optimization or encapsulation. Introducing additional compensation elements such as temperature sensors and feedback circuits[80,81] is generally more effective. Alternatively, exploring sensing mechanisms that circumvent the temperature-sensitive aspects of the sensing material[82,83] is viable, although not as a general solution. Overall, to suppress temperature effects with simple device structures and high integration remains a challenge.

Stability is a significant challenge for flexible chemical sensors, especially wearable biosensors,[36] where biofouling and bioreceptor inactivation are two major factors that affect long-term (several days) sensor performance. The fouling layer strongly influences the selectivity and binding affinity of biorecognition events and results in strong background signals as well as poor signal-to-noise ratios. One of the most commonly used strategies to combat biofouling is drop-casting protective polymeric membranes such as Nafion and chitosan.[84,85] Other anti-fouling coatings such as bovine serum albumin (BSA) and poly(ethylene glycol) are also effective.[86−88] However, a drawback of

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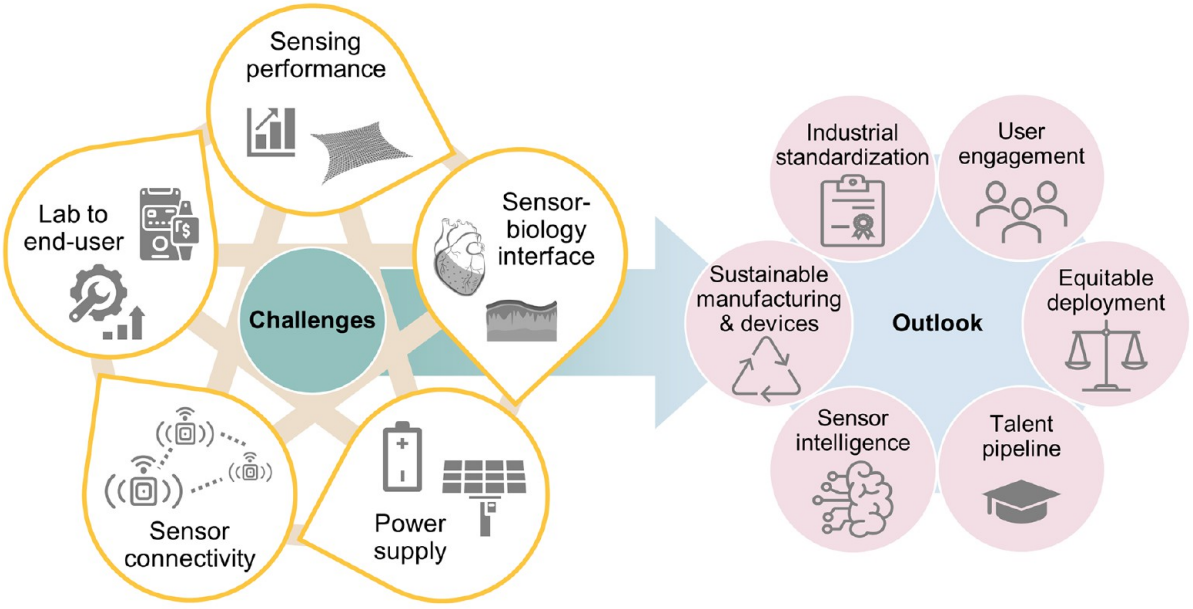

Figure 2. An overview of issues covered in this Review, including challenges for flexible sensors in the near future (left) and issues to address in the long run (right). The five aspects of challenges are interrelated, reflected by the tan lines in the background.

this surface-coating strategy is the reduction or blockade of electronic conduction between the biorecognition moiety and the transducing electrode. To tackle this problem, three-dimensional (3D) nanocomposites composed of anti-fouling agents (*e.g.*, BSA) and conductive materials (*e.g.*, gold nanowires, carbon nanotubes, CNTs) have been engineered.[89] Alternatively, surface roughness and wettability control can also circumvent this problem. For example, nanoporous Au electrodes minimized fouling by slowing down mass transport while allowing efficient small-molecule exchange.[90] Insights from skin biology, such as materials chemistry and surface texture, may provide inspirations to tackle biofouling.

Low stability of immobilized bioreceptors in the uncontrolled conditions of wearable applications (*e.g.*, changing temperature and pH) is another issue. Bioreceptors such as enzymes can easily detach from anchoring substrates/electrodes in fluidic environments (and even more so if mechanical deformation is involved) and lose their recognition function outside their operational windows.[36] To improve the long-term stability of enzymatic sensors, a nanoporous membrane with effective enzyme immobilization was robustly anchored to nanotextured electrodes, achieving continuous glucose sensing with minimal signal drift for up to 20 h.[91] Encapsulation of enzymes within electrodes through a monolithic 3D printing process is another way to improve stability.[92] Alternatively, nanozymes, *i.e.*, artificial enzymes made of nanomaterials, can be used,[93−95] though often-times compromising selectivity. Molecularly imprinted polymers (MIPs), known as "artificial receptors", can also overcome the stability issue of bioreceptors while achieving good selectivity.[96]

Besides biofouling and bioreceptor instability, there are other issues impairing biosensor stability. For example, many reported electrochemical biosensors utilize a mediator layer to reduce the potential required to trigger redox reactions for reduced interference from other electroactive molecules,[97] yet the Faradaic signal could decay over time, limiting long-term reliability. Furthermore, charge accumulation on electrode surfaces or material interlayers can lead to signal drift, which can be mitigated by nanotextured electrodes with larger surface areas and more robust bonding with sensing layers.[98] Moreover, the interactions between the active layers and biomarkers may alter the surrounding electric field, introducing microenvironmental changes as an interfering factor.

Signal drift over a relevant period of operation is an issue not only for biosensors, but also may be the number one challenge for any sensor technology. However, this issue is often ignored by the academic community outside of electrical engineering. The magnitude and predictability of signal drift often determine the lowest concentration that a sensor can accurately report over its lifetime. Flexible sensors often suffer from much larger signal drifts than their rigid counterparts, which effectively leads to high noise levels. In this regard, it is important for the community to report signal drift and its measurement carefully and precisely, and to understand the exact cause for each emerging sensor technology so that the sensor drift can be tackled effectively. For example, by designing better sensor architectures or customizing compensation algorithms and driving circuits, sensor drift can be reduced.

Stability is central to sensor practicality, yet it is often neglected in academic research. We urge the research community to place more emphasis on stability to push flexible sensors closer to commercialization. When long-term stability is not achievable, making sensors at a low cost such that they can be frequently replaced and disposed of might be another viable route to mass adoption.

Selectivity to Complex Mechanical and Chemical Stimuli. Selectivity refers to the ability of a sensor to discriminate between the analyte of interest and possible interferences.[99] It was originally defined for chemical[100] and biological[101] sensors but may be extended to include mechanical sensors (*e.g.*, pressure sensors, strain sensors, torsion sensors, *etc.*). In real application scenarios, a wide range of chemical species and mechanical forces are usually present simultaneously, and they interact with sensing materials through similar mechanisms, thus producing ambiguous sensor responses.

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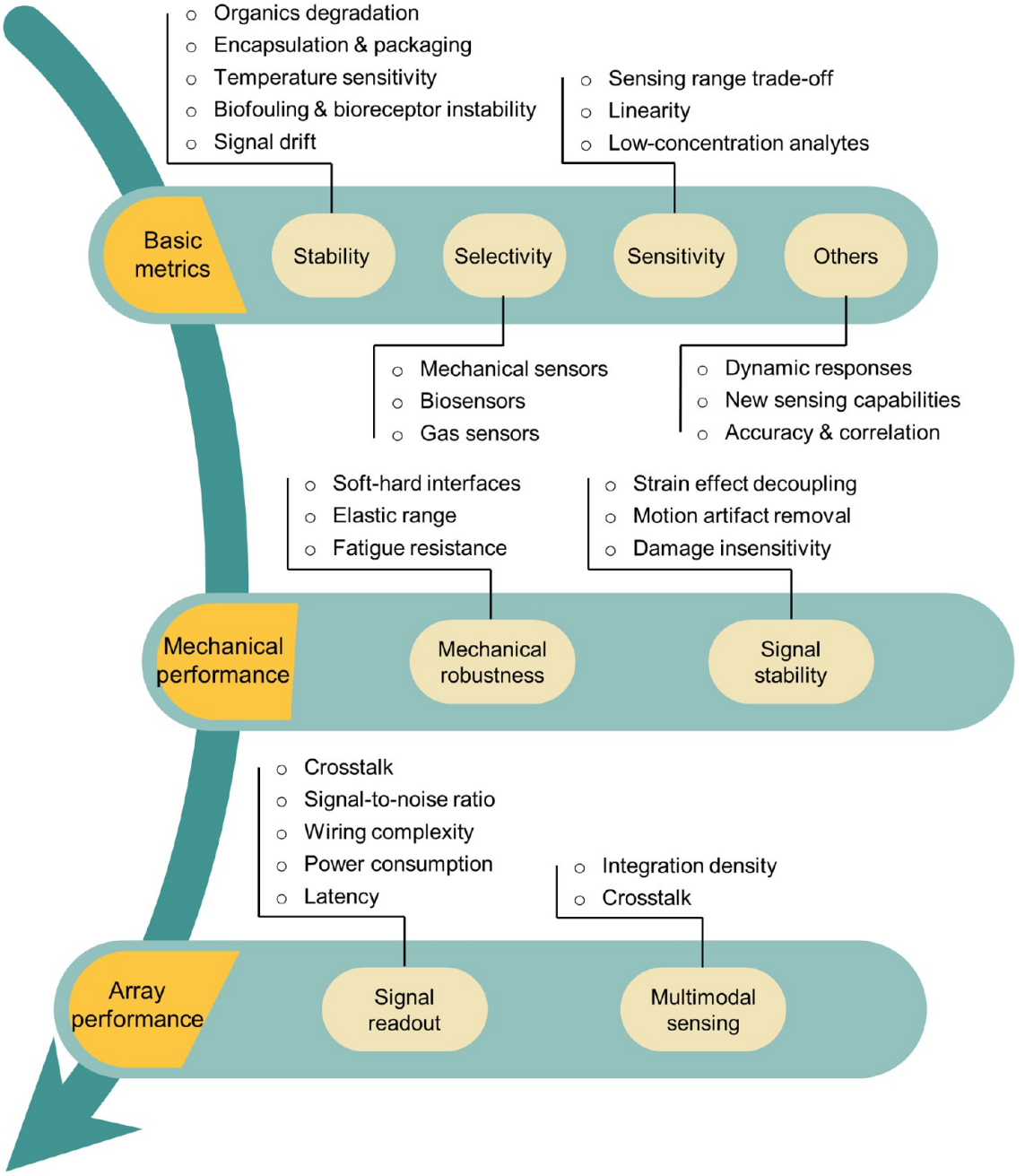

Figure 3. Overview of key issues in the sensing performance of flexible sensors.

There are two general approaches to sensor selectivity: specific sensors and selective sensor arrays.[101] Ideally, a specific sensor only responds to one analyte, and an array of such sensors would tell the exact composition of a mixture without needing a great deal of data analysis. Such specific sensors are often hard to realize. In contrast, in a selective sensor array, each sensor responds to a collection of analytes differently, and the array response collectively produces a fingerprint for a mixture. With proper data analysis, the mixture composition can be accessed. These two principles are widely applied for mechanical sensors, biosensors, and gas sensors.

Mechanical force applied on a sensor is often a mixture of pressure, tension, shear, and torsion. Decoupling these modes is important for gesture recognition, robotic control, and prosthetics. There have been attempts to fabricate 'specific' mechanical sensors.[83,102−106] For instance, a stiff and anisotropically resistive material was structured into micro-meanders and encapsulated in elastic films such that the sensor was responsive to only one direction of tensile strain and insensitive to bending and twisting.[102] Stiff platforms were embedded underneath pyramid microstructures for pressure sensors to achieve undisturbed performance at up to 50% tensile strain.[104] Although the insensitivity to other mechanical stimuli of these 'specific' sensors is not ideal due to materials and geometric limits, their performance is sufficient for non-critical applications or large values of a strain of interest (*e.g.*, joint movements). 'Specific' sensors have been integrated to achieve multi-modal mechanical sensing, where careful mechanical design is needed to isolate and distribute different mechanical stimuli to the

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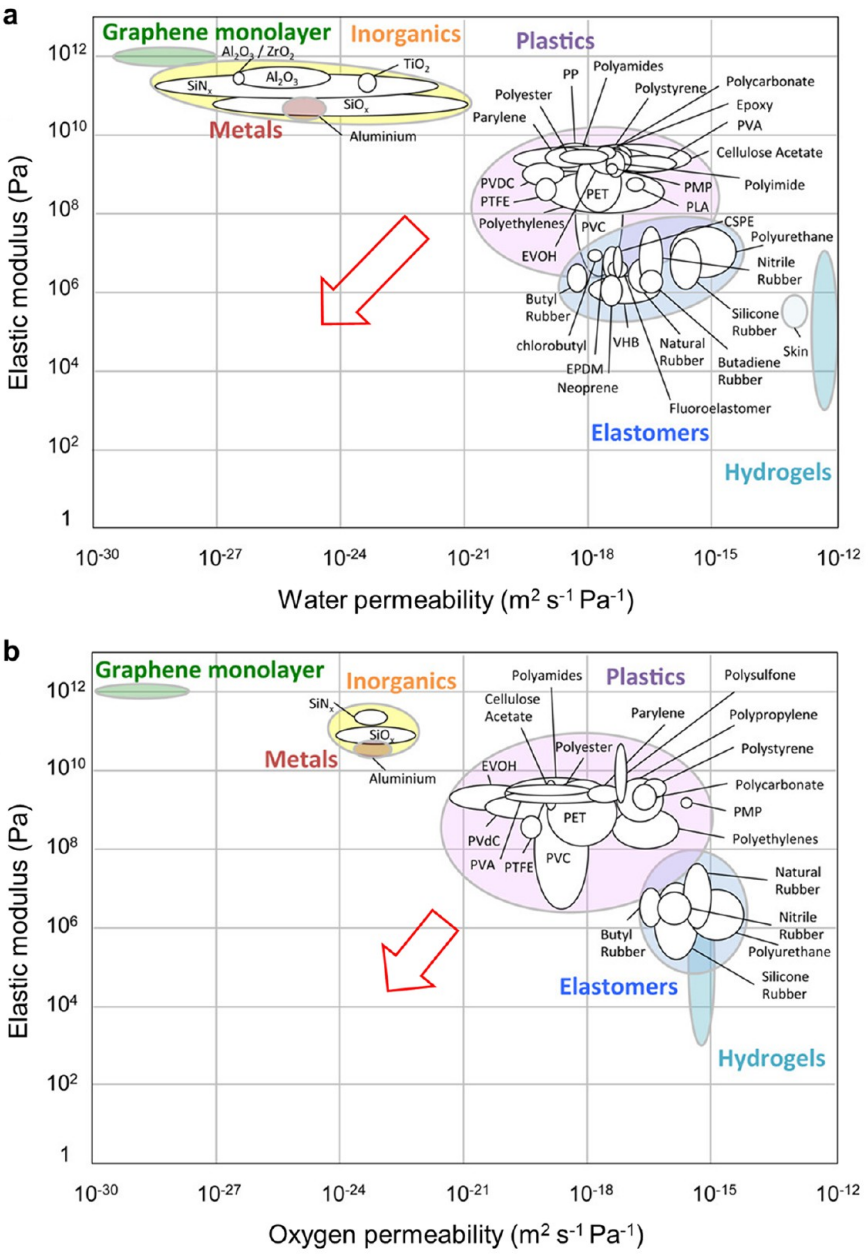

Figure 4. Barrier properties against (a) water and (b) oxygen of common materials used in flexible sensors, plotted *versus* elastic modulus. Softer materials are more flexible and usually more stretchable but suffer from poorer barrier properties. Soft barrier materials with moduli comparable to elastomers and hydrogels, as well as permeabilities comparable to inorganics are highly desirable for effective encapsulation (red arrows). Adapted with permission from ref 75. Copyright 2018 American Chemical Society.

desired sensors so that each deformation can be sensed independently.[107−109]

The other 'selective sensor array' principle takes many forms for mechanical sensors. The simplistic implementation is to fabricate deformable sensing materials[110,111] and/or design 3D sensor structures[112−116] to make the response curves different for different forms of deformation. With proper signal analyses, the correct deformation can be identified. A similar method is to integrate multiple sensors on a miniaturized 3D structure[117] or a two-dimensional (2D) surface.[118,119] The response of individual sensors differs according to the stress applied; holistic analyses of all sensor outputs derive the deformations experienced. However, using the above methods, it may be difficult to decouple a simultaneous combination of deformations (*e.g.*, compression plus shear) because the signals overlap. Advanced algorithms, such as machine learning, might be able to solve this problem. A third approach is to use materials or devices that are sensitive to several stimuli, but the stimuli can be distinguished by different measurement modes (*e.g.*, resistance and capacitance).[111] Readout electronics will be more complex for integrated devices using this strategy, which further increases system-level power consumption and hardware cost in parallel.

Biosensors are used to analyze complex mixtures present in biological samples, which may contain ions, small molecules (metabolites, cytokines, lipids, neurotransmitters, *etc.*), macromolecules (peptides, proteins, nucleic acids, *etc.*), and even viruses, bacteria, and cells. Selectivity becomes critically important in analyzing such complex mixtures as closely related

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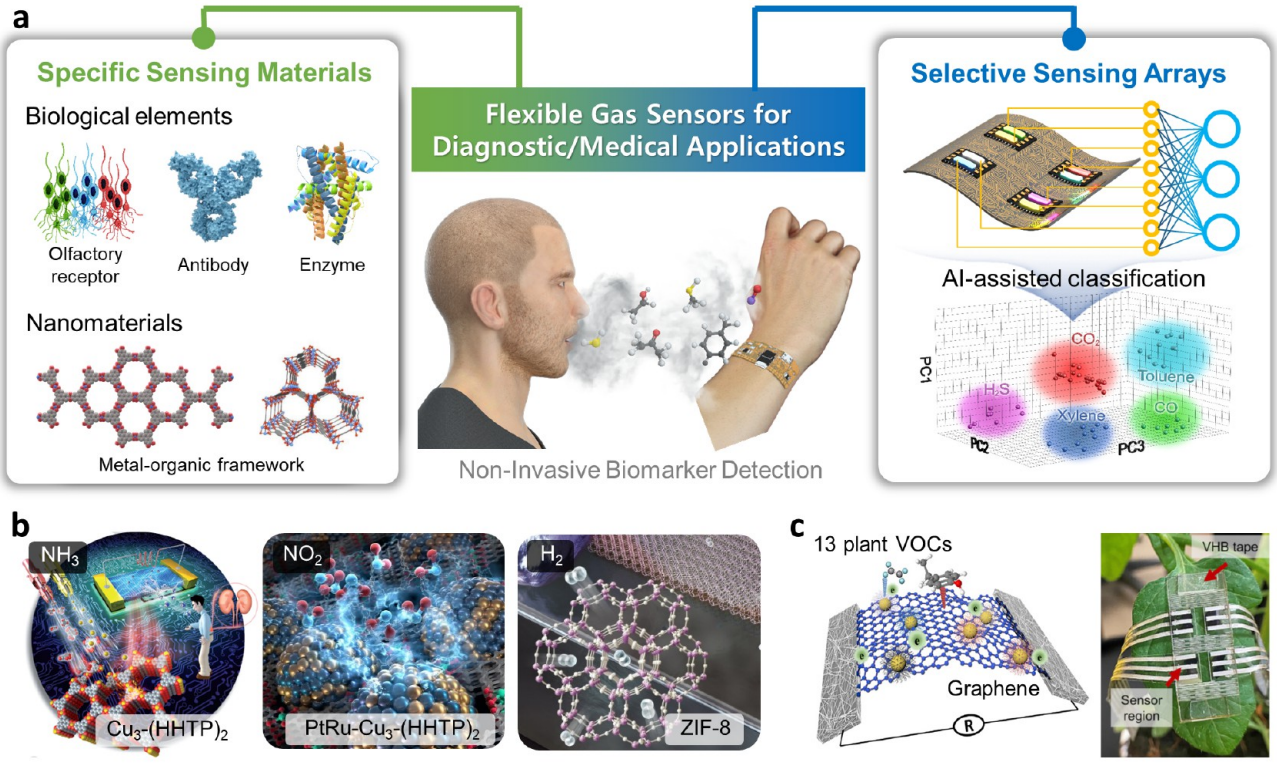

Figure 5. Selective gas sensors. (a) Overview of the strategies to achieve selective gas sensing, including specific sensing materials and selective sensing arrays. Flexible gas sensors target applications in health monitoring and point-of-care diagnostics. AI, artificial intelligence. (b) Examples of metal−organic framework-based nanomaterials with high sensing specificity to gas molecules. Cu_3-$(HHTP)_2$ (HHTP=2,3,6,7,10,11-hexahydroxytriphenylene) thin film for room-temperature NH_3 detection. Adapted with permission from ref 139. Copyright 2017 Wiley-VCH Verlag GmbH &Co. KGaA, Weinheim. Bimetallic nanoparticles (PtRu) confined in two-dimensional Cu_3-$(HHTP)_2$ for NO_2 detection. Adapted with permission from ref 140. Copyright 2021 Wiley-VCH GmbH. Zn-based zeolite imidazole framework (ZIF-8) as molecular sieving layer for selective H_2 filtration on Pd nanowires. Adapted with permission from ref 141. Copyright 2017 American Chemical Society. (c) An example of nanomaterial-based selective sensing array for volatile organic compound (VOC) identification. A graphene-based stretchable chemiresistive sensor array for identification of 13 plant VOCs. Reproduced with permission from ref 142. Copyright 2021 Elsevier.

interferents (*e.g.*, biological precursors and metabolites) are often present.[120] In this regard, nature provides many biorecognition elements that offer high specificity through interactions with metabolites and biomarkers. The utilization of bioaffinity-based receptors, including ionophores, DNAs/RNAs, aptamers, and antibodies on flexible biosensors allows selective *in situ* target recognition,[96] although sometimes at the cost of complicated fabrication and handling, as well as relatively poor stability. In this regard, artificial bioreceptors such as MIPs offer a more stable and easily processible option without sacrificing binding specificity in some cases.[96] Effective transduction mechanisms that transform the receptor-target binding to measurable electrical or optical signals are critical. Some promising examples include aptamer-functionalized field-effect transistors,[120] molecular pendulum-based biomolecular sensors,[121] as well as redox probe-tagged electrochemical aptasensors[122] and MIP-based sensors.[62] More complex biorecognition elements, including cell membranes[123] and whole cells[124−126] provide improved specificity towards some analytes, but this advantage comes with increased fabrication complexity and storage requirements. For biosensors that do not rely on bioaffinity for sensing, careful engineering of catalytic nanomaterials can achieve desirable selectivity in the (electro)-chemical recognition of some analytes.[127−129]

While biosensors are most often used for biofluid analyses, they can also be engineered to detect airborne pathogens[130] and biologically relevant gases. Gas sensors are an emerging field for flexible sensors. They provide noninvasive means of biomarker detection to inform metabolic processes and disease progression in humans and plants,[131−137] and are thus attractive for real-time health monitoring and point-of-care diagnostics (Figure 5a).[138]

Biomarker volatile organic compounds (VOCs) present in complex mixtures (often with more than a dozen of components) and a complete profile is often required for the determination of physiological status.[133,142] Some VOCs have similar molecular structures, making specific sensing challenging. Although there have been attempts to utilize biological olfactory elements, such as olfactory receptors (ORs), olfactory cells, and even olfactory organs,[143] as well as other biomolecules (*e.g.*, enzymes, antibodies, aptamers) as the recognition moieties (Figure 5a, left),[144,145] insufficient understanding of biological olfactory systems poses fundamental challenges for bioaffinity-based gas sensors. For example, the pairing relationships and the binding/unbinding interactions between gas species and ORs are largely unknown.[145] Other factors impeding the development of bioaffinity gas sensors include design complexity for liquid-phase reactions and the high cost and low stability associated with bioreagents, given that gas sensors are currently primarily used for industrial and environmental applications.

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The growing healthcare/medical gas sensors area[133] may provide an impetus to continue to develop bioaffinity-based sensing.[144] In comparison, nanomaterials with tunable structures and chemistries capable of dry-phase sensing seem to be more technically and economically viable.[52,146,147] Metal–organic frameworks (MOFs) are particularly attractive because their porous structures can *selectively* adsorb or filter gas molecules (Figure 5b).[148] However, a limited understanding of gas–MOF interactions, as well as the structure–property relationships of MOFs prevents generalized design methodologies for MOF-based gas sensors to cover wide ranges of VOCs.

In contrast to specific VOC sensors, selective sensing arrays are more widely used to recognize gas mixtures (Figure 5a, right). Combined with machine learning, this strategy has seen commercial success in electronic noses.[24] Nanomaterials are also a go-to option for selective sensing arrays due to their high sensitivity and ease of tuning surface interactions.[149] For instance, graphene functionalized with various ligands and coupled with Au nanoparticles was used to construct an 8-sensor array that could classify 13 individual plant VOCs at >97% classification accuracy (Figure 5c).[142] A recent approach achieved the fabrication and utilization of an array of 108 graphene-based sensors functionalized with 36 chemical receptors for the discrimination of 6 gas species within a minute,[150] shedding light on rapid VOC detection using large-scale sensor arrays. Overall, recent advances in flexible room-temperature gas sensor arrays have achieved lower power consumption, reduced fabrication cost, and greater wearability without sacrificing sensing performance.[142,151–155] Although machine learning algorithms capable of higher prediction accuracy can compensate for sensor selectivity shortfalls,[151,156,157] improving the specificity of each sensor remains a critical challenge.

An interesting application of selective array sensing was recently reported for triboelectricity-based material identification.[158] An array of sensors with differential triboelectric properties generated a fingerprint signal pattern when in contact with a particular material. Combined with machine learning, the accuracy for materials classification reached 97% when four sensors in an array were used. Such strategies may find wider application in flexible sensors to enable more sophisticated sensing capabilities.

Sensitivity with Wide-Range Linearity and to Low-Concentration Analytes. High sensitivity allows sensors to detect minute changes in a stimulus, to reduce false-negative signals, and to improve signal-to-noise ratio and accuracy. The sensitivity of most flexible physical sensors (*e.g.*, mechanical sensors, temperature sensors, photodetectors) is sufficient for common applications. A notable issue is the trade-off between sensitivity and sensing range in mechanical sensors. In comparison, sensitivity is more of a concern for chemical sensors, specifically biosensors that detect low concentrations of analytes present in biofluids.

The trade-off between sensitivity and sensing range, and the issue of nonlinearity exist in most mechanical sensors,[111,159–163] and are especially prominent for pressure sensors.[164] Ideally, high sensitivity across a wide force/pressure range is desirable, but is hardly achievable in bulk piezoresistive/piezocapacitive sensors, because of the stiffening effect of soft materials upon compression. Microstructuring is a common strategy to improve sensitivity,[165,166] yet this approach mostly works at low pressures. There have been many attempts to address this problem. Structure-wise, intrafillable microstructures accommodate deformed surface structures in the underlying undercuts and grooves, thereby retarding the saturation of porous structures.[167] Mechanism-wise, combined piezoresistivity and piezocapacitivity significantly increase sensitivity, even at large stress of up to 50 kPa.[168] The magnetoelastic effect is useful for pressure sensing over a wide range, from 3.5 Pa to 2000 kPa,[169] and its sensitivity is comparable to those of piezoresistive and piezocapacitive sensors.

The above methods do not solve the nonlinearity problem. One solution is using hierarchical microstructures, such as micropillars on hemisphere arrays.[170] Adding gradient charge distribution within the active material may be able to solve the nonlinearity issue. This strategy has been demonstrated in a capacitive pressure sensor, reaching a record-high linearity range up to 1000 kPa. The mechanism is gradient compressibility and dielectric property with increasing pressure, realized by a skin-like hierarchical microstructure made of materials of different permittivities.[171] This strategy may be extended to other types of pressure sensors based on gradient conductivity or gradient ionogels. Another perspective on addressing this sensitivity-range conflict is to program the sensor performance on demand based on application requirements, since extraordinarily high sensitivity is usually required for small pressure detection, whereas for large pressure, a wide sensing range is more important. A stiffness memory ionogel was developed,[172] whose stiffness could be tuned by pressure plus thermal treatment. The programmable stiffness led to programmable pressure ranges, detection limits, and sensitivity. Although an interesting concept, the practical applicability of such customizable sensors should be carefully evaluated, taking account of reproducibility, calibration, *etc.*

Generally, for mechanical sensors and other sensors involving mechanics sensing (*e.g.*, vibration sensors, ultrasound imagers[173]), sensitivity–deformability entails a balance of rigid and soft materials in rationally designed structures—rigid materials usually lead to good sensitivity, whereas soft materials enable large deformability. Integration density, system complexity, and manufacturability are key factors to consider when devising wide-range sensitive systems.

Highly sensitive wearable and implantable biosensors are strongly desired for on-body and in-body chemical sensing to aid diagnostics and therapeutics, but this technology is relatively underdeveloped. Currently reported biosensors primarily focus on biomarkers at the levels of tens of μM or higher.[174–176] There are a number of clinically relevant biomarkers such as proteins, peptides, hormones, small molecules, and drugs existing in sweat or saliva at nanomolar levels and lower.[177] To enable the detection of these biomarkers, the sensitivity of flexible biosensors needs improvement.

Various nanomaterials such as conducting polymer nanofibers,[178] graphene,[179] nanostructured gold,[180] MOFs,[181] and transition metal nanoparticles (*e.g.*, Fe_3O_4 and NiO)[127] are often utilized on the working electrode in electrochemical sensors as they can enhance the electrochemically active surface area and electron transfer dynamics, resulting in higher detection signals.[52,176] Recent reports show that laser-engraved graphene enabled the detection of sweat uric acid, tyrosine, and cortisol at sub-micromolar levels,[61,182] and dendritic gold nanostructures were successfully used to monitor micromolar levels of vitamin C and glucose in sweat.[91,183] Besides nanomaterials, micro- to macro-scale approaches can also increase electroactive surface

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areas, using printable ink formulations and 3D hybrid electrode structures.[184,185]

Signal transduction is important to sensitivity—effective transduction can amplify binding events to reach measurable signals. Transistors, including field-effect transistors (FETs)[54,120,186−189] and organic electrochemical transistors (OECTs),[190−192] are effective amplification devices.[191,193,194] When the channel of a FET is reduced to the nanoscale, the high surface-to-volume ratio enables highly sensitive detection.[195] By employing this mechanism with an aptamer, cortisol at a concentration down to 1 pM could be selectively detected.[54] In addition, reducing the molecular size of surface-bound bioreceptors, such as using oligonucleotides in place of DNAs[187] and nanobodies in place of antibodies,[192] can bring the target-binding event closer to the transducer and may therefore enhance sensitivity. This consideration can also be useful in the design and selection of aptamers, to ensure that significant conformational changes in the artificial receptor occur close to the surface so as to gate the FET channel optimally.[120] Successful engineering of peptides[196] and DNA[197] into semiconductors may allow the unification of analyte binding, transduction, and amplification in a single material, offering improvement in sensitivity and response time. Devices capable of effective amplification should be explored further for wearable biosensors. For example, subthreshold Schottky-barrier thin-film transistors demonstrate exceptional intrinsic gain of up to 1,100 V V^{-1}.[198] Schottky-contacted nanowire sensors were found to enhance the sensitivity of Ohmic-contacted sensors to light, gas, and (bio)chemicals by orders of magnitude.[199]

Colorimetric biosensors are attractive due to low cost, simplicity, and automated operation, but their poor sensitivities call for effective signal-amplifying mechanisms. Fluorescent biosensors could be a good alternative as fluorescence can boost sensitivity by up to 1000× that of colorimetry.[200] Nanocatalysts are also promising, previously achieving 100× amplification in antibody-based lateral flow immunoassays.[201] Careful design of the catalytic inorganic nanoparticles with organic recognition moieties is critical in achieving desirable sensing performance. Nevertheless, current methods for colorimetric and fluorometric signal detection by the naked eye, in-built detectors, or external cameras suffer from drawbacks such as subjectiveness, device bulkiness, and manual operation. Simple methods to quantify colorimetric and fluorometric signals digitally from wearable biosensors are needed.

Another potential way to enhance the sensitivity of biosensors is the preconcentration of target analytes through ion concentration polarization[202] or dielectrophoresis.[203] Target preconcentration has been used for wearable real-time monitoring of low-level heavy metals in sweat.[204,205] A further strategy being explored is to amplify signals using low-noise and high-gain circuits, such as differential amplifiers and charge-coupled devices.[206]

Considerations beyond the 3S's. Dynamic Responses of Mechanical Sensors. Since mechanical deformations occur time-dependently, the dynamic responses of mechanical sensors to varying strains and stresses critically determine sensor accuracy in practical use. There are three major issues in this regard: hysteresis, response time, and strain-rate dependency, which are highly interrelated.

Hysteresis refers to differing response curves between loading and unloading, presenting a fundamental challenge for mechanical sensors. It stems from the viscoelasticity of common soft materials (*e.g.*, elastomers, gels) used in flexible mechanical sensors,[110] especially when doped with conducting fillers. Micro-/nano-structuring for enhanced sensitivity adds another source of energy dissipation from interfacial contact.[207] Moreover, flexible mechanical sensors usually possess longer response times than rigid counterparts due to sluggish polymer chain movements. This difference precludes time-critical applications such as in robotic control and high-frequency applications, such as motion tracking in racing sports. Strain-rate dependency refers to the differing response curves under varying deformation rates or frequencies, leading to inaccurate readings in many applications, since most deformations encountered in daily life are not at constant speed. This phenomenon is often closely related to long response times, *i.e.*, when the structural or molecular changes in sensors cannot catch up with the macroscale exerted stress, the sensors deviate from equilibrium states to varying extents at different strain rates. Sometimes, strain-rate dependency is an intrinsic characteristic dictated by the sensing mechanism (for instance, pressure sensing based on magnetoelastic generators depends on the rate of change in magnetic flux[65,169,208]). An effective strategy to overcome hysteresis and related issues is to use rigid materials with special structural designs for strain sensing, while soft materials are still required for deformability.[209,210] Microstructuring is effective for pressure sensors through a reduction in contact area.[164] Alternatively, careful engineering of polymeric networks can mitigate hysteresis,[211−215] yet the materials fabrication can be complex and thus difficult for device integration. An emerging approach leverages machine learning to correct the errors associated with the viscoelastic properties of soft sensors for better prediction and analyses.[216]

The dynamic performance of mechanical sensors may appear trivial, yet it is critically important to practical measurements, deserving of greater attention. For example, although stretchable strain sensors using conductive elastomeric composites have been widely reported, their dynamic performance has rarely been investigated. Most studies only focus on quasi-static electric behavior, where the sensing performance was evaluated in a static state or in slow stretching−releasing processes (deformation speed <30 mm min^{-1}, strain rate <10% s^{-1}).[217] Few studies have paid attention to the signal fidelity of strain sensors at higher deformation speeds,[215,218] which is more relevant to dynamic motions in real life, such as limb movements and hand gestures (speed >100 mm min^{-1}, strain rate >20% s^{-1}).[217] In monitoring these dynamic motions, strain sensors using elastomeric composites usually experience signal distortion, which is a common yet often overlooked problem.[219−222] Dynamic responses at high and varying strain rates should be included as an essential performance metric when reporting mechanical sensors.

Sensing Capabilities of Wearable Biosensors. Wearable biosensors are still in early stages of development and many sensing capabilities await exploration and development.[36,223−225] The first area of improvement is to expand the portfolio of biomarkers that can be detected, to approach and to exceed current clinical assays. Complex biomarkers (*e.g.*, proteins, hormones, nucleic acids, small molecules, and pathogens) usually require bioaffinity-based sensing, and this strategy demands the design of effective biorecognition moieties and proper immobilization and stabilization. Sensitive and selective aptamers are being developed for a wider array of targets and they could be deployed for this purpose.[120] Moreover, some approaches require multi-step preparation

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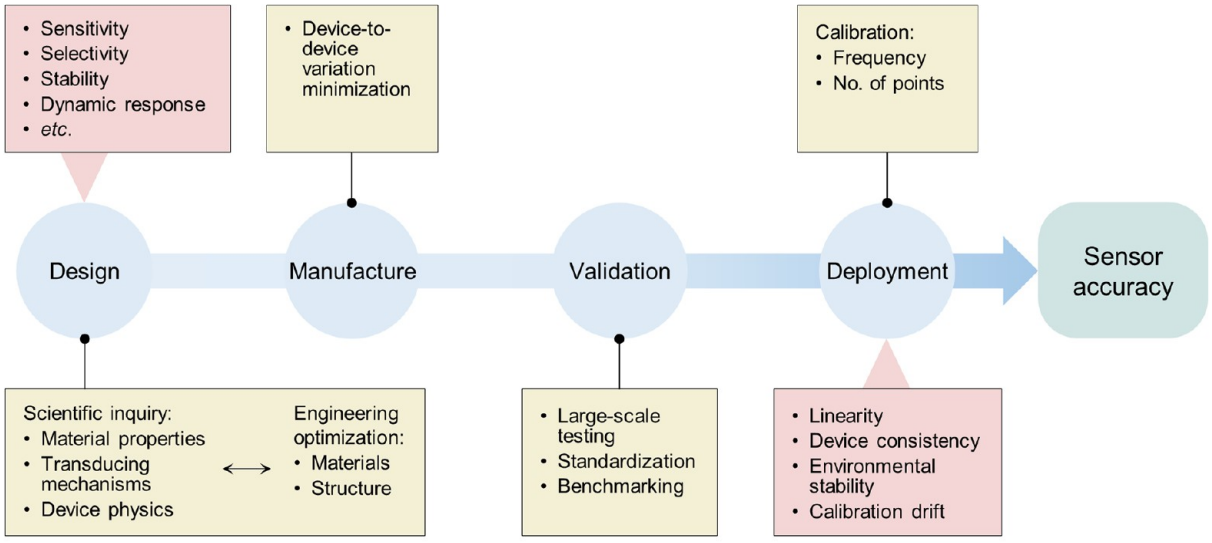
Scheme 1. A Holistic Approach to Sensor Accuracy Assurance during the Design, Manufacture, Validation, and Deployment of a Sensor Technology[a]



[a]Factors to consider are highlighted in red boxes.

(*e.g.*, immunobiosensors using antibodies),[88] making them challenging to integrate into wearable platforms. Microfluidics is one promising approach,[15,226−229] which helps to collect, to contain, and to drive biofluids, as well as to deliver and to wash out unbound detection probes or labeling reagents. In addition, to reduce the number of preparation steps and time consumed in immunosensing, development of label-free, reagent-free, and wash-free methods is also necessary.[200] Surface-enhanced Raman spectroscopy (SERS) has emerged as a powerful tool in this regard, but it requires a standalone spectrometer for signal readout.[230,231] Recent work proposed an indirect electrochemical approach based on MIPs coupled with redox-active reporters, which enabled the detection of non-electroactive species in sweat, including amino acids, vitamins, metabolites, lipids, hormones, and drugs.[228] This approach may be customized to detect a more diverse range of biomarkers.

A second area worth exploring is to realize continuous monitoring of these biomarkers, which enables real-time monitoring and prompt detection of abnormalities. Common bioaffinity assays (*e.g.*, immunoassays) of disease biomarkers involve complex steps, require accurately controlled sample volumes and receptor regeneration, and are not reversible. These features make immunoassays not amenable to continuous on-body operation. Innovative strategies need to be crafted to overcome these challenges. For example, modulating intermolecular forces between the bioreceptor and the target using proper stimuli such as heat, ultrasound, electric/magnetic fields, and chemical cues might be a viable approach to sensor regeneration.[51] Using this strategy, the regeneration of MIP-based electrochemical biosensors by current or voltage has been demonstrated.[228] A resettable electrochemical sweat lactate sensor has been developed through reversible redox reactions in a biofuel cell.[232] Regeneration of aptamers for cocaine sensing has been realized through pH-modulated conformational changes.[233] Microfluidics are a promising platform for continuous-monitoring wearable biosensors. For instance, stretchable microfluidics can expel sweat from filled channels to enable multiple usage.[234] Rational design in channel shape and wettability can accelerate sweat collection and realize continuous sampling.[235,236] High temporal resolution can be achieved through encapsulating biofluids in water-in-oil droplets and assessing the droplets sequentially, although system compactness needs improvement.[237] Meanwhile, safe, continuous, controllable, and quantitative biofluid sampling is also an important aspect of continuous biosensing. Passive microfluidics,[238−240] porous/hydrogel absorption pads,[128,180,241−244] microneedles,[245,246] iontophoresis and reverse iontophoresis[174,247,248] are common solutions, but none can simultaneously satisfy all requirements. Lastly, while wearable sweat sensors are the most often studied, other bodily fluids such as saliva, tears,[249] and wound exudate should also be explored,[224] as they may provide biomedical insights inaccessible *via* other means.

Equally important to technological advancement, robust knowledge of the clinical and biomedical relevance and correlation of various bodily chemicals is needed to guide the design and engineering of practically relevant biosensors. This knowledge often involves metabolites in biofluids not traditionally studied.[51] In each case, the contents of the fluids will need to be compared to current gold standards (typically blood) to determine whether the fluid is representative of physiological state and what conversion factors are appropriate to analyze the data obtained. Then, the advantages of more frequent and, in some cases, continuous monitoring can be realized.

Holistic Approach to Accuracy Assurance. Reporting accurate values of the parameters of interest is essential to sensors. To ensure sensor accuracy, it is important to take a holistic approach spanning the entire life cycle from the development to the deployment of a sensor technology (Scheme 1). First, during the design stage, fundamental materials research is required to understand the materials properties, transduction mechanisms, and device physics. This knowledge leads to optimized materials and device structures. Going back and forth between scientific inquiry and engineering optimization would lead to improved sensor accuracy, while the 3S's and other factors should be considered. Moving from design to deployment, well-controlled fabrication to produce consistent devices

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is critical. Moreover, large-scale validation with standardized procedures and benchmarking against gold-standard measurements are necessary to obtain reliable and trustworthy calibration curves. For biomedical sensors, validation experiments can be designed in accordance with the guidelines of the Clinical and Laboratory Standards Institute.

In real-world deployment, calibration can be a complex issue. There are two levels of consideration: the frequency of calibration during the entire sensor lifetime (manufacture, shipment, and usage) and the number of calibration points for each calibration. Calibration frequency usually concerns whether calibration can be performed by the manufacturer prior to shipment of the product. Most commercial sensors fall in this category. In this case, the cost of calibration is typically one third of the total cost of most commercial sensors today. However, the exact cost depends on the number of calibration points that are needed. If the sensor has a linear response in the needed dynamic range and if it has the same sensitivity in that range for all manufactured components but different offset values, then a single-point calibration is all that is needed. If the manufactured sensors do not have any offset in their base value with the same sensitivity, then no calibration is needed (which is rare but would significantly reduce costs). If a sensor has a linear response in the needed dynamic range but there is variability in the sensitivity from sensor to sensor, then two-point calibration is needed. If the sensor response is not linear, then multi-point calibration is needed (which is commercially unattractive). Furthermore, calibration against temperature, humidity and other environmental factors may be needed. For some emerging sensor technologies, the calibration can shift over time, for example, from the time of manufacturing to the time of usage. In that case, additional one-point or two-point calibrations may be needed prior to use, which complicate use. Therefore, it is critically important for the community to report linear response ranges, sensor-to-sensor variability, stability against environmental factors, calibration method, and calibration drift over time.

Reliable Correlations between Sensor Signals and Object Status. Data without interpretation is of little use. Making sense of data collected by sensors is equally, if not more important with high-quality data acquisition. As flexible sensors enable many parameters to be acquired in unconventional situations or from previously inaccessible locations, the correlations between these parameters and the status of the monitored objects, environments, *etc.* should be carefully examined.[250] Even for a single physical parameter, the underlying meaning can be complicated to unravel. For instance, facial strain was recently verified as an indicator of language commands through theoretical analysis and simulation,[250] permitting the use of conformal strain sensors on face to deliver language commands silently.

The correlation issue is especially concerning for biomedical applications, such as biomarker measurement for disease diagnosis[251] and physiological monitoring for health assessment.[13] A recent report found close correlations between tear glucose levels and blood glucose levels with a lag time of 10 min,[252] indicating promising noninvasive glucose monitoring by contact lenses. The study was conducted on three rabbits in the experiment group and the control group respectively, which may not be sufficient as biologically conclusive or generalizable to humans. Sweat is another biofluid in which glucose monitoring is extensively conducted.[253] Nevertheless, the correlation between sweat glucose and blood glucose can be easily altered by sample collection methods as well as skin and environmental conditions.[254] The large uncertainty renders wearable sweat glucose sensors[255] only sufficient for range estimation but not currently qualified for guiding medical interventions. Large-scale tests with standardized protocols are needed to reach robust conclusions. In addition, equal gender representation in clinical trials is also curial for flexible sensor development and their practical usage in public. Recent results on a conformable multimodal sensory face mask performed on an equal number of male and female subjects indicate that current face masks are not suitable for women subjects in general.[256] This result suggests a comprehensive mandate to be inclusive in human subject studies to have technologies be beneficial for all.

As flexible sensor technology is collecting signal types some of which are traditionally inaccessible, problems emerge in terms of the implications of sensor data. This issue calls for extensive fundamental and biomedical research, where investigations involving gold-standard tests on adequate sample sizes[257,258] are needed to test the existence of correlations and to generate reliable reference databases.

Tolerance to Mechanical Deformation and Damage. A major advantage of flexible sensors is the ability to withstand significant deformation without physical failure or performance degradation. This feature permits many use cases with which conventional rigid sensors struggle, such as conformal skin patches/tattoos and smart clothing. Nonetheless, this flexibility also poses great challenges in maintaining sensor integrity and performance under often-unpredictable mechanical interactions between the sensor and the environment.

Mechanical Robustness in Long-Term Use and at Large Deformation. Mechanical robustness describes the sensor's ability to withstand different forms of deformation without mechanical failure. Some extreme cases include exceptionally large strain and high impact,[102] prolonged cycling strain, and constant friction. While conventional rigid sensors can be protected from mechanical damage using high-performance ceramics, metals, and thermosets, deformability of flexible sensors does not permit the use of these mechanical protective materials in conventional ways. Furthermore, due to the wide variety of materials used in flexible sensors, each having distinct mechanical properties (*e.g.*, elastic modulus, Poisson's ratio, viscoelasticity) and surface properties (*e.g.*, surface energy, chemical composition), interfacial mismatch contributes a major factor to mechanical instability. The exact deformation a flexible sensor experiences varies greatly according to application, and hence exceptional mechanical robustness is not always required. Nevertheless, we highlight the most significant issues, and the principles should benefit the development of a number of flexible sensors.

Robust Soft-Hard Interfaces. One of the most prominent mechanical challenges in flexible sensors is the interfacial instability between dissimilar materials. Stress and/or strain concentration occurs at soft-hard interfaces, leading to a major source of failure through delamination/detachment. Soft-hard interfaces exist in many forms: nanocomposites, layer-by-layer laminates, interconnects, *etc.* The general principles in tackling soft-hard instability are (1) improving interfacial adhesion and (2) avoiding abrupt softness/hardness difference. Specific methods vary in different scenarios, but the principles hold.

For example, using a single materials system (or at least reducing the number of materials) can eliminate many interfacial issues.[118] Recently, a capacitive pressure sensor made entirely of CNT-doped polydimethylsiloxane (PDMS) was fabricated.[259] Tuning the dopant concentration around the

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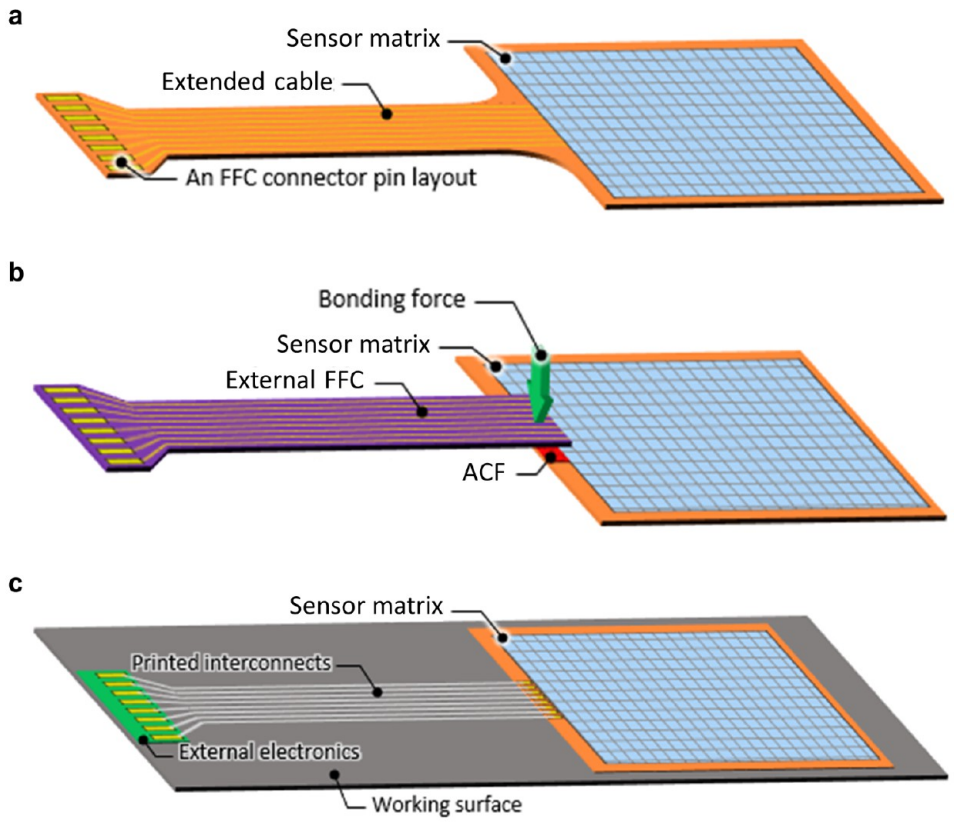

Figure 6. Current interconnection approaches for flexible sensors and arrays. (a) Extended flexible sensor system layout contains flexible cable and pins suitable for a flat flexible cable (FFC) connector. (b) External FFC is bonded to the flexible sensor system *via* an anisotropic conductive film (ACF). (c) Printed conductors connect flexible sensor system with external electronics directly.

percolation threshold realized either electrode or dielectric properties with little change in mechanical softness. The interlayers were bonded together due to the similar chemistry of the layers. The resulting sensor could maintain stable performance under 100,000 cycles of rubbing and other harsh deformation conditions. Substrate mechanical engineering is effective in mitigating stress concentration in heterogeneous stretchable electronics.[260−264] By synthesizing elastomers of different stiffness or embedding rigid islands, the area under rigid components is made harder than the surrounding area. Consequently, abrupt soft-hard transition between rigid functional components and soft substrates is avoided. Rational geometric engineering of the rigid islands can substantially suppress crack propagation at their interfaces with elastomers, extending failure strain and fatigue life.[265] Recently, a mesh polyimide network was used in place of elastomers as substrate and superstrate for hybrid integrated systems.[266] The mesh networks have reduced contact area with and more similar Young's modulus to rigid interconnects and chips, largely alleviating the soft-hard interfacial problem. Other methods include using materials with gradients of stiffness,[267] adding an interface material with medium stiffness between the soft sensor and the rigid interconnect,[268] and developing ultrathin tough adhesive films for interlayer stabilization. In nanocomposites, surface chemistry engineering[269] and interfacial microstructuring[270,271] are common strategies to improve the bonding stability between nanomaterials and polymer matrices.[272]

A particularly challenging issue within the scope of soft-hard interfaces is interconnection, which is especially a concern for system integration.[273] In particular, wearable and implantable sensors can be made ultrathin, soft, and stretchable, but poor mechanical strength challenges reliable connection with the rest of the system.[274,275] Moreover, sensor arrays (*e.g.*, microelectrode arrays for brain mapping[276]) face additional challenges in connecting high-density thin wires across long distances of soft-hard transition.

To address this problem, there are several options currently available, without using rigid wires and solders: (1) to integrate a flexible electric cable and pins into the sensor system so that it fits into a standard flat flexible cable (FFC) connector (Figure 6a);[276−278] (2) to apply an anisotropic conductive film (ACF) and bond an external FFC to the sensor system (Figure 6b);[279−282] and (3) to print interconnects over the surface of the sensor system down to the electric pads of the external electronics (Figure 6c).[273,280] The first approach is more monolithic and can be accomplished in fewer process steps, while requiring substantially larger areas for a single device. The second approach is superior in that cables and sensor systems can be fabricated separately, thereby offering high resolution and performance, but extra steps for cable bonding are required before use. The third approach is preferred in applications that require customizability in interconnection layout or do not critically demand high resolution. Besides these options, fully soft and stretchable interconnects with robust adhesion are under investigation,[283−287] which are expected to reduce interfacial mismatch with soft components significantly. Electrically conductive adhesives are commercially available as printable inks; modifying these materials to a lower rigidity will be instrumental to the large-scale manufacturing of

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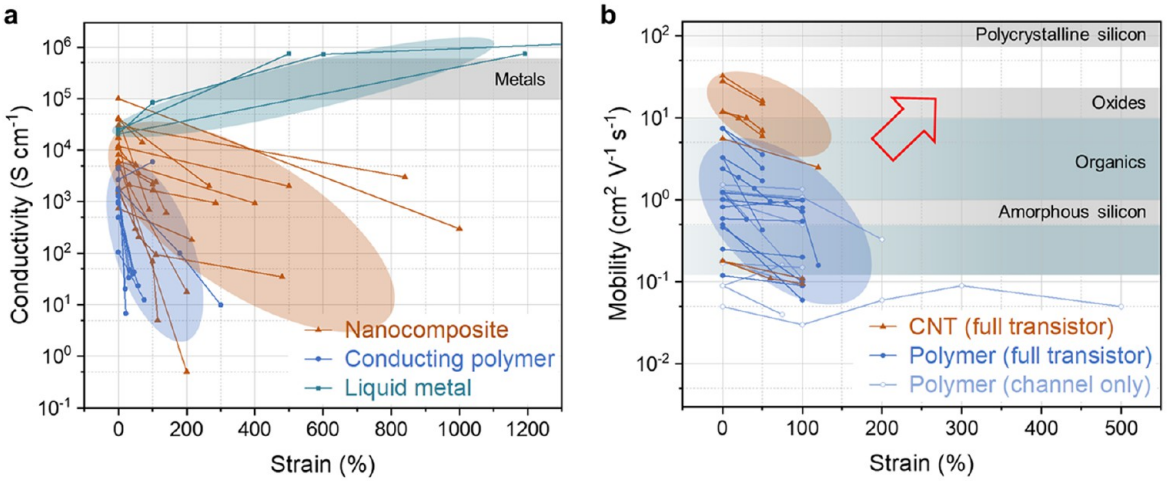

Figure 7. Performance of intrinsically stretchable (a) conductors and (b) semiconductors. (a) Intrinsically stretchable conductors are realized in three materials categories: nanocomposites, conducting polymers, and liquid metals; ionic conductors are not included. Conductivities of stretched liquid metals are calculated from resistance changes under unidirectional strain, based on the assumption of incompressible solid undergoing uniform deformation. Non-stretchable bulk metals are plotted in the gray band for comparison. Values extracted from refs 269, 285, 329−345. (b) Stretchable semiconductors are based on semiconducting CNTs or conjugated polymers. Mobility measurement was done in either stretched materials transferred to non-stretchable substrates (channel only) or fully stretchable transistors and transistor arrays (full transistor). Values for stretch directions both parallel and perpendicular to the channel length are included. Typical mobilities of common non-stretchable semiconductors are plotted in bands for comparison.[346] Red arrow indicates area for improvement. Values extracted from refs 323, 324, 347−364.

mechanically robust systems.[288] Liquid metal and conductive polymers are likely to play notable roles in these pursuits.

In parallel to engineering more robust interconnects, it is sometimes desirable to construct highly integrated systems without long distance interconnections, to minimize risk in failure and measurement instability. Such systems are like soft printed circuit boards (PCBs), where prepatterned interconnects on soft substrates are bonded to sensors and other functional components.[289] Furthermore, future flexible sensing systems will be multilayer assemblies for high-density integration and sophisticated functions. Vertical interconnect access (VIA) will then be essential. There have been efforts on VIA, but rigid materials remain the most common.[266,290,291] Future work may explore the principles introduced above for soft single-layer interconnections.[285] Another important factor to consider is the reusability of interconnects, which allows for replacement of flexible sensors. This strategy will be useful for disposable sensors, where rigid electronics (often integrated on a flexible PCB) are designed to be reusable. Reliable and reversible bonding is needed in this case.[292]

When physically integrated systems cannot deliver desirable mechanical stability, wirelessly connecting soft and hard subsystems can circumvent the issues associated with interconnection and sometimes even completely eliminate soft-hard interfaces.[293,294] In such cases, wireless communication will be challenged in bandwidth for large-scale sensing arrays and in reliability for sensors in deformation or motion.[295] With the fast-developing soft devices,[296−300] more components within a sensor system will be soft and flexible, and the soft-hard interface will be less and less an issue. The ultimate vision will be a fully soft system where soft-hard interfaces are mostly absent.

Large Elastic Range. Flexible sensors possessing reversible deformability should ideally have all the materials in the sensor deformed within their elastic limits. In some circumstances, large deformations are expected, such as devices integrated directly onto the skin (up to 60−70%[33]) or other organs (*e.g.*, heart, bladder). However, conventional electronic materials usually undergo brittle fracture or plasticity under a strain of ∼1%.[30] Hence, extending the elastic range on a system level beyond the intrinsic elasticity of constituting materials is often needed. Additionally, for practical applications, overengineering to strain values well exceeding the largest possible deformation that a sensor may experience is necessary for guaranteed mechanical safety.

There are well-established approaches to extend the elastic ranges of sensors made of brittle materials. Reducing thickness is the first approach and has been widely used to enhance the bendability of flexible electronics. Essentially, anything thinner can be flexed more.[301] 2D materials having atomic thickness are therefore intrinsically bendable, making them a popular choice for flexible sensors,[302,303] let alone their outstanding electrical, optical, and chemical properties. The second approach is to place brittle components on the neutral axis of a multilayer stack. This strategy often takes the form of polymeric encapsulations around a brittle layer, but the situation can become complex with increasing numbers of layers and large elastic mismatches between layers.[304−306] There is rich mechanics to explore for mechanically heterogeneous laminations. Building on bendability, stretchability is endowed by both structural[307] and materials[308] engineering. Wavy structures (both in-plane serpentine shapes[309] and out-of-plane buckling[310,311]), fractal patterns,[312] microcracks,[313] honeycomb architectures,[314,315] fibrous mats,[155] and woven textiles[32] are effective structural designs to confer minimally stretchable materials with large elastic stretchability. The mechanism is to convert macroscale stretching to localized bending and twisting, which are permitted by reduced thickness. Origami and kirigami employ similar concepts.[316] Moreover, for relatively rigid substrates such as leather and polyimide, adding a strain-isolation layer with substantially lower modulus (*e.g.*, PDMS) between inorganic active components and the substrate can effectively extend the system stretchability.[317,318] Structural design utilizes conven-

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tional electronic materials and processing techniques thereby offering greater electronic performance and industrial compatibility, but it introduces soft-hard interfacial instability and often sacrifices integration density to make room for sophisticated patterns.

Materials engineering towards intrinsically stretchable materials provides alternatives to these problems.[308,319−321] These strategies include fabricating nanocomposites with stretchable matrices, depositing liquid metal on elastic substrates or enclosing it within 2D or 3D elastic matrices, synthesizing functional stretchable polymers, and utilizing ionically conductive materials. Nanocomposites are a promising form of stretchable conductors, with the conductivities of the best performing composites approaching bulk metals (Figure 7a). Given the many available conductive fillers and matrix materials, composite materials properties can have wide ranges.[322] Current technical challenges are primarily low-cost and large-scale manufacturing and high-resolution patterning. On the other hand, functional stretchable polymer syntheses have advanced rapidly. Polymeric semiconductors have achieved carrier mobilities at 100% strain exceeding non-stretchable amorphous silicon,[323,324] although there remains room for improvement in mobility and stretchability (Figure 7b). In comparison, semiconducting CNTs[325] can achieve higher mobility, but strain usually causes permanent morphological changes in CNT networks, and strain-insensitive electrical performance is thus challenging to achieve.[326] In addition, energy dissipating (tough) interlayers with covalent bonding to interfacing materials could substantially increase the crack onset strain and thus delay the performance drop of conducting/semiconducting thin films on elastic substrates upon stretching.[327] Moving forward, to realize different types of sensing functions, stretchable material designs need to be created for other types of functional properties, such as electroluminescent and photoresponsive properties for optical sensing and electrochemical properties for biochemical sensing.[127,328]

The above mentioned materials target electronic sensors, where the mechanical brittleness of conventional electronic materials poses great challenges to sensor deformability. However, in biology, tissues are highly deformable yet have sophisticated sensing capabilities. Biological sensors work by the transport of ions, instead of electrons. Inspired in this direction, a strong impetus to develop ionotronics utilizing ionically conductive and highly deformable materials such as hydrogels,[296] ionogels,[172,365] and ionic elastomers[366,367] has emerged.[368] Without the requirement of incorporating electronic conduction, materials design is much simpler. To date, temperature sensors,[366,369] strain sensors,[365] pressure sensors,[366,370] electrophysiological electrodes,[371,372] and others have been realized. Major challenges in ionic sensors include adequate sensing modality and performance on par with those of electronic sensors, compatibility with electronic data processing modules, and device miniaturization.

We note that pursuing record high deformability may not always have practical significance. The purpose of high deformability should be articulated with respect to the intended application scenarios. Even for on-skin application alone, the range of tensile strain spans from 1% to 63% according to body location.[33] Therefore, the true requirement for practical applications should be determined case by case. For a sensor designed for skin integration, a stretchability of 1000% might be practically unnecessary.

Fatigue Resistance at Materials Interfaces. Improving fatigue resistance is important to sensor durability under cyclic loading and is particularly critical for mechanical sensors. The primary concern regarding fatigue resistance lies in interfacial delamination rather than the intrinsic fatigue properties of materials. This issue is closely related to soft-hard interfacial instability.[265] Hence, significant efforts should focus on optimizing sensor structures with coordinated materials properties to reduce stress concentration. Due to the multitude of materials and multilayer structures employed in flexible sensors, the mechanical interactions between layers and components can be complex. Therefore, fundamental studies on the failure mechanisms and failure criteria are important. For example, Cheng *et al.* developed an anti-fatigue strategy to prolong the fatigue life of 3D ribbon-shaped flexible electronics by switching metal-dominated failure to desired polymer-dominated failure.[373] Crack propagation in microcracked structures is another issue. Microcracks are introduced to render stretchability[313] or to improve sensitivity,[210] but they are usually unstable under cyclic loading. Crack engineering thus becomes important. Examples include substrate structural design[374] and initial crack length control.[375] On the other hand, improving the fatigue resistance of emerging soft materials such as hydrogels[213,376] may broaden their application space in flexible sensors.

Signal Stability under Mechanical Interference. Flexible sensors other than mechanical sensors should *not* respond to mechanical deformation, which can be regarded as a source of interference. Mechanical stability is an aspect of sensor stability. Because it is special for flexible sensors and represents a major challenge in sensing performance, we dedicate a detailed separate discussion to this issue.

Strain Effect Decoupling. Coupling of strain into the sensing function undesirably causes signals to shift under bending or stretching. Decoupling of deformation effect is therefore important to sensing accuracy. Most of the approaches discussed above to extend elastic range contribute to alleviating this problem, yet perfectly strain-invariant performance remains challenging to attain. The key is to minimize strain experienced by active components or to synthesize strain-insensitive active materials. In particular, the island-bridge layout is effective for array-type devices.[109,377] Active components with critical sensing functionality are connected by highly stretchable interconnects, and the majority of strain is borne by the interconnects, thereby minimizing alterations to the sensor output. To enhance the protection to active components, the island area is made more rigid than the surroundings by either inserting a hard platform[262] or tuning the chemistry of substrates.[378] Soft-hard interfacial instability is an important consideration in such systems. Another strategy is to use built-in circuits to compensate for strain-induced variation.[81,379] Since these strategies are poised to increase system design complexity, the realization of strain-insensitive sensor arrays with high density will rely on innovations in integration strategies and high-resolution high-yield fabrication. A recently proposed strategy[380] with potential to overcome these limitations is to bridge brittle functional thin films and stretchable conductors through ACFs, which, despite the cracking of functional thin films under tensile strain, offer alternative electronic conduction pathways that are unaffected by strain. The laminates demonstrated nearly strain-insensitive electrochemical sensing and stimulation using a library of brittle functional materials.

Motion Artifact Removal. Motion artifacts are noise in sensor output from motion and surface deformation of the

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monitored object. They overshadow true signals and cause measurement inaccuracy or reduced signal-to-noise ratio. Motion artifacts are a common problem for wearable and implantable sensors, and remain one of the biggest challenges for electrophysiology and its application in wearable healthcare and human-machine interfaces. The problem comes from sensor system mechanical instability, sensor-wearer interface instability, the complexity of human body movements, electrical signals generated by muscle movement, and disturbance of ionic charge distribution and dynamics inside tissues by deformation and perspiration. The first aspect has been addressed in multiple topics including soft-hard interfaces, elastic range, and strain effect decoupling. Here, we focus on strategies addressing the rest of the problems from sensor hardware optimization and signal processing.

For hardware optimization, the mainstream approach is to improve the conformability and adhesion of sensors on tissues (often skin).[381] Better conformability eliminates gaps between the sensor and the skin, and better adhesion promotes conformal contact[382] and stabilizes the interface during motion. These two factors together facilitate intimate and unaltered contact between the sensor and the skin during motion, thus reducing motion artifacts. To improve conformability, making sensors soft and stretchable is effective. This goal can be achieved through reducing device thickness for lower bending stiffness[383−386] and using polymeric materials with intrinsic low modulus and high stretchability.[387,388] For enhancing adhesion with skin,[387,389] van der Waals interactions are sufficient for ultrathin (<5 μm) devices,[382,390] while adhesive polymers or functional groups are necessary for thicker devices.[387,388] Electronic tattoo stickers[390−393] and *in situ* sensor fabrication directly on skin from liquid precursors[394,395] offer convenient ways to achieve conformability and adhesiveness simultaneously.

Pretreatment of skin, *e.g.*, hair trimming, alcohol wiping, helps to reduce surface roughness and to remove contamination for better conformability and adhesion, but compromises the convenience of point-of-care sensors. The recently proposed concept of using a damping hydrogel to eliminate low-frequency mechanical noises (such as walking and breathing) for measurement of high-frequency signals (such as speech and electrophysiological signals)[396] offers another materials engineering perspective to tackle motion artifacts.

On the systems level, special sensor layouts and system designs can also mitigate motion artifacts. For example, preparing arrays of sensors can enable a system to measure some physiological parameters despite small relative motion of the sensor and the body.[397] Employing multiple sensors with carefully designed application positions can help cancel motion artifacts in certain sensors.[398,399] Integrating other sensing modalities or mechanisms such as force, heat, magnetism, light, sound, and chemical, can buffer the influence of motion artifacts.

On the other hand, motion artifacts can also be properly handled by signal processing. Some easily distinguishable motion artifacts can be filtered by near-sensor circuits. Flexible organic electronic components, such as differential amplifiers and adaptive filters, can be seamlessly integrated with wearable sensors to perform noise reduction.[400] Noise can also be attenuated by algorithms. Beyond simple low-pass, high-pass, and band-pass filters, advanced signal processing methods such as wavelets and short-time Fourier transform have shown effectiveness in removing motion artifacts. More targeted motion artifact removal utilizes motion reference signals detected by micro inertial sensors, such as accelerometers or gyroscopes.[401] In such cases, motion artifact reduction in irregular and muscle strength exercises is challenging because accelerometer-based signals do not directly reflect muscular activities.[402] Recently, an "interface sensor" was proposed to capture the dynamic interactions between the skin and the sensor through proximity and pressure sensing. Using these types of reference signals, the estimated heart rate was determined more accurately than by conventional accelerometer-based methods.[403] Customized signal-processing strategies are needed to address human motions at different frequency, magnitude, and body position, as well as associated muscle electrical activity, deformation, and skin condition changes (*e.g.*, perspiration-caused impedance change).

Machine learning is promising for compensating for motion artifacts with greater customizability. For example, a deep learning framework accurately determined heart rate from photoplethysmography sensors without the use of reference motion sensors.[404] A neural network was trained to denoise the pulse wave signals by filtering the motion artifacts caused by respiration.[405] Such a data-based approach is more versatile and capable than optimizing hardware, first, because materials and device designs are likely to differ from application to application, and second, because amplifiers and filters can only remove noise over a limited specific spectrum. In contrast, machine learning algorithms can be iterated and updated to develop personalized motion artifact filtering protocols.

Overall, most work on minimizing motion artifacts targets electrophysiological sensors and optical heart rate monitors; future research should expand to explore other types of sensors. In particular, flexible optical sensors relying on light-matter interactions are sensitive to sensor-object relative orientation and motion, and most recently developed flexile optical sensors did not demonstrate reliable function in dynamic deformation or motion.[406−409] This issue presents a daunting challenge for flexible optical sensors. Signal processing through artificial neural networks has shown promise in overcoming this challenge.[410]

Damage Insensitivity. To maintain or to recover sensor function autonomously despite the presence of mechanical damage is the ultimate form of mechanical stability. To achieve this goal, mechanically tough, self-healing, and stiffening materials were developed, and damage-insensitive or protective structural designs were proposed.

Increasing fracture toughness helps prevent sudden failure in the presence of minor cracks. Common elastic materials used in stretchable sensors such as silicone rubbers easily break in the presence of notches due to low fracture toughness (*e.g.*, 310 J m^{-2} for PDMS[259]). To overcome this challenge, supramolecular elastomers with high fracture toughness (*e.g.*, 12,000 J m^{-2} and 30,000 J m^{-2})[411,412] were synthesized and further integrated with conductive materials to enable notch-insensitive anti-tearing stretchable conductors. Even at 250% of tensile strain, a notched conductor remained conductive without failure.[412] Meanwhile, great progress has been made over the past decade in improving the toughness of stretchable hydrogels (*e.g.*, 9,000 J m^{-2} by Sun *et al.*[413] and 14,000 J m^{-2} by Yang *et al.*[414]),[415] making them more stretchable and tough materials than some commercial elastomers. Furthermore, efforts in toughening 2D materials are producing promising results. The ability of graphene to resist fracture was significantly improved through topological design (*i.e.*, controlled distribution of topological defects including disclinations, dislocations, and grain bounda-

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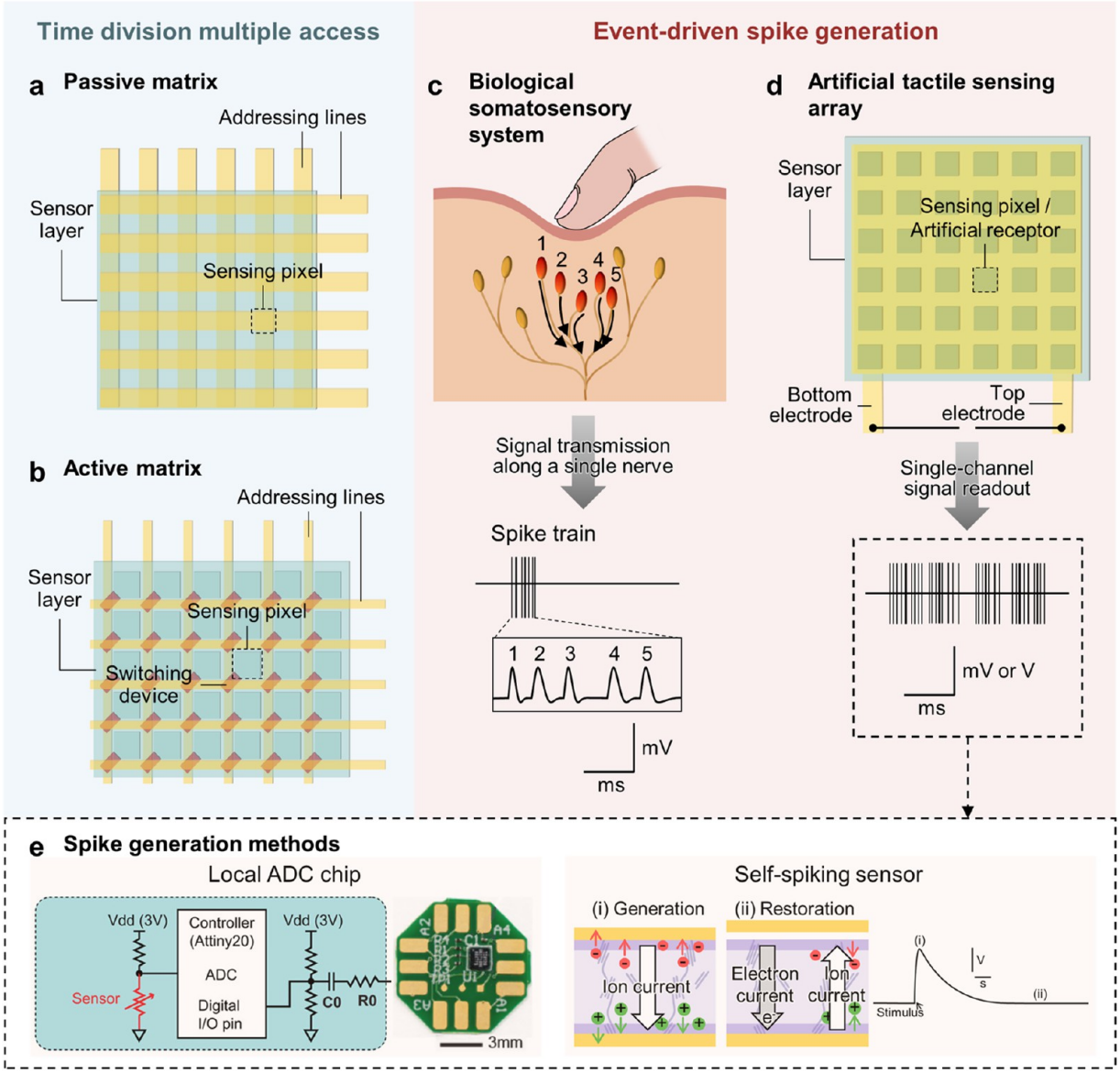

Figure 8. Conventional time division multiple access (blue panel) and emerging event-driven spike generation (red panel) as array data collection strategies. (a,b) Passive-matrix and active-matrix designs are the most commonly used array readout strategies. (c) Biological somatosensory system uses spike trains to encode tactile information with high spatiotemporal resolution and energy efficiency. (d) Artificial sensory systems can mimic the structure and function of the biological somatosensory system. Each sensing pixel generates potential spikes and is thus called an artificial receptor. (e) Two reported methods of generating spikes in individual artificial receptors include integrating an analog-to-digital converter (ADC) at each pixel and using sensing materials that can self-generate potential spikes. Circuit and photograph of one sensing pixel incorporating ADC adapted with permission from ref 464. Copyright 2019 American Association for the Advancement of Science. Schematics of self-spiking ion-electron conductor adapted with permission from ref 465. Copyright 2022 American Association for the Advancement of Science.

ries)[416] and integration with CNTs.[417] Hexagonal boron nitride, a dielectric 2D material, was reported to exhibit extremely high toughness,[418] which could provide mechanical protection in 2D devices. These advances offer potential opportunities for graphene and other 2D materials in flexible sensors.

Self-healing materials are designed to repair mechanical damage and to restore the sensing function, and the vision is to improve sensor durability and longevity, with an additional benefit of reduction in electronic waste.[419] Despite significant progress in synthesizing functional self-healing materials, including conductors[211,420] and semiconductors,[348,421] and fabricating self-healing sensors, such as strain sensors,[420,421] proximity sensors,[422] and humidity sensors,[423,424] self-healable sensors face many challenges for practical applications. Usually, the performance of self-healable materials and sensors is inferior to non-self-healable counterparts because self-healing materials are predominantly polymers with dynamic bonds and low glass transition temperatures. Furthermore, it is challenging to fabricate sensors using all self-healing materials and to ensure simultaneous self-healing of multiple components. Therefore, it might be wiser to incorporate only self-healing properties in the most mechanically fragile parts of the devices, such as surfaces superficial to the system. Lastly and critically, most devices that include self-healing materials simply demonstrate functionality. More effort should be directed towards understanding whether

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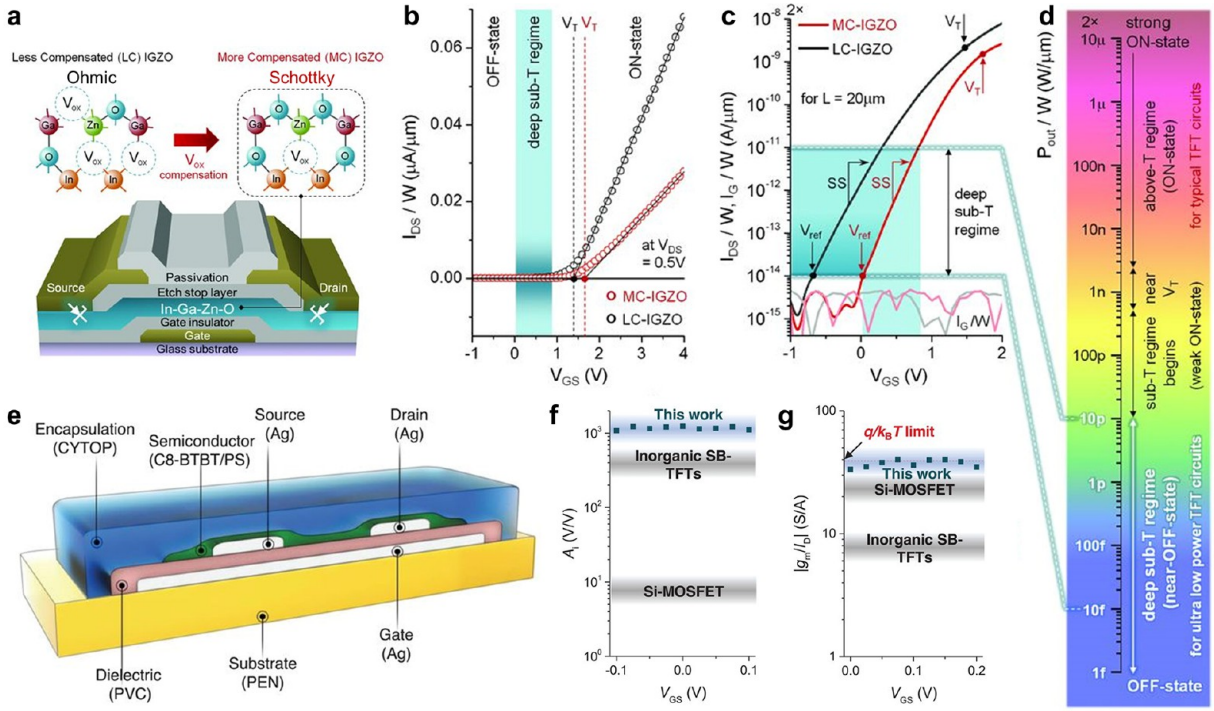

Figure 9. Subthreshold Schottky-barrier thin-film transistors (SB-TFTs). (a) Schematic of a metal oxide-based inorganic SB-TFT. IGZO, indium-gallium-zinc-oxide; LC, less compensated; MC, more compensated. (b,c) Measured input characteristics in linear scale (b), indicating V_T (the threshold voltage), and in logarithmic scale (c), indicating V_{ref} (the reference voltage), respectively. I_G, gate leakage current. (d) Conceptual color bar of output power consumption (P_{out}) for a 1 V supply, normalized with W (channel width), clearly indicating each operational regime. Frames a−d adapted with permission from ref 473. Copyright 2016 American Association for the Advancement of Science. (e) Schematic of an organic SB-TFT. CYTOP, a commercial fluoropolymer; C8-BTBT, 2,7-dioctyl[1] benzothieno[3,2-*b*][1]benzothiophene; PS, polystyrene; PVC, polyvinyl cinnamate; PEN, polyethylene naphthalate. (f,g) Comparison of intrinsic gain (f) and transconductance efficiency (g) of different transistors. Organic SB-TFTs have the best performance. MOSFET, metal-oxide-semiconductor field-effect transistor. Frames e−g adapted with permission from ref 198. Copyright 2019 American Association for the Advancement of Science.

self-healing materials can bring value to durability and longevity at device and system levels.[425]

Soft materials that stiffen at increasing strain, strain rate, *etc.* might serve as a mechanical protection mechanism for flexible sensors. Some examples include mechanochemical systems (*e.g.*, hydrogels) that become stiffer, stronger, and tougher after repetitive stretching,[426] stretchable composites and ionic elastomers with the J-shaped stress-strain curves exhibited by the skin,[367,427,428] and flexible, stiffness-changeable, and impact-protective polymers for potential impact- and puncture-resistant sensors.[429]

Besides engineering material properties, structural design provides another route to protection against damage. Discrete dispersion of rigid components in a soft polymer matrix has shown effectiveness in preventing damage by puncture or cut to the active components.[430] Stretchable armors composed of hard scales connected by soft elastomers enhance resistance to puncture, scratch, and cut, when used as an additional protective layer for flexible devices[431] or functionalized as standalone flexible sensors.[432] Such artificial armors with nature-inspired designs[433] may find wider application in wearable sensors and electronic skin. Additionally, design principles for mechanical metamaterials with extraordinary mechanical properties such as lightweight, high strength, large elastic deformation, high toughness, and supersonic impact resilience,[434−439] can be leveraged to engineer flexible sensors with high mechanical robustness.

The need to achieve mechanical robustness and stable electronic performance can be addressed, for some types of applications, with the use of liquid metals (*e.g.*, eutectic gallium indium),[440] which will likely be important components in stretchable sensors.[441] Liquid metals are softer than most sensor materials,[442] can sustain the largest strains of stretchable conductors,[285,345] suffer no fatigue issues,[285,342,443] and automatically self-heal when damaged.[342,345] There has been much progress in patterning liquid metals on flexible and stretchable substrates with sub-10-μm resolution[285,342,444−450] and processing liquid metals with industrially compatible techniques.[451] The key remaining challenges include: eliminating the risk of leakage,[452] tackling surface chemical instability,[453] and verifying biocompatibility for bio-interfacing applications.[454−456] Proper encapsulation will be critical to the practical application of liquid metals.[457]

Large-Area and High-Density Sensor Array Integration. Improving individual sensor performance sets the foundation for any large-scale integration. Flexible sensor arrays with large area and/or high spatial resolution find application in electronic skins, medical imaging, interactive displays, building-integrated electronics, among others; in these uses, flexible sensors have significant advantages over rigid counterparts. However, during array integration, challenges concerning pixel density and quality, readout efficiency, power management, and manufacturability arise; many of these issues are interrelated and call for holistic design and manufacturing strategies. Here, we discuss the most prominent challenges in signal readout and multimodal sensing.

Efficient Matrix Signal Readout. Efficient and high-quality signal readout is challenging in flexible sensing arrays that have

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high-density sensor pixels at large scales. Key targets in devising readout strategies include minimal crosstalk between sensor pixels, high signal-to-noise ratios, acceptable wiring complexity, low power consumption, small latency, small data size for transmission, manageable heat dissipation, and balanced demand on computational power for data processing.

Passive matrix and active matrix are the dominant architectures for array signal readout. A passive-matrix design, which consists of row and column lines and the sensors at the intersections (Figure 8a), is relatively easy to implement and to manufacture.[281,458] However, crosstalk between sensors *via* undesired current paths limits signal fidelity. Although highly complex readout circuits can solve this issue,[459] they introduce other problems such as reduced reading speed and accuracy, which can easily happen when the numbers of pixels become large (*e.g.*, 1000 × 1000 matrices). An active-matrix design tackles the issues of crosstalk and wiring complexity by placing electrical switches, such as transistors and diodes, at individual sensors (Figure 8b).[43,460,461] Transistors can also form amplifier circuits for local amplification at each sensing pixel.[360,462,463] Flexible active matrix is a mature technology in commercial displays.

Active matrices face challenges in electric interconnects and circuit solutions. For interconnection, the high impedance (>1 kΩ) of thin-film interconnects may lead to significant overheating and voltage drop when high electric currents (10−100 mA) pass through,[466] causing circuit failure and sensitivity loss, respectively. It is therefore beneficial to have high impedance ratios between sensors and connection lines, and the impedance of switching transistors in the ON state should be considered.[467] Furthermore, the high impedance of long interconnects and numerous overlaps between them lead to large time constants, crosstalk, common-mode noise and pickup of external electromagnetic interference during operation. In this regard, differential signal readout approach might be a universal solution.[468] For circuit solutions to drive pixels in an active matrix, the incompatible technologies for organic semiconductors (mostly *p*-type) and inorganic semiconductors (mostly *n*-type) result in difficult fabrication of complementary circuits (based on both *n*-type and *p*-type semiconductors).[469] Moreover, the possible variation of parameters between transistors in the matrix using immature materials or processes may lead to offsets, dead pixels, and variations in sensitivity. Bootstrap-type circuits will be strong candidates for overcoming these challenges.[470,471]

Transistors play pivotal roles in matrix signal readout, conditioning, and processing—their performance critically determines the signal-to-noise ratio and power consumption of the sensor matrix.[44] In this regard, current research aims at achieving comparable-to-rigid performance in stretchable transistors and arrays.[326,378,472] Improvements in operating frequency and voltage, strain-independent electrical characteristics, and power consumption are needed for effective matrix addressing. Meanwhile, unconventional operational principles may bring about substantial improvements in transistor performance. For example, subthreshold Schottky-barrier thin-film transistors (SB-TFTs) offer an ultralow-power and high-gain solution (Figure 9a−d).[473] Organic SB-TFTs can also be inkjet-printed while outperforming their inorganic counterparts (Figure 9e−g).[198] The electrical characteristics of SB-TFTs are geometry-independent, thereby accommodating the large dimensional variations in inkjet-printed devices. This feature is especially desirable in printed arrays. Amplifiers made of such SB-TFTs have ultralow power consumption (~600 pW peak power) with high gain (260 V V^{-1} peak gain), thereby achieving higher resolution (down to 3.8 μV) than other TFT technologies in electrooculographical recording.[198] While stretchable form factors of organic SB-TFTs are feasible *via* a helix structure,[474] future research in exploring large-area implementations of SB-TFT arrays may substantially improve the power efficiency and signal quality in flexible sensing arrays.

Conventional matrix solutions usually use time division multiple access for data collection, in which the changes of resistance or capacitance in all the pixels are sequentially scanned while continuously applying a bias (Figure 8, blue panel).[475] This approach suffers from limitations in energy efficiency, reading speed, and latency for high-fidelity large-scale array sensing. A hint for efficient signal readout with high spatiotemporal resolution might be obtained from the biological somatosensory system (Figure 8c). The sensory receptors generate potential spikes when an external stimulus is given.[476] As many as ~40 receptors are connected to one capillary nerve fiber, and the spike signals sequentially generated from the receptors form a bundle, called a spike train. Recognition is achieved by analyzing the patterns of the spike trains. Artificial sensor arrays mimicking such biological somatosensory systems (Figure 8d) can have multiple pixels sharing the same readout electrode/wire, thereby significantly reducing wiring complexity and readout latency. Moreover, pixel crosstalk is intrinsically not an issue, though more computational power is required for spike train analyses.[464] Lastly, using potential signal greatly reduces power consumption because the sensor pixels can be driven at low current.

Several recent reports employed this strategy and offered substantially improved sensor array readout performance. For example, Lee *et al.* proposed an asynchronously coded electronic skin (ACES) to address the large amount of pressure and temperature sensor data in electronic skins.[464] Analog signals from each sensor were converted to potential spikes by a microcontroller incorporating an ADC in each pixel (Figure 8e, left). Exceptional temporal precision of <60 ns was realized in a 240-pixel sensor array. However, distributing tiny rigid chips on flexible/stretchable substrates is a potential challenge for larger-area ACES. It would also limit device density (1 cm pixel pitch as reported[464]) and flexibility compared to active/passive matrices (<1 mm pixel pitch and full flexibility[459]). Kim *et al.* tackled this challenge by using a mixed ion-electron conductor with tunable ion relaxation time as the pressure-sensing material (Figure 8e, right).[465] An array of this material with differential properties encoded contact information (contact position and area) in output spike train signatures without in-pixel conversion by circuits, thereby improving integration density (529 pixels in 2 cm × 2 cm), system flexibility (fully flexible without rigid components), and power efficiency (no additional energy required to drive microcontrollers). Spatiotemporal resolution comparable to human skin was achieved (12−132 cm^{-2} and ≤250 Hz). Nonetheless, due to the simplistic system design, data complexity is inferior to the prior method—no quantitative contact pressure was directly attainable. Other self-spiking sensors, such as piezoelectric and triboelectric[477] tactile sensors and pyroelectric temperature sensors, are worthy of exploration and study.

Certain sensing mechanisms can also enable more efficient array signal readout. For instance, a potentiometric mechano-transduction mechanism for pressure sensing has been developed.[105] Unlike traditional resistive or capacitive sensors, this mechanism transduces pressure input into potential

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differences between two electrodes, allowing the configuration of a single-electrode-mode array with a common reference electrode, substantially reducing the number of wires and improving pixel density. Furthermore, crosstalk between pixels is minimal due to the negligible current flow, allowing simultaneous data acquisition from all pixels. Lastly, potentiometric sensing requires significantly less power (<1 nW) than conventional electronic skins. Tactile sensing arrays based on the triboelectric mechanism also have similar desirable features, as demonstrated in a 4 × 4 array.[477]

Optical readout, as an alternative to electrical readout, utilizes sensing materials or structures that report stimuli through luminescence,[478] color changes,[479,480] marker displacements,[481] or related means. It may offer better options for areal mapping because the optical output from the entire area can be accessed simultaneously without wires and circuits using well-established high-resolution cameras. However, image capture in real-world scenarios can lead to significant sensitivity loss and signal error due to suboptimal and changing lighting conditions, representing a major challenge for optical sensors. To tackle this challenge, a near-distance imaging scheme for mechanoluminescence-based pressure sensing was developed.[478] The proximity of the pressure-sensitive film and the underlying image sensor significantly improved sensitivity, giving rise to a small detection threshold at the kPa level (*vs.* typically being on the order of MPa in previous work). The use of micro- and nanoparticles also enabled high spatial resolution with a pixel size of ∼100 μm. However, the bulky and rigid complementary metal-oxide-semiconductor (CMOS) image sensor limits the wearability of the system. Nevertheless, portable optical imagers with compact design are practical to implement[481,482] and have been commercialized for tactile sensing.[483] In addition, magnetic sensing is an alternative wireless technique, which has been successfully applied for position and motion sensing,[484,485] as well as large-area tactile sensing.[486]

Compared with the readout circuits of temperature, pressure, and touch sensor arrays, data acquisition systems for ultrasound[487] and photoacoustic imagers are more complicated. Not only are the complexity of interconnects, but also the multichannel high-frequency sampling (usually >20 MHz for each channel) and ultrawide communication bandwidths (usually >1 Gbps for a system) are challenges. To address wiring complexity, row-column array is a simple and practical technique, although the crosstalk may be relatively high.[488,489] Semiconductor technology can integrate many channels of high-frequency ADCs into a small chip, or even design a local ADC bonded onto the sensor to address the multi-channel sampling problem.[490] Meanwhile, data pre-processing techniques such as transformation domain, sparse, and neural-network encoders that compress and package data at the front end in real time can help break the limitations of speed and latency in data transmission and post-processing.[491,492] High circuit sensitivity usually demands high power budgets.[397] Two recently reported techniques, resonant noise matching[493] and coherent detection,[494] were shown to increase sensitivity with modest power budgets.

While most current sensor matrices are developed for physical sensing, chemical sensing with high spatiotemporal resolution will offer vast opportunities in neuroscience and many other biomedical fields.[55,120,189,495−497] To this end, ensuring consistent and stable performance of each sensing pixel and integrating biosensing materials into microfabricated devices are great challenges.[498]

Multimodal Sensing in Compact Systems. In many scenarios, a large variety of sensors need to be implemented to obtain complex and comprehensive environmental and physiological information. The use of more than one type of sensors can also improve measurement accuracy and reduce the number of sensors required to generate insightful feedback.[499] Multimodal sensing[500] should therefore be an important feature of flexible sensors. There are generally two ways to achieve multimodal sensing: integration of multiple sensors into a single device or detection of multiple stimuli with a single sensor.[501]

The first strategy directly integrates various sensors by means of a matrix network or stack architecture.[109,290,502−504] Sensors in these systems are usually well established and have reliable performance. However, these systems require complex structure designs, fabrication, and signal readout and conditioning, hindering high-density array integration. Tackling these issues, simplistic array structure and sensor miniaturization through microfabrication of rigid materials have produced multimodal sensing arrays with reasonably high device density (*ca.* 1 mm sensor pitch).[109,505] Furthermore, the use of the same sensing materials[118,506] and the same type of output signals (and sensing mechanisms)[80,507,508] simplify manufacture and signal conditioning, respectively.

The second strategy is to realize simultaneous detection of multiple stimuli by a single sensor so as to allow high integration. This strategy will be helpful for applications with physical constraints in size, weight, and distribution. Such multimodal sensors should be able to decouple multiple stimuli without crosstalk. The most common method is to exploit differences in sensor responses to multiple stimuli for identification; some mathematics,[509] and/or machine learning algorithms[510,511] for data analysis are often needed. This approach might utilize the intrinsic multi-responsiveness of a single material,[82,510,511] a combination of different sensing materials in different parts of functional devices,[509] or arrangements of multiple sub-sensing units in 3D structures.[117] Another method is to use multiple measurement modes to decouple the signals,[111,512−515] which might suffer from complexity in signal readout and latency. The number of measurement modes (equations) should be equal to or greater than the number of stimuli (unknown variables). Performance of each sensing modality may not be optimal and difficult to improve simultaneously in such highly integrated sensors. Moreover, when a sensor becomes too multimodal, *i.e.*, simultaneously responsive to many stimuli, it can become difficult to differentiate the stimuli. In this case, integrating multiple sensors of slightly different responsiveness and analyzing the signals holistically may be a solution (much like selective sensing arrays).[155]

With regard to multimodal sensing, special concerns go to flexible image sensors and gel-based physical sensors. At present, most flexible image sensors cannot recognize multiple colors at the same time. Although color image sensing can be achieved with the help of bandpass filters, its process complexity and cost have yet to be resolved. Array integration of filter-free narrowband flexible photodetectors is critical to the preparation of color image sensors. An intrinsically stretchable phototransistor array was developed with the capability of red-green-blue (RGB) color image recognition using quantum dot-based nanocomposites for color sensitivity and an artificial neural network for compensation of mechanical deformation-caused errors.[410] Although the pixel resolution was rather low (∼1 cm pitch), this phototransistor array represents a big advance in flexible color image sensors. For gel-based strain/pressure/

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temperature sensors, there are many reports of multifunctional sensing under ideal experimental conditions where the stimuli not of interest are kept constant.[110,516,517] Future research should demonstrate decoupling these stimuli. Otherwise, the sensors can only be used in highly constrained situations, such as when there is only one stimulus without environmental interference or no quantitative information is required.[517]

SENSOR-BIOLOGY INTERFACE

A prominent advantage of flexible sensors is the ability to attach conformally on non-flat surfaces and to withstand dynamic deformations during use. This feature makes flexible sensors well suited for measurements on biological objects, including humans, animals,[518] plants, and even tissues and cells. Some future applications include wearable/implantable sensors for health monitoring and disease management,[49,50,54,519] neuroscience and biomedical studies,[520] human-machine interfaces, on-plant sensors for precision agriculture,[521−523] and many others. There have been tremendous efforts and progress in developing bio-interfacing flexible sensors, but most remain far from translation to practical applications. Bio-interfacing sensors should, on the one hand, acquire high-quality bio-signals across the biotic-abiotic interface and, on the other hand, not interfere with the normal function of biological organisms. These properties largely rely on compatible interfaces between biology and electronics, which, due to their distinct physiochemical properties, raise additional challenges (Tables 2 and 3 and Figure 10) on top of the sensing performance issues discussed previously. Although the issues presented here are categorized as materials orientated and form-factor orientated, many of them are interrelated (solid lines and arrows in Figure 10) and can be solved through the synergy of materials and form-factor approaches. For example, low bending stiffness, believed to render better biocompatibility to the sensing device, can be achieved through reducing the thickness of rigid electronic materials, varying film morphology and topology, synthesizing functional polymeric materials, or combinations thereof.

Since there is already a large and expanding collection of reviews on the topic of sensor-biology interfaces[33,49,50,74,138,249,519−522,524−534] dissecting the challenges and issues in great depth and detail, we will only touch on the overall trends in the field and highlight critical challenges that deserve special attention, in the general context of flexible sensor technology. Readers can refer to references in Tables 2 and 3 for further details.

Bio-Interfacing Materials. The most important consideration in developing bio-interfacing materials is biocompatibility. Although biocompatibility is a term frequently appearing in publications on bio-interfacing materials and sensors, more thorough understanding and investigation are needed. Biocompatibility tests are specified in a set of standards: ISO 10993-Biological evaluation of medical devices.[537] Depending on the position and duration of a tissue-contacting device, the tests required to perform vary. These may include tests for cytotoxicity, sensitization, irritation or intracutaneous reactivity, systematic/acute toxicity, subacute and subchronic toxicity, genotoxicity, among many others. Cytotoxicity tests alone do not determine biocompatibility, and biocompatibility without considering position and duration of tissue contact is meaningless, because the biological effects a material/device imposes on tissues vary significantly with these two factors. Researchers should be cautious when commenting on the biocompatibility of their devices—by providing strong evidence, defining clear scopes, and making conservative conclusions—as in refs 547 and 569.

There are many discrepancies in the biocompatibility claims of emerging materials for flexible sensors, especially nanomaterials like graphene and CNTs. This issue stems partly from the non-standardized tests conducted in different studies, and partly from the large variations in material properties due to poorly controlled syntheses and large varieties of sizes, geometries, and surface states that nanomaterials can have.[525,631,632] Defining the biocompatibility of nanomaterials requires standardization and large-scale efforts, which will take years and even decades to carry out. In this process, standards organizations (*e.g.*, International Organization for Standardization, ISO; International Electrotechnical Commission, IEC),[633] regulatory bodies (*e.g.*, the U.S. Food and Drug Administration, FDA),[536] as well as consortia and communities in related areas (*e.g.*, Institute of Electrical and Electronics Engineers, IEEE; International Union of Pure and Applied Chemistry, IUPAC) should lead the effort. Before specific standards are available, researchers should refer to similar standards like ISO 10993[537] for experimental design and report details in materials, equipment, procedures, and results using standard methods, without bias.

One specific biocompatibility problem is immune response, which should be carefully dealt with for user safety and acceptance and for sensor performance. Immune response varies greatly from person to person; some people are allergic to materials claimed to be biocompatible for the majority of user populations. For example, in rare cases, people with circulating anti-PEG (poly(ethylene glycol)) antibodies can experience fatal anaphylaxis to PEG-grafted drugs.[634] Risks associated with hypersensitive immune systems should be evaluated and clearly communicated to potential users. On the other hand, although some immune responses are not hostile and detrimental to the human body, such as fibrous capsule formation, where no serious inflammation occurs, the insulating capsule greatly deteriorates sensor performance. In such cases, it is desirable to eliminate, not only to suppress, immune responses. Current strategies focus on controlling the mechanical properties of sensors, such as reducing bending stiffness by reducing thickness and utilizing soft polymeric materials. However, device surface chemistry and morphology also play important roles in cell-materials interaction,[635] which should be explored for bio-interfacing sensors.

A major trend in materials engineering towards a more compatible sensor-biology interface is to synthesize tissue-like polymeric materials with mechanical, electrical, optical, or other functional properties (Figure 11, left). Thanks to the multi-length scale and diverse molecular design in polymeric materials, many properties can be precisely tuned and combined in a single materials system, such as softness, stretchability, adhesiveness, conductivity, biodegradability, stimuli-responsiveness, *etc.* Supramolecular polymeric materials[636] and conjugated polymers are examples of promising polymer platforms. Hydrogel, in particular, is gaining traction because of its compositional resemblance to biological tissues—water-rich and ion-conductive.[637,638] Synthetic hydrogels and hydrogels derived from biopolymers (*e.g.*, proteins, nucleic acids) have advanced significantly in functionality and performance in the past decade, and there is a rapid expansion of hydrogel-based or hydrogel-enhanced sensors.[296,524,639−641] Nonetheless, hydrogels, and polymers in general, still often fall short in functional performance relevant to sensing, particularly in conductivity and stability, compared to conventional inorganic electronic

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Table 2. Materials Considerations in Achieving Compatible Sensor-Biology Interfaces[a]

Issues	Importance	Challenges	Solutions and their limitations	Ref
Materials issues				49,50,374,519,520,526,527,535−539
Tissue-like mechanical properties (*e.g.*, Young's modulus, bending stiffness, stretchability)	Biocompatibility	Intrinsic limitation of electronic materials	Size reduction to the subcellular level: difficult handling and connection, simple functionality	540−543
	Sensor integrity and stability	Microscopic perception by cells	Functional hydrogels: limited performance and functionality, difficult miniaturization	370,372,544−548
	Conformability	Insufficient mechanical match of plastics and elastomers	Soft network materials: complex fabrication, challenging design and fabrication of 3D tissue-like materials	549
	Wearing comfort	Unusual mechanical properties of tissues (*e.g.*, viscoelasticity, J-shape stress-strain curves)	Hierarchical structures: limited fabrication methods and materials	550
			Stiffness-varying polymers: unexplored device integration, unverified biocompatibility	551,552
Tissue adhesion	Conformability	Robustness in dynamic deformation and harsh environmental conditions (*e.g.*, UV light, heat)	Mechanical contact by pressure: discomfort, risk of sensor sliding and friction, associated signal inaccuracy and tissue irritation	553
	Motion artifacts	Robustness on contaminated surfaces (*e.g.*, water, perspiration, skin secretion, cosmetics)	Medical tape: weakened by sweat and water, painful peel-off, no stretchability	554
	Device fixation	On-demand removal without residual or pain	Physical adhesion: only applicable to ultrathin devices	390,555
	Wearing comfort	Biocompatibility	Bioinspired adhesive architectures: complex manufacture, added volume	242,556−558
		Tissue-like mechanical properties	Adhesive hydrogels: large thickness, humidity sensitivity, poor permeability	387−389,546,559−563
			Dry adhesive polymers: limited mechanical compliance, unverified biocompatibility	564−567
			Additional adhesion control layer: one-time use, added volume, weight and complexity	568
Biocompatibility	Health and safety	Intrinsic limitation of electronic materials	Approved materials and biological materials: limited materials choices, limited performance and functionality	
	Sensor stability	Lack of knowledge of emerging materials	Surface treatment (nanostructures, hydrogel coatings, *etc.*): complex fabrication	524,569−571
		Nonhostile immune responses	Biohybrid implants: challenging design and fabrication	528
		Long-term effects	Tissue-like mechanical properties: limitations therein	
			Large-scale, systematic tests: lengthy process, application dependence, variance in materials	
Biodegradability	Surgical device removal	Whole-device biodegradation	Dissolvable inorganics plus organic substrates: limited choice of materials, risk of high elemental dosage	107,572−574
	Tissue regrowth	Biocompatible degradation products	Functional organics: limited performance and functionality	107,575
	Chronic health risk if not retrieved	Tuneable device lifetime	Components other than sensor outside body: wireless communication limitations, safety risks associated with percutaneous wires	572
			Systemic biocompatibility tests: lengthy process, species dependence	
Electrochemical compatibility	Signal-to-noise ratio	Ionic-electronic transduction	Conducting polymers: insufficient conductivity, difficult miniaturization	343,546,547,576,577
	Electrode size (array resolution)	Low frequency signals	Hydrogels and their composites: insufficient conductivity, difficult miniaturization	524,578
	Biocompatibility			
Growth adaptability	Conformability	Intrinsic limitation of manmade solid materials	Viscoplastic electronic materials: initial demonstrations only	579
	Biocompatibility	Minimal physical constraint on tissues		

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Table 2. continued

Issues	Importance	Challenges	Solutions and their limitations	Ref
	Fast-growing tissues and/or long-term use			

[a]Their importance, specific challenges, reported solutions to these challenges, and limitations of the solutions are listed briefly.

materials. Moreover, miniaturization is challenging, and fabrication is incompatible with current microfabrication facilities. These factors make the adoption of emerging polymeric materials challenging.

Tackling the limitations of polymeric materials, a second important research direction is the discovery/endowment of bio-relevant properties in conventional electronic materials, so as to leverage their advantages in patternability, processability, and electronic performance. Biodegradation of metals (Mg, Zn, Fe, *etc.*), semiconductors (Si, Ge), and ceramics (SiO_2, MgO, Si_3N_4) has been exploited for transient and bioresorbable bioelectronics.[519] When made ultrathin (<1 μm), the mechanical mismatch between these intrinsically rigid materials and biological tissues can be reduced. Many bioresorbable sensors made of thin-film inorganics have been reported to demonstrate good performance and biocompatible degradation *in vivo*.[572−574] However, large-scale, long-term, and systemic tests need to be done on more animal species including humans before conclusions can be reliably drawn on the biocompatibility of degradation products. Surface nanotexturing of inorganic electrodes has shown improved cell attachment and suppressed inflammation for neuroprobes.[569,570] Compositing inorganic materials with soft polymeric matrices reduces mechanical mismatch with tissues, and often requires nanofillers such as nanoparticles and nanowires.[642]

Overall, to solve the sensor-biology mismatch problem from a materials perspective, it is challenging to achieve all desirable properties (*e.g.*, mechanical compliance, adhesion, biocompatibility, electrochemical compatibility, growth adaptability) in one material[110,546,548] while retaining sensing performance comparable to conventional sensor materials, and it is even more daunting to ensure *all* materials within a system possess these properties. Therefore, rational design in device architecture to combine materials with complementary properties is necessary to achieve device-level tissue compatibility.

Biofriendly Form Factors. Form factors of bio-interfacing flexible sensors are evolving to thinner, lighter, more miniaturized, intricately structured and porous, highly integrated, and customized architectures (Figure 11, right). These features aim for the common goal of minimal interference with biological activities yet intimate tissue contact for better signal quality. The realization of these advanced form factors relies heavily on nano-/microfabrication, which endows sensors based on conventional electronic materials with almost all desirable bio-interfacing properties (Table 3), *i.e.*, conformability, permeability, imperceptibility,[596] minimal invasiveness, and 3D tissue coverage.[542] In addition, 2D materials, such as graphene,[608] MoS_2,[460,582] $PtSe_2$, and $PtTe_2$,[645] provide another means to attain the desirable form factors. Nevertheless, the fundamental limitation of these form factors lies in mechanical fagility,[555] because rigid materials have to be made ultrathin (<100 nm) with cell-compatible feature sizes (<10 μm) to be tissue-compatible. The lack of mechanical robustness makes manufacturing, handling, and applications challenging and impairs sensor stability. These issues often prevent real-world deployment, despite the use of well-established materials and processes. Improving mechanical robustness should be a priority for future research on imperceptible bio-interfacing flexible sensors.

Flexible hybrid electronics is one of the most promising form factors for bio-interfacing flexible sensors[38,50,529] to be deployable in the near future. Yet compared with other form factors such as textiles and tattoos, flexible hybrid electronics are

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Table 3. Form-Factor Considerations in Achieving Compatible Sensor-Biology Interfaces[a]

Issues	Importance	Challenges	Solutions and their limitations	Ref
Form-factor issues				33,49,529,532,580,581
Conformability	Signal quality	Intrinsic limitation of electronic materials	Ultrathin films including 2D materials: mechanical fragility, unstable interface to external circuits	386,390−392,460,555,582
	Motion artifacts	Microscale surface morphology	Soft, stretchable, viscoelastic, and adhesive polymers: limited performance and functionality, risk of irritation, difficult miniaturization	372,387−389,545,345−347,548,560,564,565
	Heat and mass transfer	Irregular and complex 3D shapes	Substrate structural engineering: complex manufacturing, added volume	583,584
		Dynamic surfaces	2D to 3D transformation: simple topography, tissue-incompatible processes	585−588
			Sol-gel materials: simple functionality	371,589
			Draw-on, print-on, and spray-on sensors: simple functionality, poor reproducibility	394,395,590−593
Permeability	Wearing comfort	Not a designed function of conventional sensors	Nanomeshes, 2D materials, and porous materials: mechanical fragility, unstable interface to external circuits	461,504,555,582,594−599
	Biocompatibility	Encapsulation		
	Reliable adhesion	Whole-device permeability	Textiles (fibers, yarns, fabrics) and multifunctional integration: degradation upon washing, rigid processors and other modules impairing wearing comfort	32,103,600−606
	Long-term use		Ultrathin hydrogels: initial demonstrations only	607
Imperceptibility (Light weight, miniaturization, tissue-like mechanical properties, no tether)	Invasiveness	System-level imperceptibility	Ultrathin and mesh films including 2D materials: mechanical fragility, challenging system integration	56,57,309,390−392,582,596,608
	Comfort and convenience	Packaging volume	Fiber sensors: difficult handling unless integrated into textiles	600,609,610
	User compliance			
Minimal invasiveness	Health risks	Skin barrier	Noninvasive deep-tissue sensing techniques: limited penetration depth, spatial resolution, temporal resolution, and wearability	390,566,611
	User acceptance	Deep-tissue signals	Microneedles: complex fabrication, low motion tolerance, ineffective passive sampling, difficult quantitative chemical sensing	612−619
		Biofluid sampling	Active biofluid induction: additional electrode and power supply, risk of irritation, concerns on drug intake	174,616
		Large device implantation	Injectable microsensors: difficult handling and connection, simple functionality	540,542
			Fiber sensors: small sensing area, difficult implantation, challenging system integration	127,544,620,621
			Contact lenses: small area, difficult integration	249,252,445,622,623
3D tissue coverage	Surface sensing on complex 3D structures	Minimal invasiveness	Self-expandable or multimodule microsensors: difficult handling and connection, simple functionality	540,542,624
	Interior sensing of bulk tissues	Precise positioning		
	Volumetric mapping	Spatial resolution	Cell seeding on electronic scaffolds: inapplicable to grown tissues	625
		End-of-life withdrawal/ degradation	Developmental biology-driven 3D assembly: inapplicable to grown tissues, cell-type limitation	527,543,626
		Immune response	Mechanics-guided 3D assembly: complex inverse design, challenging micro/ nano-scale fabrication	627−630

[a]Their importance, specific challenges, reported solutions to these challenges, and limitations of the solutions are listed briefly.

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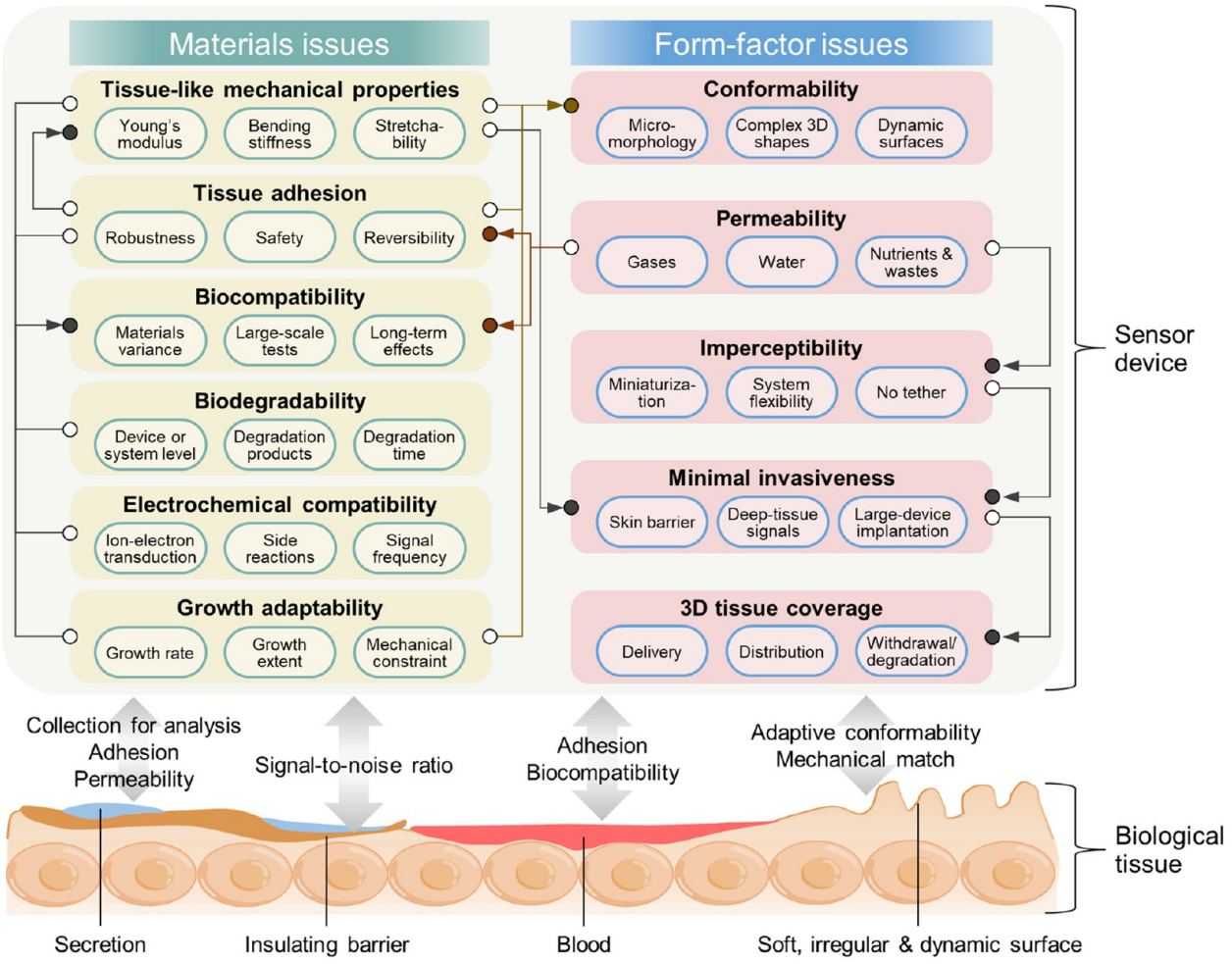

Figure 10. Challenges in achieving compatible sensor-biology interfaces. Arrows indicate the influence of one property (open dots) on another (solid dots). The issues stemming from different features of biological tissues are stated at the sensor-tissue interface and indicated by thick gray arrows.

still relatively bulky and hardly permeable. To tackle this problem, a possible evolution pathway of flexible hybrid systems could be to move non-sensor components away from directly contacting the tissue. This strategy can eliminate many issues arising from device-tissue interfaces. Meanwhile, more effort should focus on sensor optimization to make it perfectly match the tissue, and the communication between the sensor and the rest of the system should rely on wireless technology, which is critical for Sensors 4.0 in general. This concept has been demonstrated to resolve the soft-hard interface instability issue.[293] Many more issues could be solved using this strategy.

Textiles are another form factor that holds great promise.[646−648] Many advanced functions have been demonstrated on textile platforms, and integrated systems can achieve energy harvesting, energy storage, sensing, display, and simple signal processing.[604,649,650] Furthermore, industrial scale or industry-compatible production has been reported,[553,605,606,651,652] and commercial products have started to emerge.[646] Smart textiles might not be far from large-scale deployment. Nevertheless, textile sensing systems face challenges in washability, durability, wearing comfort, necessity of rigid modules, and aesthetics.

Another trend is the shift from 2D planar devices to 3D volumetric devices, in order to acquire information on 3D structured surfaces or across 3D volumes of biological tissues. While the field is in its infancy,[532] progress has been made, such as injectable self-expanding neural microelectrodes,[540,542] hybrid cardiac patches with multifunctional electronics,[625] and cyborg organoids.[626] A recent concept was proposed to build tissue-like systems from the bottom up largely or entirely using synthetic materials, mimicking the morphology, hierarchical structures, and functional properties of biological tissues.[530,653] *In situ* fabrication of materials and devices within biological organisms and tissues[530,654,655] is blurring the boundaries between manmade devices and natural organisms. More advanced functions will come at the interfaces between electronics and biology.

The form-factor challenges in compatible sensor-biology interfaces include mechanical robustness of nano-/micro-fabricated materials and devices, unaltered sensing performance, and reliable system integration between system components and with biological tissues. Innovations in device structural design, system layout and operation, and materials manufacture will bring about more effective solutions to these challenges and form factors that are presently rare (*e.g.*, mask,[130,256,656,657] suture,[658] or bandage[563]). Importantly, to design and to engineer materials and form factors that allow seamless integration with biological tissues, it is essential to understand in detail and in depth the anatomy, physiology, material properties, biological functions, *etc.* of the tissues of interest.

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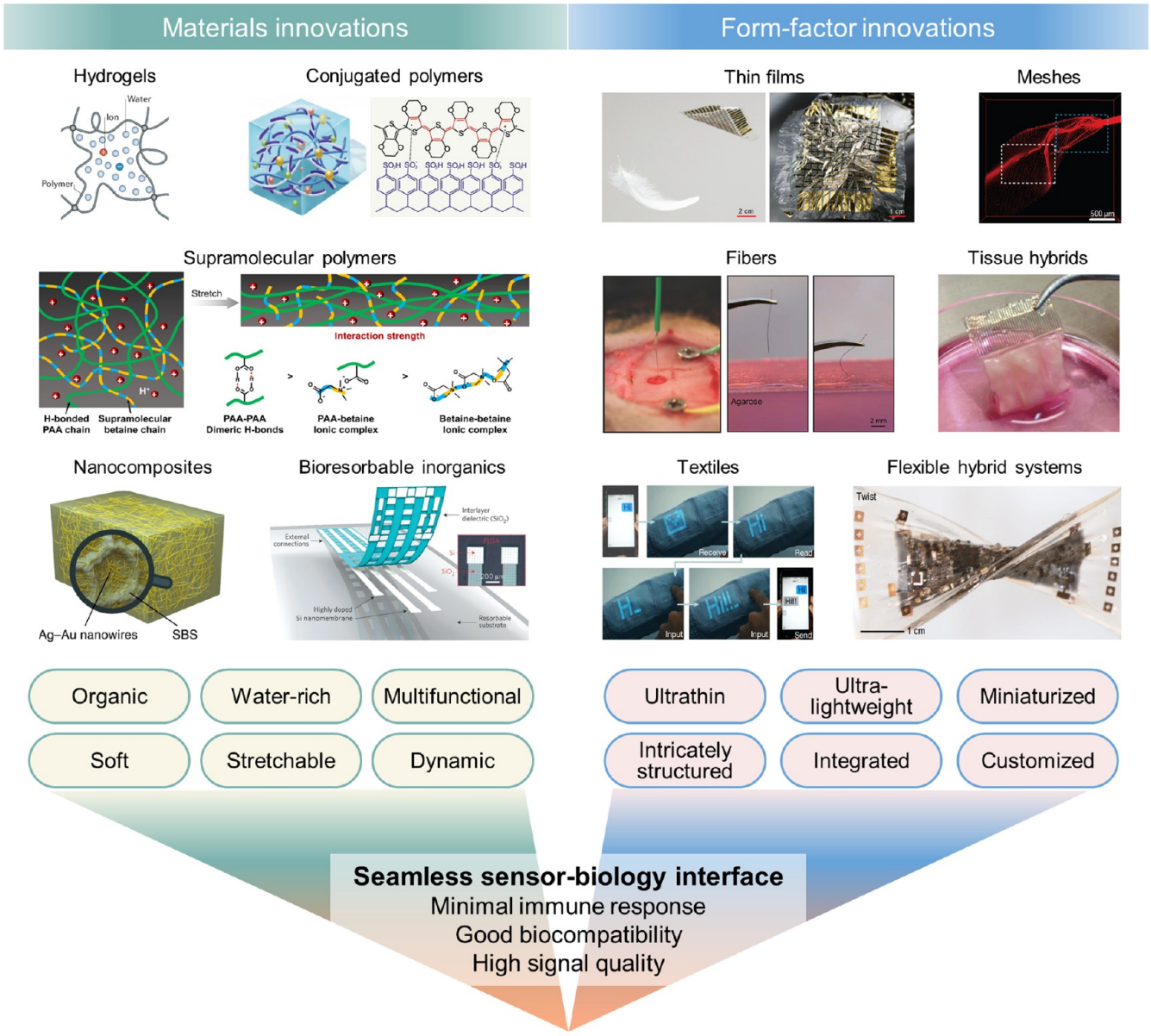

Figure 11. Major innovations in materials and form factors, respectively, towards seamless sensor-biology interfaces. Materials innovations images (from left to right, top to bottom): Adapted with permission from ref 296. Copyright 2018 Springer Nature. Adapted under the terms of the Creative Commons CC BY license from ref 565; published 2022 Springer Nature. Adapted under the terms of the Creative Commons CC BY license from ref 367; published 2021 Springer Nature. Adapted with permission from ref 337. Copyright 2018 Springer Nature. Adapted with permission from ref 643. Copyright 2016 Springer Nature. Form factor images (from left to right, top to bottom): Adapted with permission from ref 56. Copyright 2013 Springer Nature. Adapted with permission from ref 540. Copyright 2015 Springer Nature. Adapted with permission from ref 644. Copyright 2017 American Chemical Society. Adapted with permission from ref 625. Copyright 2016 Springer Nature. Adapted with permission from ref 605. Copyright 2021 Springer Nature. Adapted with permission from ref 290. Copyright 2018 Springer Nature. PAA, polyacrylic acid; SBS, poly(styrene-butadiene-styrene).

POWER SUPPLY

Power supply is foundational to the proper functioning of sensing systems. As flexible sensors take on more advanced functions and diverse form factors in more use cases, challenges emerge in sustainably and reliably powering sensing systems and networks.[659]

The power consumption of integrated sensing systems, including sensors, signal processing circuits, microcontrollers, communication modules, *etc.* as well as the interconnections between these elements, can be substantially higher than sensors alone[660] (as a reference, the power consumption of a smartwatch fluctuates within 10 mW−10 W whereas that of commercial sensors normally sits in the range of 0.1−10 mW). Large-scale (and multimodal) sensor arrays requiring simultaneous readouts of massive sensor pixels impose huge energy budgets. Systems performing continuous monitoring demand constant power supplies. All these factors contribute to high power demands of next-generation flexible sensing systems, which are not met by conventional energy storage devices.

As more sensing architectures and frameworks emerge, associated physical and resource constraints limit the use of conventional power supply strategies. For example, highly dispersed building-integrated sensor networks can have

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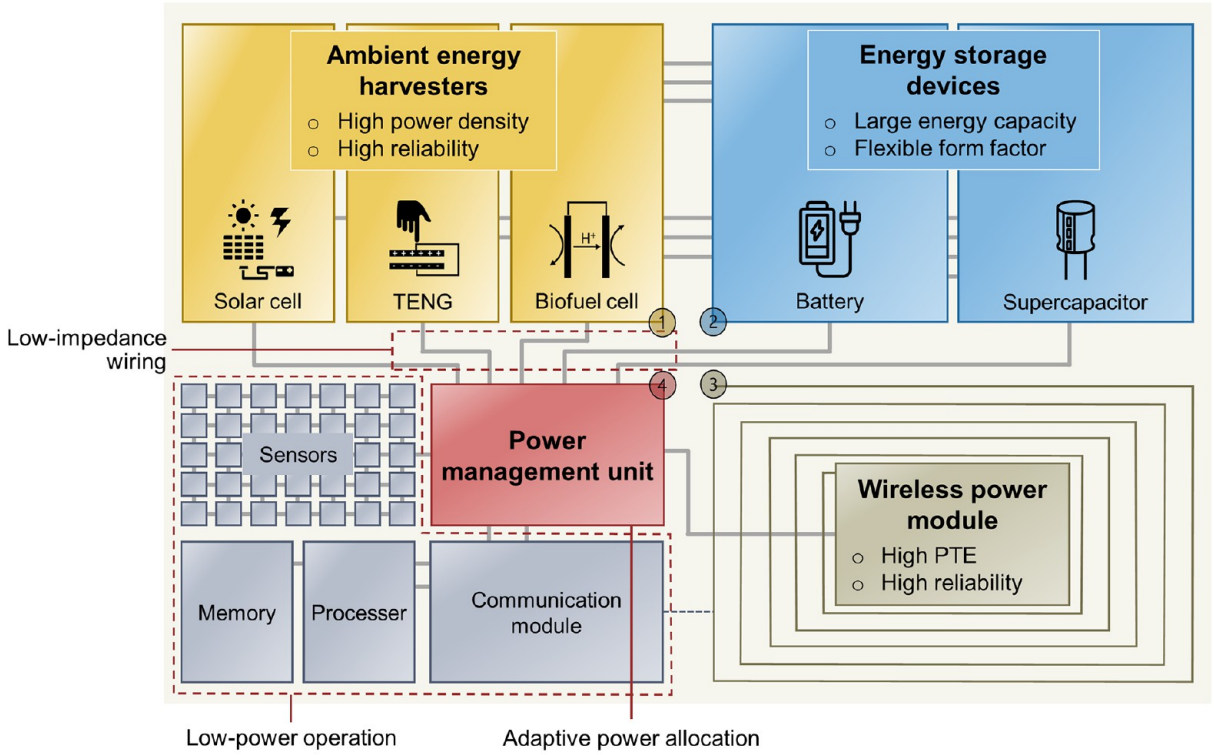

Figure 12. An energy-efficient sensing system incorporating multiple strategies for power management: reliable and high-power ambient energy harvesting (representative devices for light, mechanical, and chemical energy harvesting are shown; full list of devices is provided in Table 4), large-capacity energy storage in flexible form factors, reliable and efficient wireless power transfer, and systemic power management. TENG, triboelectric nanogenerator; PTE, power transfer efficiency.

hundreds of sensor nodes. Installing power points to each sensor node or replacing batteries periodically is expensive, cumbersome, and wasteful. Body area networks employing dozens of body-worn sensors require tetherless power sources that do not need frequent battery replacement for individual sensors.

The form factors of traditional rigid and bulky batteries hinder system miniaturization and introduce soft-hard interfacial instability,[61,63,661] retarding progress towards compact and compliant sensing systems.[274]

Battery safety is a significant issue and is in the spotlight after incidents of fires and explosions associated with battery malfunction. For human-centric sensing applications, safety of the power supply system is of paramount importance. Accident-proof designs are required, as are biocompatibility and heat-generation considerations.

Last but not least, against the backdrop of pressing sustainability crises, the currently environment-damaging materials, manufacture, and disposal of batteries call for greener energy sources in place of fossil fuels and rare materials.

Here, we discuss potential solutions to these challenges in four areas: ambient energy harvesters, energy storage devices, wireless power transfer, and system power management (Figure 12).

High-Power Ambient Energy Harvesters. The idea of having a sustainable power source near the sensor can be realized by miniaturized ambient energy harvesters integrated into the sensor powering system, which convert energy in the surroundings of the sensor into usable electricity.[662] This extra energy source then provides power that can be additional to batteries for power-demanding systems and may be sufficient on its own to power devices or systems. Some energy harvesters also have sensing functions, thus working as self-powered sensors. Ambient energy harvesters make battery-free sensors possible, significantly simplifying maintenance and reducing carbon footprint.

Common types of ambient energy harvesters used in flexible sensing systems are summarized in Table 4. Mechanical,[663,664] thermal,[665−667] electromagnetic, and chemical energies[668,669] can be harvested using portable devices, and their flexible and stretchable formats facilitate compatible integration with flexible sensors.[299,670−674] In addition, the recently demonstrated thermoradiative diode[675] may find use in cold environments in the future. Among these technologies, photovoltaics are the most mature with a long market history. Current research seeks to endow photovoltaic devices with greater biofunctionality such as conformability, softness, ultralightweight,[676] biocompatibility, biodegradability,[677] *etc.*,[672,678] as well as to develop printable manufacturing.[28,679−681] Meanwhile, exploring cheaper, safer, more stable and efficient materials is a constant pursuit.[682,683] Solely photovoltaically powered systems are feasible[676] due to the high energy density of solar radiation and the high power density of photovoltaic devices, and tuning the responsive wavelength to the near-infrared region allows for subcutaneous power delivery using an external light source.[677,684]

Another promising device is the triboelectric nanogenerator (TENG).[726] Despite its short history,[727] TENG has witnessed rapid development, and is a highly promising technology for sustainable power supplies.[728] It has high output performance (output energy density of 10^4 J m^{-3} and instantaneous power density of 10 MW m^{-2}),[692,729] as well as ultra-broad materials availability at relatively low cost,[730] simple fabrication, and

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Table 4. Ambient Energy Harvesters Used in Flexible Sensing Systems[a]

Energy source	Mechanism	Sensing function	Peak power density	Flexible form factor	Ref
Movement (touch, friction, bending, stretching, impact, vibration, sound & ultrasound, *etc.*)	Piezoelectric (also for acoustic wireless power transfer)	Strain, pressure, pulse	3–9.3 kW m^{-3}	Sheets, (ultra)thin films	685–687
			1.25 W m^{-2}	Fibers, fabrics (stretchable)	688,689
			26 mW m^{-2}	Stretchable sponges	690
	Triboelectric	Touch, pressure, strain, breath, vibration, sound, acceleration, gas, humidity	Up to 10 MW m^{-2}	Sheets, sponges	691,692
			4.3 μW m^{-1}, 1.77 W m^{-2}, 230 mW m^{-2}	Fibers, yarns, fabrics (stretchable)	689,693–695
			35 mW m^{-2}	(Self-healable) stretchable slabs	696,697
	Piezoelectric + triboelectric	Touch, bending, stepping	2.34 W m^{-2}	Stretchable fabrics	698
	Magnetoelastic	Pulse, breath, touch, pressure, bending, stepping	20–43.2 W m^{-2}	Stretchable slabs, sheets	65,68,169,208
			6.67 W m^{-2}	Stretchable fibers and fabrics	66,67
	Magnetoelectrical	Arm waving, strain	3.2 W m^{-2}	Yarns, fabrics	699
			Peak power: 20 μW	Stretchable yarn and ring	700
	Electrostatic	Stretch, twist, compression	0.55 mW m^{-2}	Stretchable slabs	701
Radiation (sunlight, light emitting diode, laser, *etc.*)	Photovoltaic	No	11.5 W g^{-1} (PCE[b] 10.5%), 4.4 W g^{-1} (PCE 5.8%), 180 W m^{-2} (PCE ~19%)	(Ultra)thin films	676,682,702,703
			2.53 mW m^{-1}, 0.61 W m^{-2} (PCE 11.9%)	Fibers, fabrics	678,704
Heat	Thermoelectric	Temperature	111 W m^{-2} at 50 K ΔT, 188 W m^{-2} at 80 K ΔT	Sheets, films	705,706
			6.5 W m^{-2} at 60-K ΔT	Stretchable slabs	707
			110 W m^{-2} at 70-K ΔT, 23 W m^{-2} at 60-K ΔT	Fibers, fabrics	708–711
	Thermocell	No	0.6–0.7 mW m^{-2} K^{-2}	Stretchable slabs	712,713
Water (moisture, humidity, sweat)	Hydrovoltaic	No	760 μW m^{-2} at 25% RH[c] and 55.2 mW m^{-2} at 85% RH	Sheets	714
			~10 mW m^{-2} immersion in DI water[d]	Thin films	715
			~70 W m^{-3} (= 21 mW m^{-2} at 0.3 mm thickness) at ~80% RH	Fabrics	716
	Hydrovoltaic + thermoelectric	No	720 mW m^{-2} at 70% RH and 10 K ΔT	Sheets	717
	Hydrovoltaic + photovoltaic	No	880 mW m^{-2} at 50% RH and 1 sun illumination	Sheets	718
Biofluids (sweat, blood, interstitial fluid)	Biofuel cell (on-skin)	Glucose, lactate, *etc.*	35 W m^{-2}	Integrated skin patches	719
			83 mW m^{-2}	Integrated sensor chips	720
			130 mW m^{-2} at 30 mM lactate	Integrated skin patches	232
			12 W m^{-2}	Stretchable sheets	721
	Biofuel cell (implantable)	Glucose, lactate, *etc.*	44 mW m^{-2} on implantation and 25 mW m^{-2} after a month	Fibers	722
			430 mW m^{-2} in 0.5 M glucose	Nanomembrane on Si substrate	723

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Table 4. continued

Energy source	Mechanism	Sensing function	Peak power density	Flexible form factor	Ref
			4.8 W m^{-2} in 5 mM glucose and 1.6 W m^{-2} after 7 days	Bioresorbable sheets	724
	CNT-OH interaction (implantable)	No	570 mW g^{-1} in 2.5 M HCl	Fibers	725

[a]Some state-of-the-art reports are listed. [b]PCE, power conversion efficiency. [c]RH, relative humidity. [d]DI water, deionized water.

versatile operation modes, enabling cost-effective mass production and customizability to suit different applications. Its biocompatibility stems from diverse materials choices, including for implantable applications.[731,732] Due to the sensitivity to deformation, TENGs can serve as self-powered sensors for various mechanical stimuli, such as pulse, breath,[693] sound, touch, and body motions;[733] with proper modification, gas[734] and humidity[735] can also be sensed.

The biggest challenge facing ambient energy harvesters is typically to produce enough power for an entire sensing system. Beyond triboelectric and photovoltaic energy conversion, the power generation efficiency and/or power density of most current technologies are insufficient to support complex sensing systems fully. While discovering energy conversion mechanisms that are intrinsically efficient (*e.g.*, magnetoelastic effect[65]) or improving current technologies through materials innovation and structural engineering (*e.g.*, using nanomaterials to increase reactive surface area) will help, integrating low-cost large-area energy harvesters in an imperceptible way might be another solution. For instance, clothing is a promising platform to integrate textile energy harvesters without significant interference to wearers' daily activities, and the surface area across the body provides ample space to collect sufficient power.[670,678,689,691,736,737] Nevertheless, comfort, convenience, aesthetics, washability, and interconnection are problems to address. Although not yet able to power integrated complex systems, ambient energy harvesters, especially self-powered sensors, can support the function of simple wireless sensors, such as active RFID tags,[738] triboelectric pressure sensors,[739−741] and magnetoelastic generator-based human-machine interfaces.[68]

Intermittency in power generation is a second problem. Ambient energy sources are usually not constantly available, including sunlight and body motion. Hybrid energy harvesters that combine two or more transducing mechanisms and scavenge energy from multiple energy sources may help alleviate this problem.[742] In addition, output power usually fluctuates with the intensity of energy sources, requiring power management circuits and energy storage devices to level the curve and to provide sustained and constant power.[685,743] However, power management circuits themselves usually require power to function.[744] To minimize additional power requirements, a power management circuit for TENGs was designed to perform effective power regulation without any additional power input,[745] which may inspire other energy harvesters. On the other hand, self-powered sensors are best positioned to address the problem of intermittency because they generate power exactly when demanding power. However, performance of self-powered sensors needs improvement. For example, the sensitivity of piezoelectric and pyroelectric sensors is relatively low. Triboelectric sensors are prone to external noise and humidity.[746] Magnetoelastic sensors need improvements in device weight and miniaturization.[65,169]

Large-Capacity Energy Storage Devices. Power delivery through electrochemical energy storage devices (ESDs) is more reliable than *in situ* energy harvesting. Common ESDs for flexible sensors include batteries (lithium-ion batteries,[747] zinc-ion batteries,[605] *etc.*)[300] and supercapacitors.[604] Goals in devising ESDs for flexible sensors include high capacity (high energy density), low-profile/imperceptible form factor (flexibility, stretchability, miniaturization), and high cycling stability (electrical and mechanical cycling). These goals, however, often entail contradictory materials and device design principles,

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raising significant challenges in crafting effective ESD solutions for flexible sensors.

In terms of current materials, electrodes and electrolytes need better designs. Flexible form factors are usually realized by reducing the thickness of electrodes, which reduces energy capacity, as well.[748,749] To improve energy capacity, stacks/arrays of flexible ESDs[315,750] and large-area fabrics made from ESD yarns[604] are viable approaches. This approach usually requires more substrate/encapsulation materials than conventional structures, reducing the overall energy density. Moreover, the use of polymeric binders to enhance electrode mechanical robustness further impairs energy density. Nanomaterials and polymers possessing both robust mechanical flexibility and electrochemical activity are needed.[315,751] Electrolytes also face performance trade-off. Conventional liquid (predominantly organic) electrolytes are the most conductive but least stable, leading to high safety risks (due to chemical reactions and leakage).[749] Electrolyte leakage and solvent evaporation also reduce energy capacity and device lifetime.[752] At the other extreme, solid electrolytes are highly stable but poorly conductive or deformable. A possible trade-off would be gel electrolytes, currently dominant in flexible ESDs. Supramolecular polymer electrolytes were recently shown to break this trade-off, achieving high stretchability, toughness, and ionic conductivity simultaneously.[753]

In terms of device performance, energy capacity, cycling stability, and safety are key metrics to improve. While energy density is a figure of merit for fair comparison among devices,[754] during practical usage, it is the total energy capacity of an (array of) ESD(s) that determines the lifetime of a sensing system, before the next charging. For a device with ultralight weight, the energy density can be extraordinarily high, but if it cannot be scaled up and integrated with other components reliably, the device would be of little practical value. Therefore, reporting energy density and demonstrating high capacity are *both* essential in ESD research. Furthermore, the stabilities of current ESDs against charge cycling and mechanical cycling are not sufficient for real-world applications. Most ESDs suffer from either capacity degradation or device failure after bending and/or stretching cycles.[755] Fiber batteries woven into textiles seem to be the most mechanically robust choice, and they allow large-area incorporation for higher energy capacity.[651,678,756] Recent reports on industrial-scale production and integration[651,756] demonstrate promise for practical use. Critically, safety evaluation is often overlooked in current flexible ESD research. For wearable and implantable applications, tests in physiological environments, potential extreme conditions, and simulated long-term use should be conducted.[757] The work on sweat-activated battery[758] is a good example of prioritizing biosafety in ESD design. Recent developments in sweat-activated batteries have improved capacity[759] and power density[759,760] as well as realized more form factors such as bandage[761] and textiles.[762,763] Mechanistically safer ESDs such as zinc-ion batteries[757] and supercapacitors might be suitable for safety-demanding applications. Some cutting-edge design principles for safe ESDs[764−766] can be applied to support flexible sensors, and fundamental understandings of ESD safety such as thermal runaway in lithium-ion or lithium batteries[767−769] will be critical in guiding the design of safer lithium-based ESDs.

Materials research on ESDs and sensors are mutually beneficial and synergistic. Some materials that are initially developed for sensing applications may be repurposed for energy storage and *vice versa*. For example, membrane materials developed for sodium-ion batteries may double as materials for sodium sensing. Self-healing conductive hydrogels may function as both strain sensors[420] and electrolytes in supercapacitors.[770]

Efficient Wireless Power Transfer. With power generated by ambient energy harvesters and held in energy storage devices, the next problem is to transfer the power conveniently, efficiently, and reliably to sensors. The conventional method relies on wired power transmission and may not work effectively for emerging flexible sensor technologies, such as body area networks. In these scenarios, integrating an energy harvester and/or an energy storage device to every sensor node *via* wired connections causes significant installation and maintenance challenges, and limits sensor node mobility/wearability. If multiple distant sensors share the same power source, wired connections can become cumbersome and unsafe. To address these issues, wireless power transfer (WPT) is likely a more suitable strategy.

Current dominant WPT methods include near-field and far-field radio-frequency (RF) techniques. These RF technologies have both power transfer and data communication capabilities and thus can enable highly autonomous or fit-and-forget sensors that are lightweight, tether-less, and require minimal maintenance, which are particularly suitable for automation, security, safety, and productivity related applications. Near-field technologies are based on inductive coupling and magnetic resonance,[622,771] and far-field technologies are based on radiative power transfer.[772,773] Near-field techniques can achieve high-efficiency power transmission yet only over a limited distance (a few centimeters), and there are strict requirements for transmitter-receiver alignment. Far-field techniques can cover large areas (a few square meters), but due to omnidirectionality, their power transmission efficiency is low and subject to obstructive interference (especially from the human body). Mechanisms such as coherently enhanced WPT and exceptional point WPT, as well as metamaterials and metasurfaces for WPT[774] may offer better solutions over traditional methods. Besides electromagnetic techniques, ultrasound is also a practical method, currently a mainstream technique used for implants, due to its low attenuation by biological tissues and high safety.[775−777] But because it is highly directional, small-area single-node applications are most suitable. Recently demonstrated body-coupled electromagnetic power transmission also showed significantly (30−70 dB) lower path losses through the human body than far-field RF transmission.[778] Without limitations in the location of transmitters and receivers, it can cover the whole body from head to toe (2 μW extracted on the head from a 1.2 mW transmitter on a foot, sufficient to operate low-power sensors), and is thus a promising technology for body area networks.

The abovementioned technologies based on electromagnetic energy transmission can also be used to harvest ambient electromagnetic energy emitted from power lines and electronic devices, as well as pervasive wireless communication networks, leading to an energy recycling effort for sustainability. However, ambient electromagnetic energy shares the same instability/intermittency issue with natural ambient energy sources yet has relatively low power density and recoverable power (10 nW−100 mW[772,778]). Hence, ambient electromagnetic energy might be a good add-on but is likely not a staple energy source.

Major challenges in WPT lie in device miniaturization, coupling distance increment, and transmission efficiency improvement. For human-centric sensor networks, convenient power transmitter location and usage[293] should be devised to

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circumvent the requirement of skillful periodic charging. Biocompatibility and long-term stability of implantable wireless power modules need to be investigated. Effective WPT solutions for kilometer-range sensor networks also need to be developed for agricultural, industrial, and environmental settings where minimal human intervention is present.[779]

Holistic System Power Management. Holistic power management at systems levels can be implemented from multiple perspectives (Figure 12, red panel).[780] First, reducing the power consumption of individual modules in a sensor system is fundamental. Some examples of recent efforts to this end include: sensing mechanisms or materials engineering that lead to ultralow- to zero-power sensors,[44,781,782] power-efficient readout architectures for sensor arrays (detailed in section Efficient Matrix Signal Readout),[465] low-power wireless communications technologies (detailed in section Sensor Connectivity), flexible memory with ultralow switching current density,[783] and flexible complementary circuits with ultralow driving voltages.[469] In addition, low-impedance interconnections in integrated systems are also critical for improved power efficiency.

Second, a combination of multiple energy harvesting and storage strategies according to application requirements and constraints should be considered.[742,784] In such cases, power management circuits that solve the impedance mismatch between high-impedance energy harvesters (such as triboelectric and piezoelectric nanogenerators) and low-impedance energy storage devices (such as supercapacitors and lithium-ion batteries) are critical.[785] Such impedance mismatches can significantly reduce system efficiency during operation. However, the additional power modulation circuits and elements[660,738,743,785] (*e.g.*, transformers to regulate generators' voltage output, charge pump circuits to increase power output of biofuel cells, maximum power point tracking circuitry to vary optimum electrical operating point of photovoltaics[786]) increase design and manufacturing complexity as well as implementation cost, and reduce system compactness. Thus, the integration levels of various energy harvesting and storage devices with other components in the system is critical.[787] One attempt to address this issue is a battery-in-sensor developed by inserting an isolation layer into a solid-state zinc-ion battery. The device delivers power that changes with the external pressure, thereby achieving self-powered pressure sensing with high integration.[788] More inspiration can be drawn from the simplistic integration of self-powered sensors and wireless communication modules towards fully power-autonomous systems.[739−741] Nevertheless, there is a trade-off between sensor accuracy/controllability/reliability and system complexity, awaiting better solutions.

Biofuel cells are poised to be incorporated into system-level designs. Because their output power depends on the concentration of an analyte (*e.g.*, glucose, lactate, alcohol), they can be used as biosensors in addition to energy harvesters.[232,720,789] They have been integrated with piezoelectric nanogenerators[720] for self-powered touch-based sweat sensing, and with TENGs and supercapacitors for textile sensing systems.[784] Furthermore, biofuel cells have been integrated with near-field communication electronics,[790] magnetic human body communication,[789] and electrochromic displays[232] to realize battery-free data communication and readout. Nonetheless, biofuel cell implementation is often limited by their operational lifetime, which is on the order of a few days, before enzyme degradation impairs power output. Future work utilizing either non-enzymatic sensing or engineered enzymes and biomaterials for improved operational stability as well as further integration with other energy harvesting mechanisms is expected to make a significant impact on self-powered biosensors and holistic power management approaches.

Another system-level approach is to use microcontroller units or power management integrated circuits (ICs) to manage the power flow and usage by various system components for maximum energy efficiency.[691,786,791,792] For example, the system could be in a sleep mode when no alarming stimulus is present, but the energy harvesters could be functioning to store energy in batteries. Once the sensor is triggered by an alarming stimulus (most likely a self-powered sensor), the power management circuit instructs the communication module to start functioning to transfer sensor data wirelessly for prompt action. When multiple components are working simultaneously and the energy storage level is low in the battery, the system can enter a power-saving mode with reduced signal processing and data exchange. This strategy is much like how smartphones manage power usage. Power consumption of the power management system itself is an important factor to consider.

SENSOR CONNECTIVITY

Sensor connectivity refers to the information exchange among sensors, as well as between sensors and control devices (*e.g.*, smartphones, computers). Connectivity is important because in many cases, a large group of sensors holistically reflect the status of the monitored subject/environment (*e.g.*, health monitoring,[793] posture and motion tracking,[293,794] environmental monitoring[21]), or spatially distant subjects need to be monitored simultaneously (*e.g.*, large-scale behavioral neuroscience in animals[795]). Sometimes it is the sensor-sensor interactions that produce meaningful data (*e.g.*, COVID-19 contact tracing). A connected sensor network can be established through either wired or wireless communication. The latter is gaining traction in recent years because it can utilize the power of cloud computing and convenient data sharing and management, improve the wearability and implantability of bio-interfacing sensors, and simplify sensor installation in IoT applications, enabling sensing paradigms including Wireless Sensor Network (WSN)[796−798] and Wireless Body Area Network (WBAN, IEEE 802.15.6).[787]

There are several information-carrying media through which wireless communication can be established, such as acoustic waves,[775,799] optical signals,[684,800] and RF electromagnetic waves.[801] RF communication methods are most commonly used, because of their versatility through different data transfer mechanisms (magnetic inductive coupling, magnetic resonance, far-field radiation, *etc.*) and a wide frequency range, leading to communication protocols with distinct characteristics suitable for different applications (Table 5).

Each RF technology has its pros and cons, and there is no one-size-fits-all solution. RF data transmission can be categorized by its range of operation into near-field and far-field technologies. Near-field technologies are characterized by short ranges and low data rates. Established protocols include radio-frequency identification (RFID)[796,803,813,814] and near-field communication (NFC),[815] for instance, while other near-field protocols designed for specific sensors have been reported as well,[622,816,817] which require specially designed readers. These technologies have the advantage of supporting wireless power in addition to data transfer, and are therefore particularly well-suited to operate passive sensors with no battery and minimal

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Table 5. Radio-Frequency Wireless Communication Protocols Commonly Used in Wireless Sensor Networks[a]

Technology	Range	Frequency	Data rate	Network topology and transceiver type	Power consumption	Existing applications	Examples relevant to flexible sensors
NFC	5−25 cm	13.56 MHz	106, 212, 424 kbps	Peer-to-peer Passive, semi-passive	3−15 mW	Contactless payment, ticketing, medicine and healthcare (*e.g.*, patient charts tagging)	445,502,802
RFID	25 cm−100 m (frequency-dependent)	LF: 120−140 kHz HF: 13.56 MHz UHF: 865−956 MHz (far field) Microwave: 2.45−5.8 GHz (far field)	10−640 kbps	Peer-to-peer (unidirectional) Passive, active	10 nW−200 mW (frequency-dependent)	Manufacturing parts, retail items (apparel, footwear)	293,803
RuBee	15−30 m	131 kHz	1.2 kbps	Peer-to-peer Active	40 nW[804]	Real-time asset visibility in harsh environments, defense and industrial IoT[805]	–
UWB	1−1000 m	3.1−10.6 GHz	22−600 Mbps	Peer-to-peer, star, mesh Active	<50 mW	Radar imaging	492
Bluetooth	10−300 m	2.4 GHz	780 kbps−3 Mbps, up to 25 Mbps	Peer-to-peer, star (seven slaves) Active	10−100 mW	Earphones, smartphones, smartwatches	63,661,806,807
Wi-Fi	70−250 m	2.4 and 5 GHz	11−54 and 150 Mbps	Infrastructure-based Active	835 mW	Smart home, wearables, streaming	63,657
ZigBee	10−100 m	868 and 915 MHz, 2.4 GHz	20, 40, 250 kbps	Peer-to-peer, star, mesh, cluster tree Active	36.9 mW	Home automation, traffic management	808,809
LoRa	Urban: 2−5 km Suburban: 15 km	869 and 915 MHz	290 bps−50 kbps	Peer-to-peer, star Active	1.5−100 mW	Smart cities, logistics and transportation management, smart buildings	810,811
NB-IoT	Urban: 1−8 km Suburban: 35 km	LTE frequencies (several bands within 0.41−5.9 GHz)	160−250 kbps	N.A.	106 mW	Asset tracking, sensor networks, smart cities, industrial monitoring	812
Cellular network (*e.g.*, GSM, GPRS, LTE)	1−10 km	4G: 2−8 GHz 5G: 450 MHz−6 GHz, 24−53 GHz	4G: 100 Mbps 5G: 20 Gbps	N.A.	High	Cell phones, tablets, IoT	–

[a]NFC, near-field communication. RFID, radio-frequency identification. LF, low frequency. HF, high frequency. UHF, ultrahigh frequency. UWB, ultra-wideband. LoRa, long range. NB-IoT, narrowband-Internet of Things. GSM, global system for mobile communications. GPRS, general packet radio service. LTE, long-term evolution.

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electronics.[818] However, near-field technologies are sensitive to transmitter-receiver misalignment and limited by the short range of operation (usually <5 cm). In contrast, far-field technologies support long-range, high-data rate transmission. They include standards such as Bluetooth, Wi-Fi, and 5G, which can be used by sensors to stream data continuously to a base station several meters away. However, far-field transmission requires power at the sensor. Because of radiative losses, power consumption of far-field communication modules often occupies the majority of a sensor's energy budget. Far-field signals are also radiated far from the sensor, which raises security concerns due to the possibility of eavesdropping.

The connectivity requirements of different types of IoT networks vary widely, depending on applied purpose and resource constraints including battery life, available bandwidth, buffer size, processing capacity, form factor, transmission media, *etc*. To construct an efficient wireless sensor network, it is wise to select the best fit (often a trade-off) for each sensor node and it is often necessary to combine several protocols in a suitable topology to provide full network connectivity. For example, in a complex WBAN for health management, sensors carrying various forms of information are worn, attached, or implanted on or in the human body. These sensors can be connected *via* short-range wireless technologies, such as ZigBee, Wi-Fi, and Bluetooth for continuous data streaming to a gateway device such as a smartphone. This strategy will ensure compact form factors at sensor nodes and acceptable power consumption that can be handled by portable batteries. The gateway device then forwards the data to a remote server for access and feedback by healthcare providers. This remote data transfer can be realized by telecommunication techniques such as Worldwide Interoperability for Microwave Access (WiMax), long-term evolution (LTE), or Satellite, which also allow communications between several gateway devices.[787]

Improved throughput, reliability, and security are the primary goals of modern communication technologies.[801] General research directions towards faster data transfer, lower latency, smaller circuit footprint, enhanced energy efficiency, *etc*. will benefit flexible sensor networks. For instance, high speed and low latency will be critical for real-time feedback systems as well as sensor arrays. Meanwhile, there are some issues that are specific to flexible sensor networks, regarding power consumption, body interference, and data security, dictated by emerging application requirements.

Lowering Power Consumption. Data transmission puts a heavy energy burden on wireless sensor networks. Depending on application, power requirements vary, but in most cases, the wireless communication network consumes more power than sensors *per se*, and sometimes power consumption by communication can account for nearly 80−90% of total power consumption. Adding large-capacity batteries and energy harvesters around sensors to support such high energy demand is a straightforward solution, but it is not always feasible or ideal for a WSN.[787] Hence, reducing the power consumption of wireless communication is of paramount importance for flexible sensors.

There has been much work on improving the energy efficiency in data transmission through antenna configuration, circuit design, modulation scheme, network topology, *etc*. For example, combining surface and bulk acoustic wave resonators with active CMOS circuits for RF transmitters and receivers has great potential for both ultra-low power consumption (nW to pW) and good noise performance.[819] An 800 MHz on-off keying (OOK) transmitter utilized a MEMS-based RF oscillator for carrier frequency generation, leading to a 120 Mbps data rate with an energy efficiency of 5 pJ b^{-1}.[820] For receivers, the passive gain approach could be effective in achieving good sensitivity at low power consumption, as demonstrated in high-Q film bulk acoustic resonators.[821] In addition, emerging techniques like long range (LoRa)[822] and ultra-wideband (UWB)[798,823] are amendable to low-power implementation through spread-spectrum modulation techniques. On the network level, the mesh topology is favorable in that data are passed through intermediate devices to reach their destination, allowing reduced power consumption and dynamic network connections.[786] Software Defined Networking[824] is expected to reduce network management complexity and power consumption at sensor nodes, although the actual benefits will need to be verified in specific application scenarios.[787]

Besides improving the energy efficiency of communication technologies, reducing the amount of data transferred can alleviate the issue starting at the source. This efficiency can be achieved through edge computing systems integrated near sensors to process signals for reduced data size prior to transmission. Specifically, edge systems can decide which data to transmit and which to discard, trim redundant data, and instruct the transmission of meaningful data only. For example, in real-time monitoring of building structures or environmental safety, only when abnormal events occur do data need to be transmitted immediately for swift action. Other data can be stored temporarily in local memory and deleted after a period of time. In more advanced edge systems, signals can be processed into digitally interpretable features and labeled data with significantly compressed size. All these functions will contribute to faster and more energy-efficient data communication.

Overcoming Body Interferences and Constraints. Flexible sensors have broad applications in physiological monitoring on the human body, yet the body poses several critical challenges in wireless communication.[787,801] First, biological tissues absorb electromagnetic radiation strongly within 1−10 GHz, where common RF wireless techniques reside.[825,826] This absorption causes significant path loss and energy waste (significant attenuation, *ca*. 80 dB, when the antenna is in the vicinity of or attached to the human body[826,827]). Alternative signal carrying media with lower tissue absorption include ultrasound[775,777] and near-field electromagnetic waves,[801] but these techniques suffer from difficulty in miniaturization and sensitivity to transmitter-receiver misalignment, which severely impairs connection stability during body movements. Furthermore, body movement also leads to unreliable connections when body parts obscure the transmission pathway. For the same reason, the medium through which signals are transmitted keeps changing, making design of communication systems challenging. On the other hand, wearing comfort and implant safety raise additional materials and form-factor requirements in the design of communication modules, such as softness, stretchability, miniaturization (especially antennas), biocompatibility, among many other aspects in achieving a compatible sensor-biology interface.

Multiple directions of research are meant to address the above issues. The first is to utilize clothing as a medium for confined signal transmission, targeting wearable sensors all around the body.[828] Conductive traces laid out around the body act like highways for wireless signals to travel, circumventing the issue of body absorption and enhancing transmission efficiency. For instance, far-field RF signals can be guided by metamaterial

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textiles with comb-like motifs that support the propagation of surface waves much like surface plasmons of optical frequency.[829] When devices are placed near clothing, the emitted wireless signals can be confined to within 10 cm of the body and the transmission efficiency increased by 3 orders of magnitude. This approach can be used to extend the range of near-field transmission.[794,830] Using embroidery or a heat press process, near-field relays can be attached onto clothing to establish near-field communication between nodes more than 1 m apart. Recent advances have realized washable and stretchable electronic textiles for wireless communication.[802]

The second major on-body wireless communication paradigm under investigation is body-coupled communication or body channel communication (BCC), where the human body is exploited as a medium for signal transmission. This can be done in three ways: capacitive coupling, galvanic coupling, and magnetic resonance coupling. Capacitive coupling is currently the most popular method because of less body attenuation at high frequencies (>10 MHz), leading to long range and high data rate.[827,831,832] A transmission loss <30 dB was achievable over 1 m distance on the body,[833] meaning that capacitively coupled BCC can potentially cover the whole body, within and between the torso, limbs, and the head. Moreover, the use of high frequencies and capacitive coupling ensures that the signals do not interfere with electrophysiological monitoring and are safe within specific absorption rate limits. However, capacitively coupled BCC suffers from several challenges in practical use: varying ground effect, varying skin-electrode impedance, varying body composition between body parts and individuals, multipath and interference issues. Some solutions to these problems include constant impedance monitoring and compensation, and pseudo and hybrid orthogonal frequency-division multiplexing (OFDM) transceivers.[831,834] Magnetic resonance coupling, as a relatively less studied means of BCC,[835] has potential advantages of insensitivity to body motion with comparable or even less pass loss than capacitive coupling.[836] For all BCC methods, standards that guarantee the safety and performance on users with different body size, composition, *etc.* are needed.

The third branch of research efforts to improve the communication reliability of on-body sensors is devising form factors of RF devices that can adapt to body movements, geometry limitations,[787] and tissue softness. The antenna is an important component in RF communication, occupying a relatively large volume in the communication system. Consequently, there have been many efforts in rendering flexibility, stretchability, and miniaturized size to antennas.[293,295,445,799] Structural designs, including 2D serpentine, 3D helical, 3D spiral, and 3D buckled shapes, are effective to achieve good mechanical compliance while maintaining high conductivity. Unconventional materials such as liquid metal and nanomaterials offer another dimension of design freedom in achieving multiple antenna forms and functions. Textile-based antennas are integral to smart clothing systems. Although comparable-to-convention performance has been achieved in some of these form factors, issues and challenges remain, such as maintaining electromagnetic performance (bandwidth, gain, radiation efficiency, working frequency) during miniaturization, shielding interference from surrounding biofluids, ensuring reproducibility and environment-resistance of textile antennas, among many others. On the other hand, circuits play decisive roles in RF communication performance, being the 'mini-brains' of communication systems. While silicon-based CMOS chips offer superior performance in this regard, their rigidness leads to interfacial mismatch with biological tissues and soft-hard interfacial instability in an integrated system. TFT-based flexible communication chips may alleviate these issues. With the downscaling of TFTs and improved circuit design, TFT-based RFID and NFC chips will continuously bring down the power consumption,[466] and may be extended to cover a larger variety of wireless techniques. Recently, intrinsically stretchable transistors[378,837] and diodes[298] were fabricated, and simple wirelessly accessed sensors without any rigid components were demonstrated.[293,298] These efforts will contribute to fully soft wireless communication systems. In all, as wireless technologies continue to evolve, the design of unconventional form factors will face great opportunities and challenges.[801]

Enhancing Data Security. Data security has always been a concern for wireless communication because wireless signals are often dispersed in free space, prone to eavesdropping. In human-centric applications, this problem becomes more critical when sensitive personal data are collected, or healthcare decisions are made on the basis of sensor data. In these scenarios, data breaches can have life-threatening consequences.

There are generally three ways to enhance data security in wireless sensor networks. The first strategy is to use transmission schemes that are insensitive to eavesdropping, targeting short-range communication from the fundamental. In this aspect, near-field techniques[805] are better than far-field ones because of small range, small electrical size, and low-power operation. Moreover, UWB is inherently secure. Its low signal energy reduces the probability of detection.[798] Recently proposed textile-facilitated far-field and near-field communication technologies address this problem by confining wireless signals within 10 cm from the human body.[794,829,830] BCC also guarantees highly secure data transmission by constraining signals within the human body.

The second approach is to strengthen cryptographic systems through data encryption and authentication.[838] As the computational capability of supercomputers and quantum computers keeps evolving, it becomes increasingly easier for hackers to crack encrypted information.[839,840] Light encryption methods based on quantum-resistant algorithms are in high demand. On the other hand, adding authentication mechanisms throughout the network for data input, access, and sharing among nodes[787] allows only authorized users to access data. Biometric authentication, including basic fingerprint and facial recognition, as well as emerging ideas on biochemical and biophysical status (breath odor,[841] sweat composition, heart rate, blood oxygen,[842] *etc.*), is a reliable method based on the distinct and unique profile of each individual. However, this method requires an additional set of authentication sensors on each sensor node, complicating system design and increasing cost. Two-factor authentication (2FA), also known as two-step verification, using communication devices outside the sensor network is a simpler solution. Note that any implementation of security measures puts additional management complexity and energy budget demands on the network. Lightweight techniques are highly desirable.[843]

Recently proposed networking and data management frameworks can also deliver enhanced data security. For example, Software Defined Networking is a networking framework with reduced network management complexity and power consumption, and has recently been proposed to provide security and authentication services in sensor networks.[787] Blockchain is another promising technology to be explored in distributed sensor networks to store personal data securely while allowing data tracking.[10,787,844]

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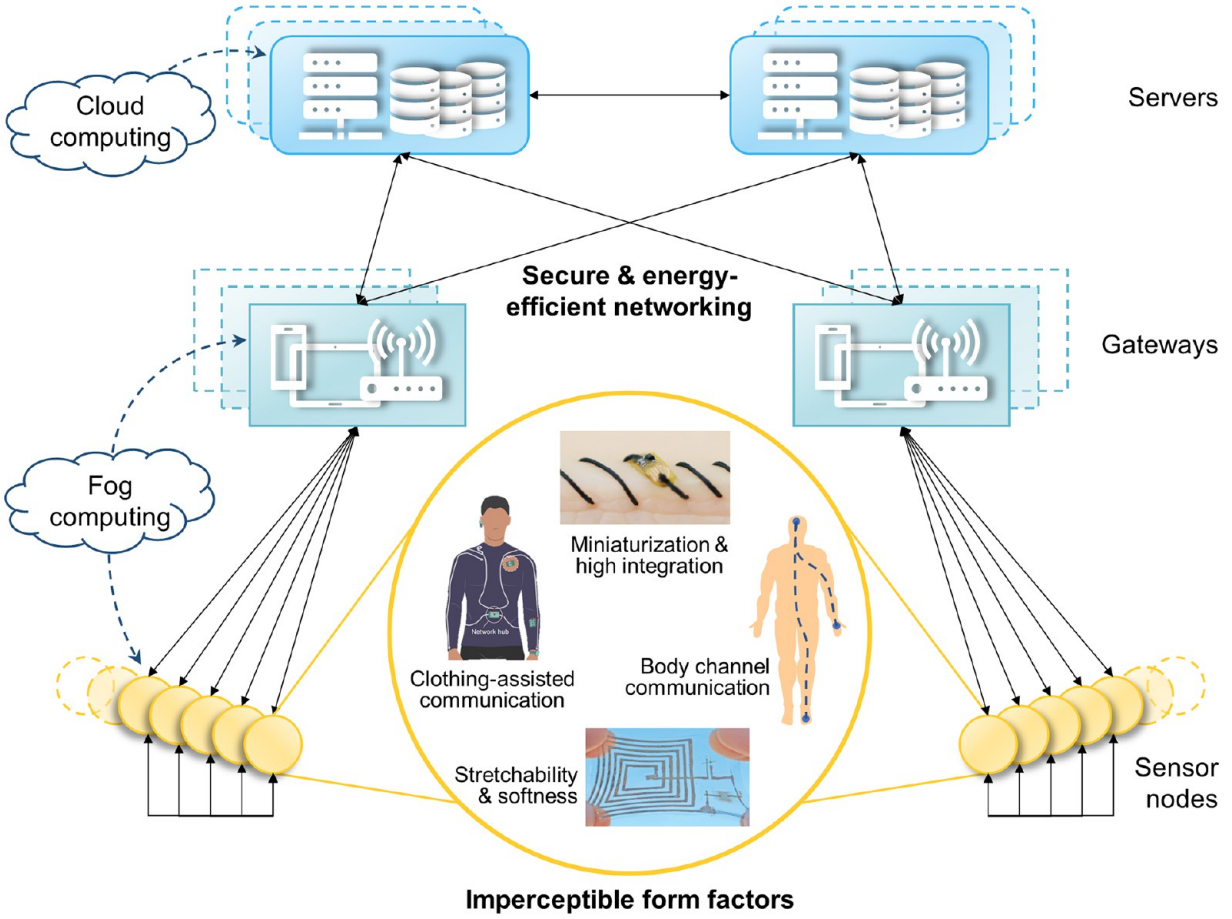

Figure 13. Outlook for flexible sensor networks. Black arrows denote connectivity. A group of sensor nodes can communicate within themselves and may be accessed by more than one cloud server. Due to dense connection, the two networks merge into one. Ultimately, numerous sensor nodes may be connected in a 'meganetwork' involving more gateways and servers (dot-outlined shapes). Cloud computing and fog computing will be instrumental in the realization of extensive sensor connectivity. Images for "imperceptible form factors": Adapted with permission from ref 829. Copyright 2019 Springer Nature. Adapted with permission from ref 658. Copyright 2021 Springer Nature. Adapted with permission from ref 298. Copyright 2021 Springer Nature.

Besides the above mentioned three critical challenges, there are many other issues in the connectivity of flexible sensor networks. For example, changing data volume over time (*i.e.*, dynamic traffic) leads to load imbalances in data storing and processing at back-end servers,[787] and is an emerging issue for continuous monitoring. There will be interference between sensor nodes and from other wireless devices operating at overlapping frequencies, as the number of wirelessly connected devices experiences dramatic growth. Overheating on sensor nodes[787] will be an issue scaling with data volume. If higher frequency communication modules are incorporated (*e.g.*, 5G), heat management will be a great challenge concerning user safety. Continuous chip innovation to reduce power consumption is key. Convenience, safety, and reliability of wireless communication are constant pursuits for flexible sensor networks.

Closer collaborations between researchers in the fields of flexible sensors and wireless technologies are needed to tap the full potentials of both areas. Despite ongoing research advances in wireless technologies (*e.g.*, 13.56 Mbps data rate achieved by near-field inductive coupling[845]),[801] a majority of reported flexible sensing systems still use commercial and conventional wireless communication modules[21,61,63,661] with rigid form factors, limited ranges, and high power consumption. These choices are understandable based on the consideration of the need for system robustness and compatibility with established protocols. However, to integrate sensor and communication technologies seamlessly in terms of device structure and operation mechanisms, as well as to exploit the state-of-the-art advances in both areas,[502,658] teamwork between sensor developers and wireless technology engineers will be greatly beneficial. In this way, both sensor and communication technologies can be tailored to suit each other's need for potential synergistic effects; systems can be designed from the bottom up to achieve high levels of integration, and additional merits or functionalities of wireless communication can be discovered. Such advances would likely impact other areas of data networking.

On the basis of reliable implementation of wireless communication on a single sensor node or multiple sensor nodes,[293,794,829,830] the next step is to expand to networks, where dozens of sensor nodes communicate with each other and with gateways and servers (Figure 13). More complex network and data management problems will emerge in this endeavor, requiring cutting-edge solutions developed for conventional sensors (*e.g.*, wireless technologies in IoT and WBAN), and tailor-made solutions for flexible sensor networks.

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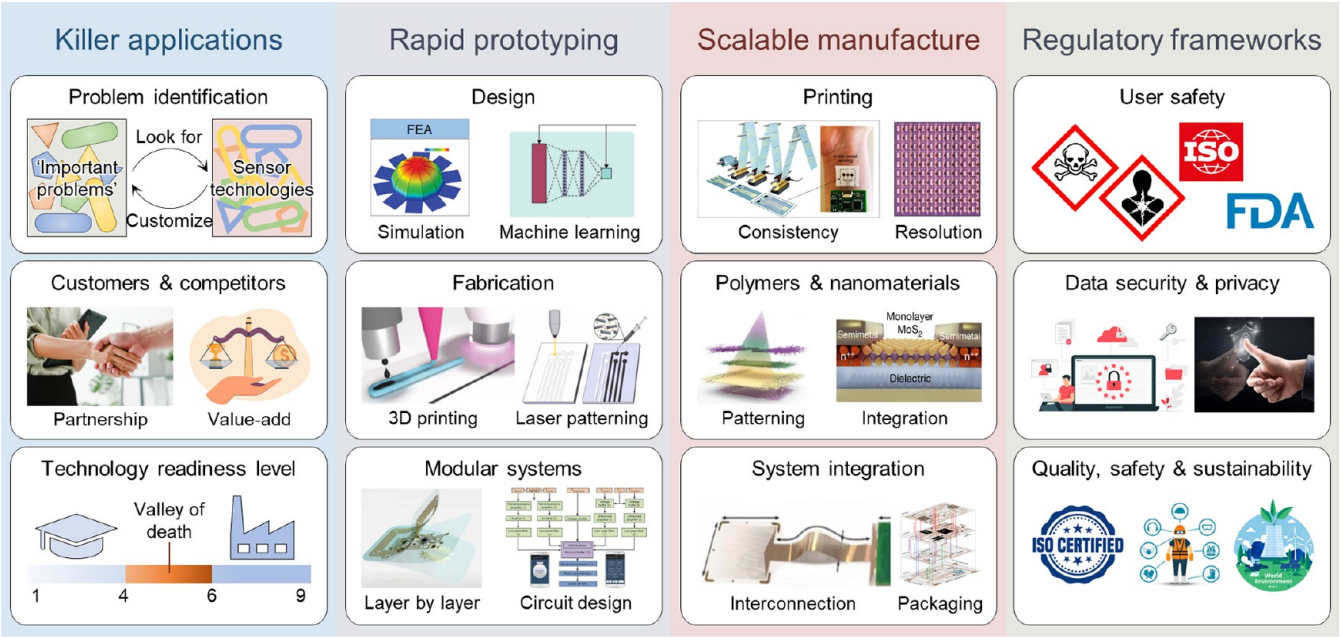

Figure 14. Key issues to address during the translation of flexible sensors from labs to end-users. Images under "Customers and competitors" designed by Freepik. Images under "Design" adapted with permission from ref 628. Copyright 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Adapted with permission from ref 851. Copyright 2022 Wiley-VCH GmbH. Images under "Fabrication" adapted with permission from ref 852. Copyright 2020 Springer Nature. Adapted with permission from ref 853. Copyright 2021 American Association for the Advancement of Science. Images under "Modular system" adapted with permission from ref 854. Copyright 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. Adapted with permission from ref 84. Copyright 2016 Springer Nature. Images under "Printing" adapted with permission from ref 855. Copyright 2018 American Chemical Society. Adapted with permission from ref 397. Copyright 2021 American Chemical Society. Images under "Polymers & nanomaterials" adapted with permission from ref 837. Copyright 2021 American Association for the Advancement of Science. Adapted with permission from ref 856. Copyright 2021 Springer Nature. Images under "System integration" adapted with permission from ref 276. Copyright 2022 American Association for the Advancement of Science. Adapted with permission from ref 290. Copyright 2018 Springer Nature. Images under "Data security & privacy" and "Quality, safety & sustainability" designed by Freepik.

Data storage is essential to support connectivity. Data can be stored in local memories at sensor nodes or transferred to and stored in centralized data centers. The first strategy will benefit fast data communication but requires either heterogeneous integration of rigid memories or flexible memory devices, which are still in the early stages of research.[783,846,847] The second strategy is suitable for long-term, robust storage of large datasets. However, the escalating energy demand of data centers is a pressing issue to address.[848,849] Meanwhile, algorithms that compress data size should be implemented near sensors and/or in the cloud. Overall, high-density and low-power memory devices are critical to support the expanding sensor adoption.[850]

LAB TO END-USER

Flexible sensors will have societal impact only when they go out of laboratories. The route from lab to end-user is thorny because the market for flexible sensors is complex—they are not a single type of product nor are they being proposed for a single application; products and processes are at varying stages of technology readiness; manufacturing flexible sensing systems involves many players spanning various value chains; the software, data, and customer service associated with sensing technology require long-term sustainable management.

Here, we identify four challenges along the translation path (Figure 14). First, killer applications in which flexible sensors are likely to be the dominant technology should be identified so that research and development can be focused and efficient. Second, effective design and fabrication strategies are needed to facilitate rapid prototyping, where critical modifications to the systems can be made for greater usability and reliability in real-world settings. Third, going from lab/prototype-scale to industrial-scale manufacturing is essential for mass deployment. Production automation and fundamental process understanding are crucial. Fourth, regulatory strategies targeting issues arising from unconventional use cases deserve early attention, and companies should ensure they comply with the regulations.

Killer Applications. Flexible sensors are expected to revolutionize many fields because of the capability of continuously and wirelessly reporting the physicochemical status of irregularly shaped and dynamically deforming objects. A survey of research over the past decade has revealed the potential use of flexible sensors in many fields beyond healthcare, such as interactive teaching and surgical modeling, expression and creation (music, visual arts, textiles, and fashion), robotics, prosthetics, brain-computer interfaces, urban planning, buildings and infrastructure, agriculture and veterinary care, climate, renewable energy, and ocean and space exploration.[857] Which of these potential applications demonstrated in labs are worth the translational effort remains a tough yet critical question. Not all flexible sensor technologies are equal and distinguishing between hype and reality is an increasing challenge for stakeholders. The following principles provide useful guidance to avoid common pitfalls.

First, the sensor technology should solve real and prevalent problems (*i.e.*, 'important problems'), which will determine the existence and scale of potential markets. This would require a mindset shift from 'a solution looking for a problem' to 'a problem looking for a solution'. Decades of research have built

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up versatile toolkits for flexible sensor design and manufacture, which should be leveraged to engineer practical solutions to real-life problems. However, many researchers continue blindly improving a single or few performance metrics of flexible sensors while ignoring the specificity of signals to be measured. For example, existing flexible pulse sensors[858] rarely take account of the comprehensive requirements of sensor performance. To detect a clear, undistorted pulse waveform, the sensor must have high sensitivity and good linearity within the measurement range under a specific preload (20−100 kPa)[859] and in the frequency band of 0.1−20 Hz.[860]

To identify 'important problems', researchers should be guided by a combination of empathy and statistics, to seek out high-granularity problems that cause intense human suffering. Looking at the lists of the top 100 causes of hospitalization, the top 100 crop-killing parasites, the top sources of foodborne illness, *etc*. can help determine whether the sensor technology can be applied to a problem that is not being well addressed and if addressed would greatly improve life. For example, according to the World Health Organization, among the leading causes of global death in 2019 are cardiovascular, respiratory, and neonatal conditions; ischaemic heart disease, dementia, and diabetes are the fastest growing conditions and are among the top 10 causes—chronic health conditions are plaguing the aging population. Therefore, long-term daily health management could be an important application space for flexible sensors.[10,39] Similar guides can give a sense of the magnitude of environmental or industrial problems.

Second, deeper understanding of the problems, markets, and potential customers requires close discussions between sensor developers and end users.[861] Design thinking would be helpful in this process,[862−864] which entails that sensor designers should put themselves in the shoes of the intended users and try to understand the genuine constraints of a particular problem. Specifically, it is critical to speak to many potential customers and understand whether they will certainly purchase the hypothetical product in large amounts once it is available. This sort of inquiry is critical to the success and direction of any new enterprise. In general, academic startups can be at risk because few scientists are trained in the techniques of customer validation. Many academic labs spend years developing viable technologies and then spend years chasing nonexistent business opportunities with those technologies. Small commercialization grants with strict research deliverables can become a distraction if they lead the scientists-turned-entrepreneurs away from finding customers and generating revenue. The tension between the academic instinct to raise technology readiness levels (TRLs) and the commercial need to find customers can lead to the undoing of startup companies.

Taking healthcare sensors as an example, identifying unmet clinical needs requires partnerships, or at least conversations, between researchers and physicians/clinicians. One recent example is that through collaboration with neurosurgeons, researchers identified that current neurostimulators cannot accommodate tissue growth in pediatric populations.[579] To solve this problem, the researchers developed a morphing electronic stimulator, which can expand together with growing tissues for chronic neuromodulation. Another approach is to identify real-world medical problems by focusing on a specific disease. Some diseases might be readily monitored or treated *via* flexible sensors with application-specific designs. One successful example is the prevention of pressure injuries through continuous monitoring of pressure and temperature at multiple body locations for patients confined to beds.[865] Beyond developing soft, skin-mountable flexible sensors, a few technical advances, such as battery-free and wireless designs and multiple-site measurements, were crafted to solve problems encountered in operating hospital settings.

It is critical to determine market sizes for new technologies. This can be done by multiplying the number of probable customers by the expected price of the product and the expected quantity of the product they will purchase. When imagining a customer for a hypothetical product, it is important to understand the spending power of that customer, and how well the product would compete with other priorities that the customer may have. Furthermore, it is important to assess whether a hypothetical product will solve an urgent need for a customer. Many potential sensor applications could be described as convenient, or nice to have, but they do not have the urgency necessary to drive sales. When market size estimates are made cautiously, rather than optimistically, they can be useful in assessing the viability of business opportunities.

The third consideration is competitiveness against conventional sensor technology. Modern electronics has advanced in both performance and cost. In many applications, miniaturized rigid sensors are strong competitors to flexible sensors. It is therefore important to develop flexible sensors that bridge the gap between conventional MEMS sensors and targeted applications and that offer distinct value propositions over incumbent technologies. One area where flexible sensors are strong players is human-centric applications, where sensors are worn on the body surface, penetrate the skin, or are implanted deep inside tissues. These human-centric applications could branch into many subcategories, such as daily health/fitness monitoring, athletic performance analysis, point-of-care diagnostics, remote patient monitoring, vital sign monitoring in hospitals, soft robotics, (neuro)prosthetics, extended reality,[866] and the metaverse. Soft and stretchable skin electronics monitoring vital signs for neonatal intensive care[502,867] are a promising area. Because of the small body size and sensitive skin of newborns, attaching multiple bulky electronic monitors around their bodies causes much discomfort and even damage, and prevents skin contact with parents and easy caregiving. In such cases, soft wireless sensors offer obvious advantages over conventional monitoring devices. This technology has led to a spin-off company, Sibel Health, which recently received FDA 510(k) clearance. Very low cost per unit sensors (most probably realized by printed sensors) are likely to have a strong presence in ubiquitous sensing, such as food spoilage detection in packaging,[45,868] temperature mapping in industrial and electronic applications, building and equipment-integrated sensing for preventative maintenance, and hazardous gas detection in military, industrial, and public settings.

The fourth prerequisite for any translational effort is that the sensor technology developed in labs must demonstrate an adequate TRL of at least 6. Most reported flexible sensors are around TRL 4 or below, where proofs-of-concept are demonstrated in laboratory conditions.[869] Reaching a TRL of 6 entails "prototype demonstration in a relevant operational environment",[869] meaning that the sensor technology should work properly under real-world conditions, including when subjected to unpredictable handling by users. However, moving from well-controlled laboratory settings to uncontrolled practical settings is the hardest step in technology translation, and so TRL 4 to TRL 6 is often referred to as the "valley of death", where many promising technologies fail. In this regard,

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packaging is critically important to successful sensor deployment in real-world scenarios. We need to face the reality that most academic labs do not have the necessary resources or motivation to work on high TRL technologies. Instead, institutions with focused resources dedicated to translational work may be more productive. Imec[870] and InnovationLab[871] are good examples, bridging the gap between academic research and industrial applications. Existing infrastructure in manufacturing facilities, supply chains, peripheral services, trained workforces, policies, and legislation all impact the feasibility of technology translation.[872]

Rapid Prototyping. After the initial demonstration of proof-of-concept sensor systems, modifications need to be made to satisfy the practical requirements in real-world settings, and a large amount of data might need to be collected to define the final product. This step requires fast prototyping, *i.e.*, producing customized devices over a short period of time and in large quantities. During this prototyping stage, integration strategy and the coordination between components and subsystems are critical to system performance.[869] Sometimes, the individual components may not be cutting-edge technologies, but proper integration can present a system with advanced functions, where stability is the key.[806] Note that a complete set of solutions, from hardware to software, from device to data, should be prototyped holistically for a particular real-world scenario,[63,502,661,794,873,874] because data without interpretation are of minimal use.

Effective design tools can help expedite prototyping and break the limitation of lack of access to fabrication facilities. This primarily relies on electronic computer-aided design (ECAD), also known as electronic design automation (EDA), to construct a virtual version of the designed device, to simulate, to analyze, and to verify the performance, and to generate essential process parameters for manufacturing. Mechanical simulation such as finite element analysis (FEA) is frequently used and has proven helpful for mechanics optimization in stretchable systems.[875] Molecular dynamics simulations facilitate the understanding and design of functional polymers[372,876,877] and nanomaterials.[878] Numerical simulations also help with microfluidics optimization in wearable biosensors.[228] Such electronic design processes allow for more cost-effective, systemic, and logical optimization, yet they require a solid understanding of the processes happening across materials and interfaces. Moreover, design is a holistic process involving materials science, mechanical engineering, electrical engineering, *etc.*, demanding a collective effort from multidisciplinary teams.

Despite the convenience offered by EDA tools, current design processes still rely on human proposal and manual input, resulting in tedious iteration and slow optimization. Machine learning may be effective to expedite complex design tasks. For example, FEA-trained neural networks could propose the correct 2D design for 3D shapes,[851] which are relevant to 3D conformal sensors.[585−587] Although there are ongoing efforts on machine-learning-enabled flexible systems optimization focusing on mechanical[879] and electrical[880,881] performance,[882] many other performance metrics and manufacturing parameters need to be considered. The ultimate goal is the incorporation of electrical, mechanical, thermal, power, and other features into one design package, where AI self-proposes several designs and fabrication procedures with different trade-off considerations. Nevertheless, empirical validation should never be overlooked.

Following design is fabrication. A number of fabrication strategies for rapid prototyping have been proposed, such as printing, vinyl cutting, and laser patterning. These fabrication processes generally share the features of digital control, customizability, simplicity, low-cost equipment, moderate scalability, and short production time. For example, inkjet printing of conductive inks, extrusion of insulating pastes, plus *in situ* plasma-activation of electrode surfaces produced implantable neuromuscular electrodes that can be customized to fit different tissue sizes and shapes.[852] 3D printing is also a good option for prototyping. There are already commercial 3D printers tailored for soft and stretchable electronics (*e.g.*, NOVA by Voltera). Notable advances were recently made on 3D-printed sensors and electronics,[883−888] such as fully 3D-printed photodetector arrays[889] and microelectrode glucose biosensors.[92] By printing different materials monolithically, device robustness is generally improved over made-and-assembly devices. Vinyl cutters are handy equipment to fabricate 2D structures in stretchable devices, offering significant savings in time and cost compared to photolithography.[890] Although the minimal feature size attainable is relatively large (~250 μm), this scale is sufficient for skin electronics. Combined with multiple processing and transferring steps, "cut-solder-paste" fabrication was used to produce modular and reconfigurable electronic tattoos within 2 h.[854] This cutting method applies to most metals,[891] as well as graphene.[391,392] Lasers can be used in many ways for prototyping. For example, laser scribing is used to pattern functional materials such as graphene on polymer substrates,[182] and ongoing efforts focus on expanding the materials library that can be processed by this method.[892] Laser patterning of absorbent substrates has been used to define the traces for aqueous MXene ink deposition.[853] Lasers have also been used to tune the sensitivity of strain sensors through substrate micropatterning.[893] A common limitation of the above methods is that these processes primarily deal with patterning of conductive materials, and the customized sensors are therefore mainly electrodes, except for 3D printing, which can fabricate more complex sensors. Expanding processing capabilities to cover wider ranges of materials and devices would facilitate prototyping of flexible sensors with greater functionality in various form factors.

At system levels, modular design[854,894,895] offers more customizability, reduces design cost, and improves development efficiency, in analogy to the chiplet technology for rigid ICs.[896] In this LEGO-like integration paradigm, compatibility between modules becomes critical. In particular, circuit design is of paramount importance for smooth information and power flow across modules. Simple circuits near sensors for signal preprocessing to standardize the data format enable modular sensing integration, without the need for changing the central control unit during customization (*e.g.*, microcontrollers).[897,898] Additionally, such circuits can be fabricated *via* low-cost solution processes together with sensors, offering greater convenience during prototyping.

A prototyping platform with industrially relevant facilities for both design and manufacture allows sensor developers to test their designs on larger scales and to collect more data for design refinement. This would be extremely helpful in crossing the "valley of death". Nevertheless, building such an infrastructural and technological platform is a daunting task, calling for large investments as well as participation from industry and academia, across the entire value chain. Governments will need to play leading roles in this endeavor.

Scalable Manufacturing. Successful prototyping does not guarantee market launch. The next important step is to move from prototypes to samples that are manufactured in production

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lines. Scalable manufacturing entails the ability to produce devices in large quantities with consistent performance at reasonable costs. Throughput of lab-scale production is minuscule compared to industrial manufacture[27] and lab-produced sensors usually suffer from large device-to-device variation, impairing the reproducible and reliable sensor performance required in commercial products. Moreover, during manufacture translation, sensor and system performance should not be affected significantly although certain compromise might be needed.

A general guideline for scalable manufacture is that manufacturing processes should be largely, if not fully, automated, with detailed in-depth study of process parameters. Instead of reinventing the wheel, utilizing existing industrial manufacturing facilities with slight modification is more viable to large-scale fabrication of flexible sensors. Such facilities, based on current knowledge, include those used for microelectronics, MEMS, displays, textiles, polymer processing, and paper printing. A few examples implementing this tactic are stretchable circuits by transfer printing of microfabricated silicon nanoribbon-based circuits,[377] silicon microneedle arrays on flexible substrates by dual-side lithographic microfabrication,[618] and large-area pressure sensors made *via* a track-etch membrane template.[899] Printed electronics, in particular, are at the confluence of electronic materials processing and traditional printing on paper or textiles.

Printed electronics technology enables fabrication of large-scale, low-cost electronic devices on a variety of substrates (*e.g.*, paper, plastics, textiles, leather, wood, metals, ceramics, glass), instrumental in the development and manufacture of flexible sensors. It presents major cost and scalability advantages over conventional MEMS sensors, enabling many killer applications. Moreover, printing offers a promising strategy for monolithic integration of various devices onto flexible substrates.[28] A wide variety of printing techniques are available and have been extensively reviewed.[28,900] Nanomaterials-based printing techniques, formulation of printable inks, post-printing treatment, and integration of functional devices are important topics and have recently progressed substantially.[900−902] Fully printed sensors,[874] displays,[903] energy devices,[680,904] memory devices,[905] transistors and circuits,[198,397] and integrated systems[906] have been demonstrated.[28,44,679,900,907] Nevertheless, printed devices are limited in feature resolution (1−100 μm) and device consistency. While targeting low-performance (and low-cost) applications can circumvent these limitations, crafting solutions to improve processing quality is essential to expand the application space of printed sensors.[907] Two specific areas facing considerable challenges are: tailoring ink compositions to a specific printing technique while keeping the printing process low-cost and high-speed, and obtaining decent electrical conductivity at sufficiently low temperatures to prevent degradation and damage of plastic substrates or biological tissues.

Polymer-based functional materials possess advanced mechanical (*e.g.*, stiffness variability)[419,551] and biological (*e.g.*, self-healing)[424] functionalities while preserving adequate sensing performance. They are the enablers of next-generation flexible sensors including intrinsically stretchable sensors and soft sensors for imperceptible skin electronics and implantable bioelectronics.[297,908] Moreover, their solution processability and potential recyclability[909] promise reduced environmental impact compared to inorganic-based electronics. However, scalable and high-quality manufacturing is a bottleneck for real-world deployment of polymer-based sensors. This impediment is because the processing of recently developed functional polymers (often with lower modulus and/or higher stretchability) is generally incompatible with electronics microfabrication, leading to difficult device integration.

Poor stability of polymers in harsh processing conditions is a major source of manufacturing incompatibility. For example, thermal expansion of polymers, especially stretchable ones, needs to be managed for high-resolution devices. Otherwise, different layers do not match well, leading to low device yield and consistency. Another problem is the poor chemical orthogonality between organic photoresist and organic electronic materials. Complex processing steps and additional material layers are needed to circumvent this issue,[353,547,910] leading to low device uniformity and resolution (feature size >100 μm). A monolithic microlithography technique was recently reported to overcome this challenge,[837] where UV light directly wrote micropatterns into electronic layers. The key to this technique lies in stretchable polymers with both electronic functionality (conductor, semiconductor, insulator, and dielectric) and UV-crosslinkability. The technique achieved record high device density for stretchable arrays (42,000 transistors per square centimeter) and small feature sizes (2-μm channel length) and enabled wafer-scale fabrication of ICs with high device yield, 98.5%. Future research should employ similar polymer design principles to expand the materials libraries that can be processed using this technique.[911] Overall, developing materials with better tolerance to processing conditions is critical to high-quality manufacture of polymer-based sensors.

Nanomaterials integration in flexible sensing systems presents another manufacturing challenge.[912] Large-scale production with consistent materials properties from batch to batch is a prerequisite for industrial applications but is currently unavailable for most nanomaterials. Furthermore, defect-free processing and precise patterning are critical for sensors that require high-quality nanomaterials.[272,913−916] In particular, for 2D materials,[917] the interfaces with substrates, metal contacts,[856,918] and dielectrics should be cleanly controlled, as the properties of atomically thin 2D materials are greatly affected by the quality of their surfaces and interfaces. Moreover, integration processes that are compatible with current MEMS fabrication should be developed. Alternatively, formulating printable inks is another route to apply nanomaterials at scale.[680,900]

The last manufacturing challenge lies in system integration. At present, heterogeneous integration or flexible hybrid integration is probably the most feasible, scalable, and cost-effective option for building advanced sensing systems.[28] Miniaturized microelectronic devices based on silicon technology are mass-produced with high performance, while organic or nanomaterial-based devices can meet requirements like large area and flexibility. Integrating these two kinds of devices takes advantages of the two approaches in both performance and manufacture. Importantly, the integration process can be achieved by adaptation of existing equipment and processes used in electronic packaging, polymer processing, and textile industries.

Soft-hard interfaces, interconnections, and packaging are major challenges in integrating devices with great variations in sizes and mechanical properties on a single thin-film or fibrous substrate. We lack effective strategies addressing these issues to ensure system reliability. A feasible route is to increase the level of integration in such heterogeneous systems towards

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monolithic integration. Instead of manufacturing individual components separately and assembling them on a common substrate, most system components could be manufactured monolithically on a single platform, with the addition of a few separately manufactured parts. For example, a sensor system might be entirely manufactured on a printing platform, but with pick-and-place mounting of a few silicon chips for essential needs.[28] This strategy requires the printing platform to be extremely versatile to handle multiple types of materials with sometimes incompatible processing conditions, which is a major challenge in printed systems. Such monolithic integration currently costs considerably more than heterogeneous integration. Using fewer materials to realize more functions is a rational strategy to alleviate this issue.[444]

Scientific and engineering development being one aspect, financial and infrastructural supports are pivotal in tapping the full potential of research outcomes. Currently, a large fraction of funding for sensor research is directed towards exploratory endeavors, but the development of production equipment that could later be used to generate revenue tends to be excluded from funding. Such funding often puts startups in difficult positions because all of their time and energy is dedicated to tasks that cannot generate revenue. The only path to revenue for most companies is to make large and reliable batches of their products. Therefore, to jumpstart the field of flexible sensors, a large amount of funding should be earmarked for the development of high-risk but potentially high-reward manufacturing capabilities. Moreover, academic institutions would be wise to nurture laboratories that invest heavily in developing the next generation of automated production equipment.

New materials and manufacturing technologies require years of development prior to commercialization. It took the semiconductor industry decades to evolve to a high-speed high-performance mass manufacturing technology.[79] Luckily, flexible sensors have the existing semiconductor industry and other related sectors as stepping stones. We might not be too far from their large-scale manufacturing.

Regulatory Frameworks. It is essential for any technology to be legally approved before its market launch. This gives consumers assurance and fosters trust in the products. As flexible sensors collect massive data and are often used in close proximity to humans, explicit regulations and restrictions need to be in place to ensure user safety, data privacy, and proper handling of ethics issues. Physical safety of sensor devices should be thoroughly examined in terms of toxic substance, biocompatibility, electrical safety, mechanical safety, *etc.*,[537] especially for devices employing unconventional materials and/or designs and deployed close to humans. Regulations for healthcare and medical sensors are more stringent due to critical health consequences associated.[10,537] Therefore, it is important to receive feedback from regulatory bodies such as FDA early when designing sensors for medical use.[520] Special safety concerns for bio-interfacing devices, beyond the biocompatible considerations outlined above, should be addressed. For example, accidental ingestion is a big risk for small, wireless monitoring devices used on infants.[919] Catastrophic battery failure or circuit overloading could lead to injurious thermal loads on the skin.[920] Repeated application/removal of skin-interfaced devices can lead to skin injuries in vulnerable populations.[568] Furthermore, there should also be data privacy regulations to prevent data breach and misuse. As flexible sensors enable many unconventional use cases, regulatory frameworks will need time to refine and to suit different products, and there will likely be disputes and ambiguities in the early deployment stages. In addition, for healthcare sensors, reimbursement coverage by governments and/or insurance companies will be crucial for widespread adoption.

Since flexible sensors manufacturing involves materials and processes, regulations in manufacturing should also be considered with the aims of quality assurance, worker safety, and environmental protection. Quality management systems and standard operating procedures should be set up and documented properly. Equipment, facilities, and processes should be qualified and validated in terms of reliability. All these manufacturing compliances should be audited periodically. Safe work practices with nanomaterials and organic materials during production, storage, transportation, and processing should be determined and codified. This process entails systematic examination of potential health and environmental risks posed by newly introduced materials and processes and coming up with proper handling protocols.[921]

Although complying with all related regulations may restrict and retard the broader deployment of flexible sensors, it is worth the effort for a sustainable growth of the sector. Regulatory considerations should be factored in as early as possible in the design process to avoid repetitive and costly adjustments at later stages.[921]

In addition to challenges in market identification, prototyping, manufacturing, and regulations, there are other business considerations along the commercialization path of flexible sensors. For example, how a startup should define the scope of its product is a question. It can be attractive to try to produce a complete sensor product, but it may be better to produce components and sell them to existing sensor manufacturers. When working with large entities that are potential partners, it is critical to understand common conventions of business development. Generally, partnering conversations are cordial and slow-paced, and there is no expectation of over sharing information. It can be disheartening to see that good intentions to help people using new technologies would not make their way to end-users because of poor market entry strategies, small market size, difficult fund raising, improper business models, *etc.* To maximize the chances of market success, researchers should improve their business awareness.

Case Study. When considering future commercial applications of flexible sensors, it can be helpful to study successful devices on the market as well as their failed predecessors. Although not a flexible sensor technology yet, continuous glucose monitoring (CGM), which uses wearable sensors to assess glucose levels continuously, resonates with the idea of using flexible sensors on the body for health monitoring. Since its conception in the early 2000s, CGM has emerged as a flagship technology for biosensing and has started to revolutionize diabetic care.[922] With a large worldwide prevalence of 540 million people in 2021[923] and a health expenditure of $760 billion in 2019,[924] diabetes remains a prime target for innovative sensing technologies. The CGM offers advantages in continuous monitoring, increased comfort, and more convenience than conventional finger prick tests. Major CGM manufacturers, Abbott, Dexcom, and Medtronic, all utilize subdermally implanted sensors to monitor interstitial glucose levels. The strong correlation between glucose levels in blood and readily accessible interstitial fluid has been pivotal to the commercialization of CGM devices. This highlights the potential of detecting well-known analytes in minimally invasive biofluids (*e.g.*, sweat, tears) and the importance of establishing strong

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correlations with gold-standard bio-samples (*e.g.*, blood, cerebrospinal fluid). Patient adoption of CGM devices has been rapidly expanding, as evidenced by a 237% revenue increase of Dexcom between 2018−2021 and a forecasted global CGM market of $15 billion by 2032.[925] The success of CGMs has also led to the idea of assigning glucotypes in non-diabetic individuals,[926] in which people can track their glycemic responses to get more precise ideas of their predisposition to diabetes. Companies such as Levels Health and Nutrisense now sell CGMs with related software and information to those interested in monitoring their glucose responses in the context of weight loss, athletic performance, and improved general wellbeing. The commercial integration of CGM devices with autonomous insulin delivery pumps also represents a key innovation in the field of closed-loop therapeutics.

In addition to the success stories, understanding where certain technologies fail can be just as insightful. The first noninvasive (wearable and not subdermal) glucose meter to receive FDA approval was the GlucoWatch by Cygnus, Inc., in 2001. Instead of relying on an implanted sensor, the device used reverse iontophoresis, in which mild electric currents are applied on the skin to extract interstitial glucose. However, due to a combination of regulatory and technical setbacks, the device was removed from the market in 2007. Regarding regulatory hurdles, after FDA approval but without established insurance reimbursement codes, the high cost of the device limited its use. This highlights the importance of understanding not just regulatory pathways, but also insurance and healthcare reimbursement processes. On the technical side, some users reported discomfort after a few days of use, likely due to the current densities required for glucose extraction. The intellectual property was eventually purchased by Johnson & Johnson, and substantial research efforts continue to address the technical limitations of noninvasive biofluid sampling.

Within the flexible sensor sector, integrated skin patches for vital sign monitoring are an active area where many startups have emerged in recent years, such as MC10, iRhythm, VitalConnect, Chero, LifeSignals, BioIntelliSense, Sibel Health, and Sonica. These sensors are designed to generate medical grade data for clinical decision-making to improve in-patient experience or shift in-patient care to homes through remote monitoring. The market entry strategy is mainly through hospitals and healthcare providers, where insurance reimbursement can strongly affect patient adoption. Although some sensors from these companies have received FDA approval for medical use, the real clinical benefits, and thus the market, still await large-scale validation. To this end, many startups have been partnering with medical researchers and companies to conduct clinical trials, first to help simplify the trial process and second to test patient satisfaction and clinical outcomes when dealing with specific medical conditions. Likewise, MC10, a pioneer in skin-compliant multimodal vital sign monitors, was recently acquired by Medidata, who conducts clinical trials through its Sensor Cloud platform. Some companies have been experiencing rapid growth in sales since the COVID-19 pandemic, largely driven by the strong push for telemedicine in the healthcare industry. This accelerated digitalization is likely to continue providing strong momentum for remote patient monitoring technologies.

A few lessons can be gleaned from these early flexible sensor startups. First, most of the commercialized sensors use incumbent semiconductor technology to manufacture their key components, and it is the packaging that gives rise to mechanical compliance (*e.g.*, thin-film plastic substrates, silicone encapsulation). This highlights the pivotal role of packaging strategies. Second, medical validation is a lengthy process that involves multiple parties and a large population of study subjects. Extensive collaboration is therefore critical to startups developing healthcare sensing technologies. Third, most companies offer not only sensor hardware, but also data analysis capabilities, for instance, to diagnose a certain disease from sensor signal patterns. Although well-engineered flexible sensors can generate high-quality data, their real value depends on the usefulness of these data. Therefore, demonstrating the benefits of leveraging sensor data over conventional decision-making practices is important for any sensor technology to move towards commercialization.

In all, given the large diversity of potential applications of flexible sensors, the pathway from lab to end-user is equally diverse. Customized strategies should be devised for each use case. En route to ubiquitous adoption, many issues outside the domains of science and engineering will emerge.[927]

OUTLOOK

We have discussed the challenges in sensor and system performance and the issues along the way to commercialization. For long-term sustainable growth of flexible sensing technologies, several issues need to be factored in to guide research and development efforts, including environmental sustainability, industrial standardization, user engagement, and deployment to larger and diverse populations.

Sustainable Manufacturing and Devices. Flexible sensors are meant to be mass-deployable technologies applied in many aspects of life. An accompanying problem is the environmental impact such a prevalent technology may produce.[29] Electronic waste and semiconductor manufacturing have put a huge burden on our planet. Flexible sensors should at a minimum not exacerbate the problem, and even better if they can ameliorate it.

Hazardous, resource-intensive, and environment-damaging materials sourcing practices such as mining should be minimized as much as possible. Carbon as an abundant element, compared to many metals (*e.g.*, precious metals and rare earth metals), is a promising ecofriendly alternative as a functional material. Different forms of carbon (carbon black, graphite, graphene, graphene oxide, reduced graphene oxide, single-walled and multi-walled carbon nanotubes with or without functional modifications, and many more) *via* various production and processing techniques can cover a wide spectrum of properties, including insulating, semiconducting or conducting,[928] mechanical flexibility or rigidity, electrochemical activity, *etc*. Toxic elements should also be avoided (*e.g.*, developing lead-free perovskites) to minimize environmental and biological damage after product disposal.

Manufacturing of flexible sensors should adopt a low-carbon approach, such as additive manufacturing, solution processing, and low-temperature processing. Printed electronics often follow these principles and are therefore more environmentally benign than conventional microelectronics towards large-scale flexible sensor deployment. There is strong industrial interest in replacing PCBs, which are made using energy-demanding processes and harsh chemicals, with hybrid printed electronics (*e.g.*, the ECOTRON project by TNO at the Holst Centre[929]). In addition, sustainable manufacturing can be facilitated by industrial IoT and data analytics. For example, using sensor technology to detect leaks and improper material usage can help minimize waste. Digital data analysis can help remove

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superfluous steps and illustrate where to focus efforts to eliminate excess material and energy consumption. Such digital strategies towards sustainable manufacturing are being explored by many well-known brands, such as Apple, Microsoft, and Amazon.[930]

End-of-life disposal of used devices should be responsibly dealt with from the initial design stage. If the device is designed to be a long-term functional product, materials and systems durability are priorities, so that the product lifetime can be extended. If the device is designed to be disposable, the materials and device structure should allow easy recycling or impose minimal environmental impact when disposed of in landfills. Electronics recycling is not an easy task due to the highly mixed nature of materials in downscaling to nanostructures, use of nanocomposites and nanoinks, *etc*. Therefore, there is a pressing need for effective recycling strategies of electronic waste. A few examples of recent progress in this area[909,931−933] include aqueously recyclable circuits,[934] recyclable and reconfigurable hybrid integrated sensor patches,[935] and upcycling of compact discs for stretchable biosensors.[936] Nanomaterials manufactured bottom-up show promising recycling potential when the polymer substrate/matrix and the working solution are properly paired.[937,938] A more advanced concept over recycling is disassembly for remanufacturing,[939,940] which may be explored in the future. Besides recycling, another strategy is to synthesize or to utilize degradable materials to minimize the impact of disposal (*e.g.*, gelatin-based all degradable on-skin sensor patches,[941] degradable pressure sensors based on MXene/tissue paper[942]). The use of biological or biologically derived materials (*e.g.*, silk,[372,943,944] pollen,[945,946] wood,[947] leather,[948−950] biosynthesis by bacteria[951]) in flexible sensors is a budding field and might be the ultimate solution to 'environmental imperceptibility'.[952] Still in their infancy, biological materials-based devices are rather primitive with unsatisfying performance, stability, and reproducibility. Overall, life-cycle analysis is necessary to get a full picture of the environmental impact of a certain material or device.

Lastly, policies and legislation are critical to overcome the inertia in traditional manufacturing and end-of-life practices. Since many flexible sensors are manufactured using cheap plastics, they tend to be single-use and disposable without sufficient long-term stability. The economics alone will not encourage sustainable handling of such devices, as the cost of recycling will outweigh that of manufacturing new devices. In this case, governmental intervention through policies and legislation such as carbon taxes will help shift the balance and encourage responsible sensor manufacture and disposal. In the long run, research on converting waste plastics into high-value materials or products[953] would drive a sustainable 'circular sensor economy'.[11]

Industrial Standardization. As sensor systems become more complex, involving a multiplicity of disciplines and technologies, standardization becomes more important than ever. Standardization is needed in terminology and nomenclature, materials specification and characterization, device/component specification, sensor/system performance evaluation, software interfaces, communication protocols, data management, *etc*. Among these aspects, materials specification and sensor/system performance evaluation deserve special attention.

Specifications in materials properties are crucial for downstream materials processing and device fabrication—they directly affect the quality of produced parts. Nanomaterials properties are sensitive to minute structural alterations. Hence, standardized descriptions of nanomaterials morphology is key to their ubiquitous adoption.[954] For instance, a Technical Committee has been assembled by ISO to establish base values for 19 measurable characteristics (*e.g.*, lateral size, number of layers, oxygen content) of graphene materials. Moreover, standard testing methods are of paramount importance to fair reporting nanomaterials' intrinsic properties[633] because the high surface activity of nanomaterials makes them prone to influence from the testing environment and interfacing materials.[914] Strain coupling into materials' performance adds another dimension of testing complexity. For example, when characterizing the conductivity of stretchable conductors (and mobility of stretchable semiconductors), the interfacial contact with rigid electrodes (and rigid dielectrics for semiconductors) during stretching should be well maintained to eliminate any interfacial effects that can distort the true properties of materials under test. However, standardized materials specifications are hard to achieve in newly developed materials, due to a lack of batch-to-batch consistency in production. Many of the newer elastomer products have yet to develop sufficiently to have standard and reliable synthesis protocols. In addition, since stretchable electronics are in early stages of development, many of the commercial elastomers are not produced in high volumes, so there has been little incentive to develop highly standardized synthesis methods. The same problem exists for nanomaterials, whose unreliable production hinders standardization in material specifications.

As flexible sensors expand the functionality of incumbent sensor technologies, many new performance metrics need to be well defined and tested using explicitly specified protocols for fair comparison between devices and products.[648] For example, how permeability tests should be done for 'breathable' sensors, what parameter should be used to quantify breathability, and how much of this parameter indicates safe usage for skin? There are contradictory claims on the permeability of PDMS (positive claims in refs 60 and 955 and negative claims in ref 602), which causes much confusion when selecting the encapsulation material for on-skin sensors. This discrepancy likely originates from non-standardized testing methods (sample thickness, temperature, humidity at both sides of material, *etc*.),[956] and the variability in intended application scenarios (skin position, skin sensitivity of subjects, *etc*.). Given that the insensible perspiration rate and exercise perspiration rate can differ by one or two orders of magnitude,[580,602] and the water permeability of normal skin is between 240 to 1,920 g m^{-2} day^{-1},[60] a 'safe' range and a 'comfortable' range of water permeability should be defined accordingly, and the same applies for gas permeability. Likewise, there is an urgent need to define the performance metrics of other descriptive terms, such as stretchable, adhesive, conformal, and to specify the best benchmarking practices.[957] Moreover, for flexible and stretchable sensor systems, mechanical reliability tests need to be standardized.

Standardization spells out the foundations and best practices for sensor design, manufacturing, and operation, thus facilitating communication and collaboration between various partners in the field to expedite technology maturation. It drives economies of scale and eliminates barriers to trade; it also boosts consumer confidence and promotes sustainable development, thereby fostering sector prosperity in the long run. However, the process of standardization faces many challenges. It usually requires some degree of market penetration, so that industrial players can be involved in the process and real-world issues can be properly

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addressed. However, most flexible sensor technologies remain in research or in the process of lab-to-market translation; they are not sufficiently mature to put forward clear incentives for standardization, since standardization is a time-consuming and complex process.

User Acceptance and Engagement. There can be barriers to accepting flexible sensor technologies that interface intimately with the human body. There are also risks of stigmatization, particularly for wearers with certain diseases. One way to address these issues is to conduct comprehensive user studies to identify the optimal body locations to place sensors, with a balance between data collection quality and user preferences.[958] Alternatively, developing transparent, ultrathin, and invisible sensors would reduce the risk of stigmatization. Every stakeholder within the field of on-body sensors has a responsibility to address fears, preconceptions, and misconceptions. To this end, researchers can work with designers and artists to package sensors with artistic and fashionable designs. Such convergence can also lead to artwork and exhibitions to improve the public's awareness of on-body sensors and the importance of health monitoring. Different sociocultural ecosystems must be factored into designs as well. We believe that public opinion will lean towards acceptance as knowledge increases and human-centric applications begin to improve lives.[79]

There will also be anxieties about privacy and data security.[79] To address these concerns, regulatory frameworks and legal structures must be in place, clearly communicated, and strictly enforced. Medical and health data must remain individual property, and their use should require consent. It should be articulated who has access to which portions of the user data, and confusing and vague privacy policies should be avoided. For instance, researchers may use health data with users' consent for the benefit of society without knowing the identities of the individuals. These principles are to ensure that data are not exploited for discriminative or malicious purposes, such as setting insurance premiums on the basis of health data or selling data for profit. On the technical front, security protocols should be developed to guard against attacks, so as to gain user trust.

Translating data into useful forms rooted in human needs[79] and presenting them in a user-friendly way will be essential for long-term user engagement. This issue is often overlooked by sensor developers. For example, in spite of strong sales, around 50% of wearable fitness monitors are abandoned in the first year of use.[959,960] This attrition was found to derive from decreased interest in the technology after its novelty wore off, perceived lack of benefit relative to intrusiveness, poor experience with the user interface, and frustration with technical problems.[960−963] Therefore, it is critical to make technologies simple and convenient to use with tangible improvements to life. Raw data are of little use for a general user,[79] especially when a handful of sensors work cooperatively. Instead, sensor data should prompt action (*e.g.*, by alerting the wearer to the risk of heart attack and suggesting intervention measures)[79] or provide insightful analyses of states (*e.g.*, by estimating the remaining service life of a structure or facility). Reward or feedback mechanisms may be included to make sensor use more interactive and interesting. When users find sensors helpful in improving their daily lives, they will tend to appreciate the benefits and thus be more compliant with the instructions and eventually rely on the technology.

For human-centric applications beyond healthcare, such as augmented reality and virtual reality, social-science studies will be crucial to understanding the short- and long-term impacts of these forms of human-machine interactions—how they shift our mindsets and change our behaviors—and to revealing unintended consequences. We must develop flexible sensor technology responsibly, being mindful of its repercussions.[79]

Equitable Deployment. Flexible sensors are expected to help solve critical challenges facing humanity, including those in healthcare, aging populations, food security, among many others. The benefits should be shared by both developing and developed countries. In addition, some flexible sensors can be manufactured using less expensive materials and processes than conventional sensors/machines, making them suited for deployment in less developed regions, for instance, to replace bulky high-tech equipment in hospitals for more accessible clinical care.[964] There have been promising attempts to deploy flexible sensors in low-resource settings.[502,793,867,965] However, the cost-effectiveness of these technologies has yet to be examined, which is essential for sustainable deployment in the long run. In particular, medical devices are usually single-use and disposable, which makes them costly if used in large numbers. Making devices reusable is an effective way to normalize costs but is often limited by sterilization and regulatory concerns. To deploy sensor technologies in less developed regions, infrastructural and regulatory support should be taken into account. For example, is wireless infrastructure available and capable of supporting data transmission within the sensor networks? Are power sources readily available for frequent charging? Is there a regulatory body taking charge of the sensor product and are the regulatory frameworks in place for market entry? All these questions need to be answered and integrated into sensor design and translation for wide deployment around the world.

Talent Pipeline. To sustain the growth of flexible sensing technology, a talent pipeline that continuously provides a qualified workforce is critically important. As sensing is an interdisciplinary subject, conventional curriculum structures and rigid course selection confined within specified majors do little to help prepare engineers and innovators for the future sensor sector. Educational innovation is an acute need and is underway in some institutions. For example, programming for signal processing and data analysis is such an important component of sensing that it should be a core part of graduate training programs in chemistry, biochemistry, and biomedical engineering, to train next-generation chemists, biologists, and engineers working at the interfaces of (bio)chemistry and engineering.

Sensor Intelligence. Intelligence is the most prominent differentiator of Sensors 4.0 *versus* previous generations of sensors. Although intelligence is not exclusive to flexible sensors, much research in intelligent sensors and flexible sensors goes hand in hand. Here, we provide a brief overview of the ongoing efforts and future directions for intelligent sensors in general, with special focus on their demonstration and application in flexible sensors.

We envision that future intelligent sensors should possess the following characteristics (Figure 15): (1) fully autonomous (closed-loop) operation from stimuli detection and signal processing, to data analysis and feedback, while maintaining communication with operators/users,[563,771,807,966−968] (2) capability to analyze complex sensor signals (multimodal and multiplexed signals, array signals, and sensor networks) to provide accurate and customized analysis of specific situations and to produce actionable feedback, (3) robust performance under non-ideal conditions including tolerance to errors and

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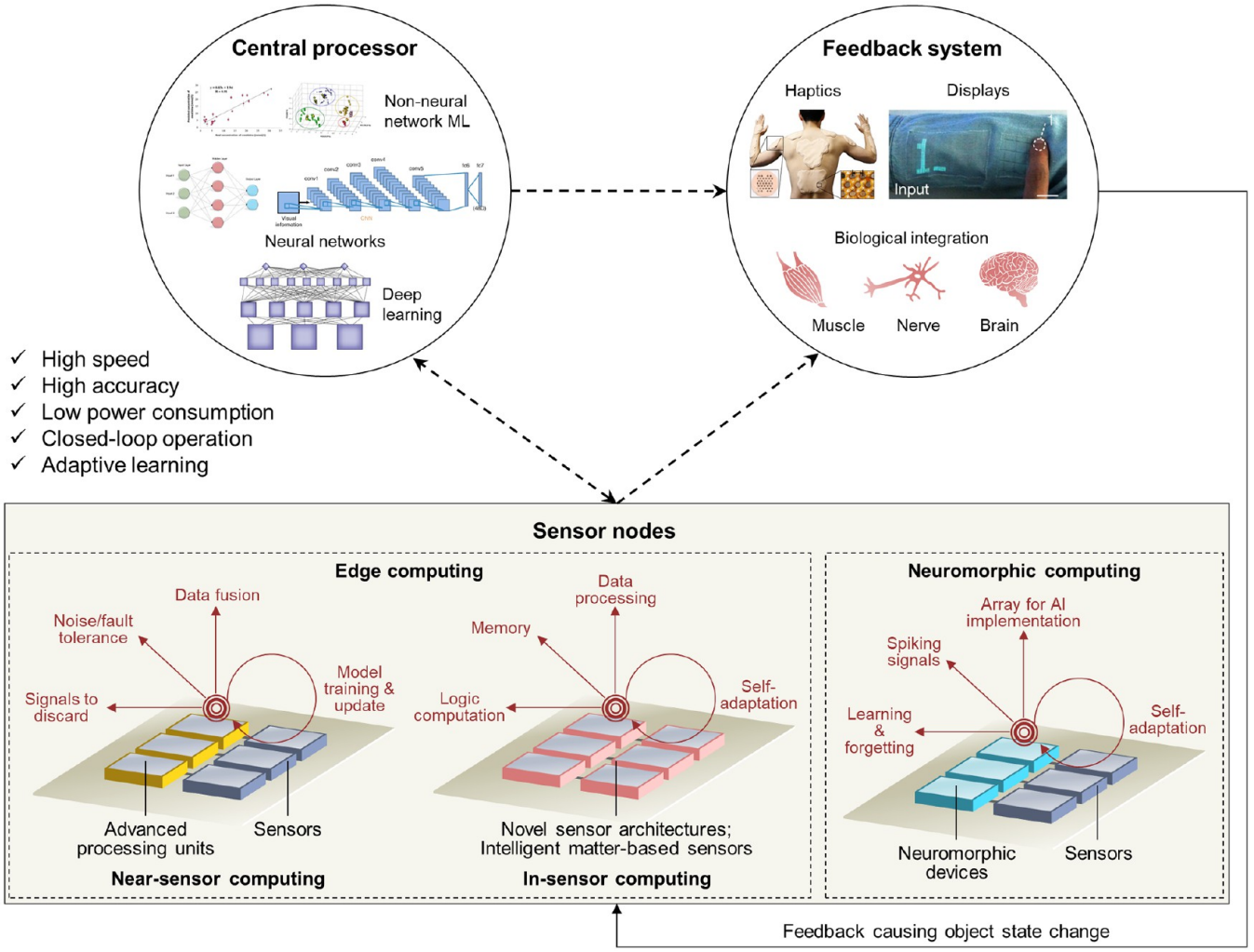

Figure 15. A vision for intelligent sensing systems with advantages listed on the left. Edge computing (including near-sensor and in-sensor computing) and neuromorphic computing are plausible ways of achieving sensor intelligence. They are not mutually exclusive and may be implemented in a single system. AI algorithms will be implemented in both central and edge processors. A feedback mechanism not only informs the user but also completes closed-loop operation. Integration with biological tissues permits two-way communication in various forms (details in Figure 16). Dashed black arrows indicate the direction of data flow. Images of non-neural network ML (machine learning) adapted with permission from ref 156. Copyright 2018 American Chemical Society. Neural network schematic adapted with permission from ref 969. Copyright 2020 Springer Nature. Deep learning schematic reproduced with permission from ref 970. Copyright 2015 Nature Publishing Group. Haptics image adapted with permission from ref 895. Copyright 2022 Springer Nature. Display image adapted with permission from ref 605. Copyright 2021 Springer Nature.

noise, and adaptability to changing environments, (4) learning capability to refine and improve performance with continued usage, (5) fast response (real-time feedback) with high energy efficiency, and (6) compact, lightweight (and flexible for bio-integration) form factors. These features will empower intelligent sensors to solve complex and unstructured real-world problems efficiently and reliably, while requiring less maintenance and management.

To achieve these ideal characteristics in future intelligent sensors, research efforts are underway in innovating advanced algorithms for data analysis, implementing edge computing to extend sensor capabilities, and inventing neuromorphic hardware for next-generation sensory computing architectures.

Advanced Algorithms. Conventional algorithms for signal processing and data analyses perform well enough for simple data forms. However, they become inefficient or incapable when datasets become large,[10,209] complex,[10,661] non-linear,[209] high-dimensional,[971] erroneous,[972,973] or with unclear correlations.[390] Therefore, more powerful algorithms, predominantly machine learning (ML) methods have been proposed to overcome these challenges and shown promise in flexible sensor applications, such as sign language recognition,[969,974,975] electronic skins,[41,976,977] human-machine interfaces,[972] and biosensing.[224,973] Besides handling challenging data, ML can also be used to compensate for sensor performance deficiency, such as signal noise,[410,978] drift, and limited range of detection.[979] Additionally, ML allows for the fusion of multiple types of data for more accurate[10,499,969] and/or more insightful[10] analyses.[500] ML can be used to adapt to the dynamic properties of uncertain systems and can support fast and real-time analyses of big data.

Core ML methods for flexible sensors include non-neural network methods (*e.g.*, linear regression, principal component analysis, support vector machines) and neural network methods (*e.g.*, multilayer perceptron, convolutional neural network, recurrent neural network).[973] To deal with the increasing

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amounts and complexity of sensor data, deep learning, a subset of ML, is being developed, which can automatically learn features or rules from raw data with less human intervention than traditional ML algorithms.

Despite the benefits offered by ML algorithms, they suffer from major drawbacks including reliance on training quality, heavy computing burden, and data transfer issues. As ML algorithms rely on big dataset training to refine model accuracy, a reliable source of high-quality training data is important to algorithm performance. However, high-quality training data are not always accessible in sensor applications. Deviations in training datasets from data collected in real-world settings can lead to suboptimal performance in deployment. Furthermore, the implementation of ML algorithms often requires powerful computers, which are not accessible to general sensor users. Hence, cloud computing through online servers is a more viable option, which demands frequent data transfer between sensor nodes and cloud servers. The resultant heavy data traffic puts pressure on high-speed low-latency wireless communications, as well as power supplies on sensor nodes. Energy consumption for algorithm implementation should be considered, given the ballooning carbon footprint of cloud computing data centers.[980]

Meanwhile, we should be careful in the development and use of ML for sensor data interpretation. The lack of a physics foundation in black-box models hinders interpretation and generalization. Sound and relevant physical, chemical, and biological knowledge should be incorporated in the learning process of ML models with frequent reality checks.[981] Theory-driven ML that seeks causality by integrating prior knowledge and big data has shown effectiveness in solving problems in biology,[982] climate,[983,984] and many other scientific and engineering fields.[985−987] Likewise, appropriate sensing theories can be integrated in the loss function, initialization, architecture design, *etc.* for hybrid modelling of ML algorithms[986] used in flexible sensors.

Edge Computing. Expanding sensor networks will generate huge amounts of data in widely distributed sensor nodes. Conventional processing architectures, where data in the sensor nodes are transferred to centralized processing units for computing and storage, will lead to high energy consumption and large latency.[41,988,989] To tackle these problems, edge computing is preferred, where data are processed locally near the sensor nodes. Edge computing distributes computation tasks throughout a sensor network, facilitates quick data analyses, and reduces computational burden on the central processing unit. It can also offer a layer of encryption to sensitive data before transmission.[990] Near-sensor computing and in-sensor computing are two available paradigms to implement edge computing.[991]

Near-Sensor Computing. The most straightforward way to realize edge computing is to place processing units beside sensors and integrate them on a single platform. Because conventional processing units are based on rigid chips, flexible hybrid integration is the common approach.[502] Here, the main challenge lies in reliable integration and manufacture to ensure mechanical stability. In addition, these systems often present low-density and low-level sensory processing capabilities; much effort is therefore needed to improve integration and functional complexity of hybrid sensing systems.[266,290,468] Moreover, long distances (from micrometer to millimeter scales) between sensing and processing units are unavoidable due to different manufacturing processes, resulting in long parasitic resistance−capacitance time delays and high-power consumption.[991] Emerging integration concepts, such as 3D monolithic integration currently under development for rigid electronics,[992−994] should be explored in flexible sensing systems.

To overcome the mechanical and manufacturing incompatibilities between rigid processing units and flexible sensors in flexible hybrid systems, flexible and even stretchable ICs (and memory) are emerging solutions and have seen significant recent progress.[326,378,466,469,783,995,996] Processing functionality, including strain compensation,[379] signal amplification,[400] frequency modulation,[997] and sensory adaptation[998] have been demonstrated. However, the scale and complexity of flexible ICs need improvement towards elevated signal processing and computing power. In particular, high-performance *n*-type organic semiconductors should be developed for complementary circuit implementation.[999] In addition to conventional interface circuits, emerging computing devices offer opportunities in near-sensor computing.[1000] For example, recent work integrated flexible memristor arrays with pressure sensor arrays to deliver ultrafast (400 ns), energy-efficient (1000-fold power reduction) tactile sensory processing.[1001]

To boost the computational capabilities of near-sensor processing units, state-of-the-art technologies such as on-chip AI processors could be incorporated.[996] Compared to conventional AI methods implemented on a cloud, edge AI can realize real-time data fusion and offer lower power consumption. A critical challenge for edge AI implementation is near-sensor model update. Current practice usually requires offline training before being implemented in a near-sensor system.[1002,1003] When the training data fail to capture a broad spectrum of conditions in deployment, without prompt model update, classification accuracy of the model will decrease.[1004] This issue is particularly problematic for low-power systems operating lightweight algorithms. Algorithm design with balanced training requirements and model performance is necessary, and effective online training approaches should be developed.[1005]

In-Sensor Computing. In-sensor computing is a paradigm where computation tasks are executed within sensors at the device or material level, unifying sensing and processing in a single device. Such processing approaches reduce data transfer and data format conversion that occur in physically separate sensing and processing units, realizing ultrafast and energy-efficient responsive systems in a simplified architecture.

In-sensor computing can be realized by rational device design with careful materials engineering. Environmental adaptation has been demonstrated using this strategy.[1006] For example, a bioinspired organic transistor was designed with two functionally complementary bulk-heterojunctions to realize active adaptation to light intensities.[1007] Likewise, a dynamically adaptive vision sensor with both photopic and scotopic adaptation was achieved using a 2D MoS_2-based phototransistor array.[1008] Processing functions other than environmental adaptation have also been reported. For instance, Mennel and co-workers developed an image sensor that could capture optical information and simultaneously implement an artificial neural network for image processing directly in the sensor.[1009] Innovations in device physics and in-depth investigations into energy-matter interactions are needed to discover and to engineer more functionality into in-sensor computing devices.

On the other hand, intelligent matter, implemented by molecular systems and soft materials, has been explored to execute in-sensor computing.[1010−1013] Intelligent matter can interact with the environment by receiving and responding to external stimuli, and simultaneously implement data processing

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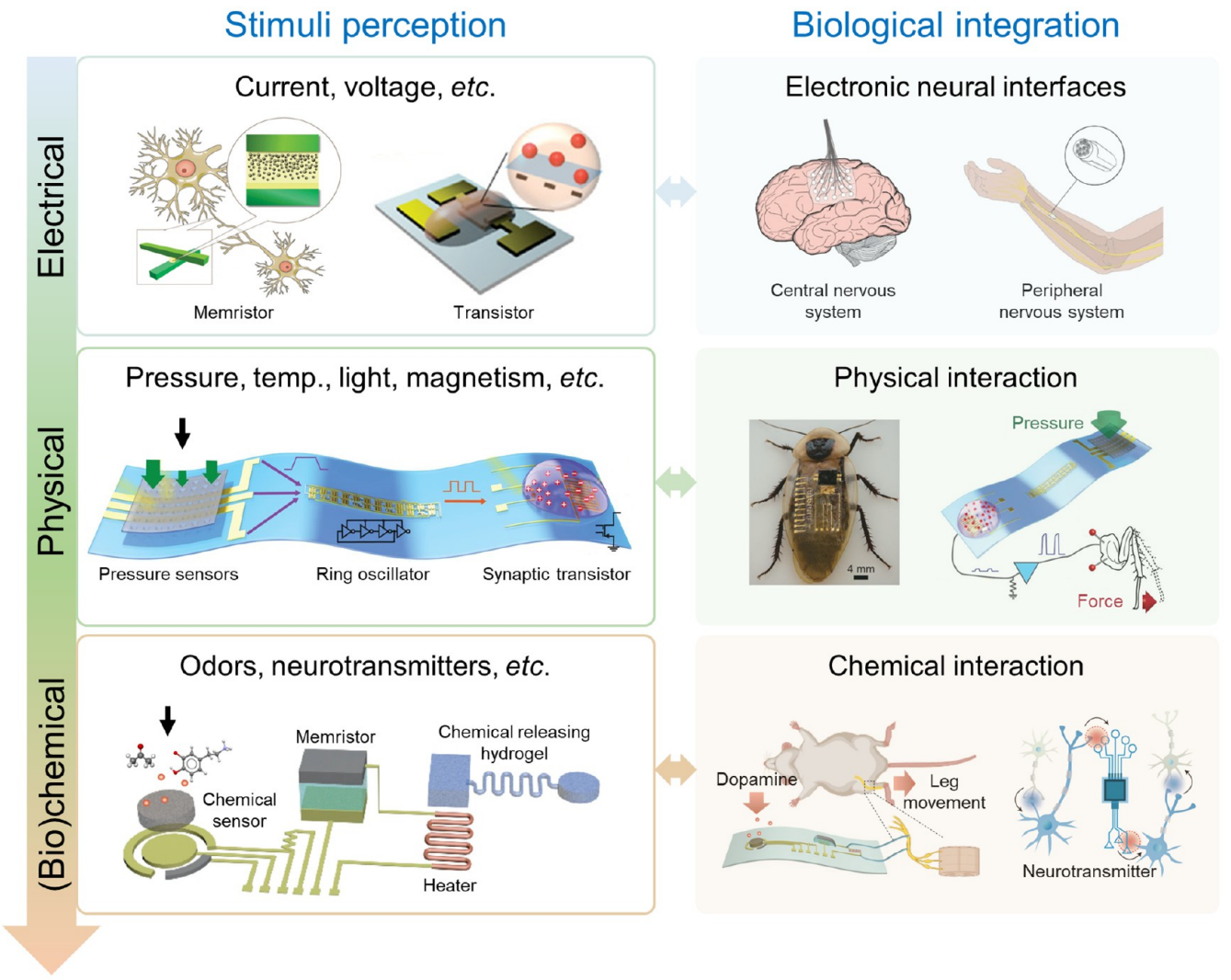

Figure 16. Evolution of flexible artificial sensory devices and systems for bio-integration. Memristor schematic adapted with permission from ref 1067. Copyright 2010 American Chemical Society. Transistor schematic adapted with permission from ref 1053. Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Electronic neural interface schematics adapted with permission from ref 1068. Copyright 2020 Springer Nature. Pressure sensory artificial neuron and bio-integration images adapted with permission from ref 1055. Copyright 2018 American Association for the Advancement of Science. Chemical sensory artificial neuron and bio-integration schematics adapted with permission from ref 1039. Copyright 2022 Springer Nature.

and storage at the matter level by adapting structures or internal states. As a source of inspiration, an octopus has more than half of its neurons distributed in its arms. Although mimicking the sophistication of an octopus is incredibly challenging, there are some examples of simple logic being done in soft materials without conventional logic devices.[1014−1017] While in-sensor computing using intelligent matter is still in its infancy, it is an area of opportunity for truly intelligent materials that can process information locally and respond appropriately.

Neuromorphic hardware. Human sensory systems can perform sophisticated functions while being highly energy-efficient. They rely largely on the structure and operation of the nervous system including the brain, spinal cord, and peripheral nerves. Capable of emulating aspects of nervous system sophistication and efficiency in sensory information processing, neuromorphic electronics may play important roles in intelligent sensors. However, conventional sensors, circuits, and processors are not built to implement neuromorphic sensory processing and computing efficiently. To fill this gap, neuromorphic devices with various materials and device physics have been proposed and intensively studied.[1018−1020]

Promising neuromorphic devices include memristors,[1021,1022] spintronics,[917,1023] synaptic transistors,[1024−1029] and memtransistive synapses (a combination of memristors and transistors),[1030,1031] with features including analog computing and parallel storage and processing, in stark contrast to conventional digital processers. Individual neuromorphic devices when integrated with sensors or embedded with sensing functions can preprocess sensory information in a delocalized manner, providing a promising route to edge computing. When interconnected in large scales, neuromorphic device arrays can be used to implement artificial neural networks more efficiently than conventional processers.[1032,1033] However, much current work only simulates neural networks by extracting device parameters, instead of implementing physical demonstrations of array hardware.[1034,1035] Actual physical implementations face challenges in device yield and consistency, array integration, system robustness, *etc.*

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Sensory demonstration based on neuromorphic devices has been successful in producing artificial sensory systems mimicking biological counterparts. The building blocks of artificial sensory systems, besides sensors, are artificial synapses and artificial neurons. An artificial synapse emulates the characteristics of a biological synapse, such as long-term and short-term plasticity modulated by spike inputs, enabling memorization, learning, adaptation, and other biological computational capabilities. Currently reported artificial synapses are modulated by diverse stimuli such as electrical input,[1018] light,[1036,1037] chemicals (neurotransmitters),[1038−1041] temperature,[1042] and combinations of the above (*e.g.*, electrical and optical inputs[1027,1043]). Electrical modulation offers greater convenience in integration with other electronic devices including sensors, while other modulation modes permit direct sensing by artificial synapses.

Artificial neurons transduce analog sensory stimuli into spikes (although some stimuli are naturally in a spike form such as sound and vibration[1044]) and subsequently relay the spike-encoded information to artificial synapses for processing. The spike form can encode rich information in its frequency, duty cycle, number of spikes, *etc.*, and is easily handled by digital processors and synaptic devices. It offers superior power efficiency, as noted above, due to event-driven operation. However, research on artificial spiking neurons that do not rely on complex ICs[513,978,1045−1051] has been hampered by a dearth of available materials and devices. Recent advances in artificial neurons and artificial synapses include reconfigurations between the two on demand in a single device,[1052] which will enable more powerful and adaptive algorithm implementation.

Integrating sensors, artificial synapses, and artificial neurons produces artificial sensory systems (Figure 16, left).[1019,1039,1053,1054] Artificial tactile systems[513,978,1055−1058] and artificial visual systems[1048,1059,1060] are the most developed; fusion of these two sensory modalities for improved recognition accuracy[1061] or biomimetic learning behavior[1062] has also been demonstrated. Artificial olfactory systems[1049] and artificial gustatory systems[1063] have been proposed, representing emerging directions for chemical sensing. In addition to the five senses, artificial reflex arcs can also be produced by integrating additional actuators,[1064,1065] and artificial proprioception was recently demonstrated in animal leg movement control.[1066]

The development of this area has shifted from pursuing biological fidelity in artificial devices to exploiting the advantages of biology-like perception to empower and to connect humans and machines. To this end, research efforts have been dedicated to making artificial sensory systems flexible and stretchable.[1019,1055,1057,1060,1066] This will enable seamless integration of machines for intelligent robots[1000,1058,1069,1070] and connection to biological tissues[1039,1055,1066,1071] for human-machine interfaces, neuroprostheses, and cyborgs to repair, strengthen, and augment human perception (Figure 16, right).[468,908,1072,1073] Challenges exist in thoroughly understanding biological sensory systems (as a source of inspiration for the conceptual design of artificial counterparts), array and system integration with densities and complexities on par with biological systems, and functional bio-integration.

CONCLUSIONS AND PROSPECTS

Sensors have become indispensable in modern society and in the era of big data and digitalization. To achieve massive sensing scales and sensing on ubiquitous objects, flexible sensors enable us to advance beyond conventional rigid sensors by enabling high-fidelity measurements on complexly shaped and deforming surfaces, as well as (potential) low-cost large-area manufacturing. These features allow flexible sensors to excel in various applications, such as wearable health monitoring, smart packaging, and building-integrated sensing. Despite the strong impetus and fast progress in research, industry and market adoption of flexible sensors awaits the future. With the objective of identifying roadblocks, we analyzed key challenges concerning the performance, fabrication, and commercialization of flexible sensors and systems, and proposed possible solutions to these problems.

The performance of flexible sensors pertaining to stability, selectivity, and sensitivity needs improvement. Stability is the greatest challenge, calling for effective packaging strategies and encapsulation materials. Nonetheless, temperature-associated instabilities are hard to solve using these strategies. Specifically, for wearable biosensors, biofouling and bioreceptor instability are the key issues. Smart surface engineering and immobilization strategies are needed, and molecularly imprinted polymers have emerged as one promising alternative to biological receptors. Signal drift over relevant periods of operation should be properly reported and handled for emerging sensor technologies.

Selectivity is a major concern for mechanical sensors, biosensors, and gas sensors. Specific sensing materials and selective sensing arrays are two general approaches to improve selectivity. Although both strategies have produced promising results for mechanical sensors, trade-offs in the complexities of sensor design and data analyses exist. Selective biosensors usually require the use of biological recognition elements, which offer exceptional specificity yet are sometimes hampered by poor stability. Nanocatalysts can deliver specificity in some cases. Closely related to biosensors, flexible gas sensors are an emerging field, where materials engineering towards specific gas sensing remains a fundamental challenge. Selective sensing arrays are more commonly used, in which algorithms for pattern recognition are decisive in detection accuracy.

Simultaneous achievement of high sensitivity, wide sensing ranges, and linearity is a major challenge for mechanical sensors. Traditional strategies of microstructuring and materials engineering can be used to achieve compromise. Recently proposed sensing mechanisms still need refinement, and the emerging idea of on-demand performance programming offers customizable sensors for different applications. Sensitivity is a critical challenge for biosensors to detect low-concentration biomarkers that are clinically relevant. Nanomaterials play central roles in this regard, being catalysts, electrodes, and/or parts of transducing devices. Although fluorometric sensing offers substantially improved sensitivity over colorimetric sensing, simple and accurate signal detection is a bottleneck. Analyte preconcentration and signal amplification by circuits are also options to improve biosensor sensitivity.

In addition to sensitivity, selectivity, and stability, the dynamic responses of mechanical sensors should be considered as an essential performance metric and properly tested and reported in future research. Hysteresis, response time, and strain-rate dependency are major concerns. Although structural and materials engineering helps to some extent, effective solutions remain elusive. Wearable biosensing awaits improvements in diversifying accessible biomarkers and consolidating continuous monitoring capabilities. To this end, label-free, reagent-free, and wash-free sensing methods, as well as regeneration strategies are needed. Importantly, sensor accuracy assurance should be

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factored in during the entire process of sensor development to deployment. Calibration is particularly critical yet often overlooked by the research community. Equally important to accurate sensing is establishing robust correlations between sensor data and the status of the monitored objects/environments. This is a serious issue for health monitoring sensors, where many biomedical questions await large-scale systemic investigation and validation.

Mechanical tolerance is the second important aspect of flexible sensor performance. Flexible sensors need to survive mechanical deformations during use. The most prominent challenge is at soft-hard interfaces, and interconnections are particularly concerning. Improving interfacial adhesion and adopting a gradual change in modulus are proven principles, and ongoing work proposes various implementations. Many solutions have been proposed for interconnections in flexible hybrid systems, but the results are not yet satisfactory. Soft interconnects with strong bonding in versatile application scenarios are desirable. Alternatively, wireless connections between subsystems can be adopted. A second issue is extending the elastic deformation range of flexible sensors, which has been addressed by structural engineering and materials innovations. Notably, ionically conductive materials such as hydrogels offer soft and stretchable materials platforms for sensor development. However, there is still much to do to achieve satisfactory performance and realistic manufacturing. Third, fatigue should be considered for sensors undergoing repetitive deformations. Interfacial engineering and crack stabilization are important topics.

Flexible sensors also need to retain stable function under deformation. Decoupling the strain effect on signal output is a challenge. Although efforts to extend the elastic range contribute to mitigating this problem, perfectly strain-insensitive performance is challenging to achieve. Motion artifacts are serious problems for wearable sensors. Enhancing sensor conformability and adhesion and incorporating multiple sensors in a system are effective approaches, but it is challenging to remove all motion-associated noise solely *via* hardware optimization. Signal processing for noise filtering requires customized solutions to address complex human motions. Machine learning is showing early promise for this purpose. Specifically, developing flexible optical sensors that can retain stable performance under deformation or motion remains a fundamental challenge. Lastly, to make flexible sensors resistant to mechanical damage, tough, self-healing, and stiffening materials are being developed. However, sensor performance with these materials is usually unsatisfactory, and system-level validation of device longevity and durability is largely lacking. Structural design provides an effective alternative. Flexible electronic armors and mechanical metamaterials are worth exploring.

Array integration is a third aspect of flexible sensor performance. Signal readout through passive and active matrices are established solutions, but issues exist in electrical interconnects and circuit solutions. Low-impedance interconnects and high-performance transistor arrays in flexible and stretchable form factors are desirable. Readout strategies mimicking biological sensory systems may fundamentally overcome limitations in spatiotemporal resolution, energy efficiency, and wiring complexity of current electrical readout strategies. Optical readout circumvents many issues encountered in electrical readout, but reliable image capture becomes a bottleneck. Ultrasound and photoacoustic imagers impose more demanding requirements in array signal readout, calling for better solutions. Chemical sensing arrays offer a plethora of exciting opportunities. Multimodal sensing is an important feature of sensor arrays. Challenges include compact and simplistic design, high-density integration, addressability, and effective stimuli decoupling. Flexible imagers responsive to multiple colors are particularly difficult to realize, but recent developments in quantum-dot-based photodetectors are shedding light on this topic.

Compatible interfaces between flexible sensing systems and biological tissues are another important area of research, primarily for human and animal body-integrated sensing. While this topic has been extensively reviewed previously, we highlighted emerging trends. Soft, stretchable, adhesive, biocompatible, biodegradable, electrochemically compatible, and growth adaptable materials are desirable. Biocompatibility is a top priority when designing materials for bio-interfacing. Correct interpretation of the term and thorough experimental validation are required. Functional polymeric materials, such as conjugated polymers and hydrogels, are promising materials, and bioresorbable inorganics have been demonstrated with respectable performance and straightforward fabrication in nonpermanent implantable devices. Achieving biofunctionality without compromising sensing performance is a challenge for materials development. Conformability, permeability, imperceptibility, minimal invasiveness, and 3D coverage are some key form-factor features that need to be achieved. Microfabrication and nanomaterials form the pillars of advanced form factors; however, mechanical fragility is a challenge for practical applications. Flexible hybrid electronics and smart textiles are promising systems. Electronics-biology integration in 3D on cellular and even subcellular levels is merging these two conventionally distinct fields, where exciting opportunities await.

In addition to sensor performance, power supply and data communication also critically affect system performance. With more demanding power usage and physical constraints, there are both needs and opportunities in high-power ambient energy harvesters, large-capacity energy storage devices, and efficient wireless power transfer in flexible, stretchable, and miniaturized form factors. Holistic power management strategies are necessary for complex systems. Connectivity, especially wireless communication, will be integral to future sensing systems. Reducing power consumption, overcoming interferences and constraints associated with the human body, and enhancing data security are primary issues concerning flexible sensing networks.

Nanomaterials and nanotechnology play pivotal roles in solving the challenges facing flexible sensors.[1074] The small dimensions and large surface areas of nanomaterials render high sensitivity to external stimuli, as well as fast reactions and mass transport. Hence, nanomaterials and nanoengineering have been key to improving the sensitivity and selectivity of biosensors.[200] Nanocatalysts, nanoenzymes, and nano-structured membranes and interfaces help tackle the instability of bioreceptors. Nanomaterials provide viable routes to specific gas sensing through precise structural and chemical control. Micro- and nano-structuring have been sought-after solutions to improve the sensing performance of mechanical sensors, including sensitivity, linearity, and sensing range. Quantum-dot-based photodetectors are showing promise in RGB-responsive flexible imagers. Moreover, nanoscale dimensions are beneficial to mechanical compliance and biofriendly form factors, leading to better biocompatibility and signal quality. For example, the addition of nanofillers in elastomeric matrices enables intrinsi-

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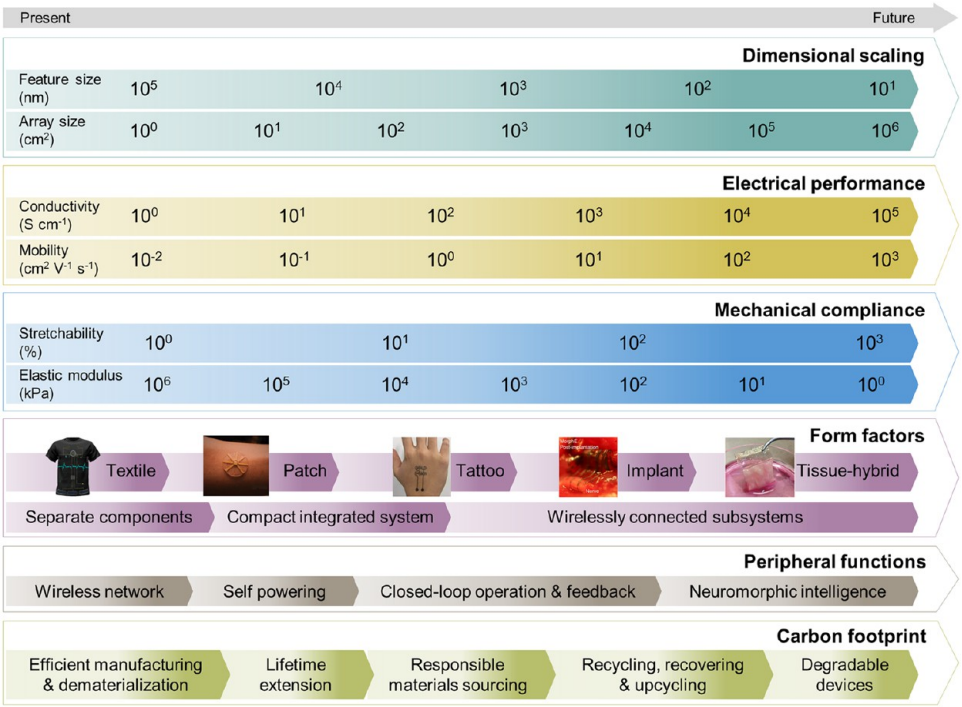

Figure 17. A technology roadmap for flexible sensors and systems. Evolution with time is not drawn to scale. Images from left to right: Adapted with permission from ref 647. Copyright 2021 American Chemical Society. Adapted with permission from ref 235. Copyright 2021 Wiley-VCH GmbH. Adapted with permission from ref 118. Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Adapted with permission from ref 579. Copyright 2020 Springer Nature. Adapted with permission from ref 625. Copyright 2016 Nature Publishing Group.

cally stretchable functional materials. Electronic tattoos based on 2D materials enable conformal and imperceptible sensing, and nanomeshes permit unobstructive mass transport on biological surfaces. Nanotexturing device surfaces also helps combat biofouling and enhances cell adhesion and proliferation. Furthermore, the exceptional electronic, optoelectronic, electrochemical, and chemical properties of some nanomaterials enable high-performance devices. For instance, nanomaterials are extensively studied for energy harvesting and storage devices. Their high surface area and electrochemical activity promote energy conversion at materials interfaces.

Despite the desirable device features offered by nanomaterials and nanotechnology, there remain many challenges limiting their adoption in commercial flexible sensors. First, there is a lack of understanding of analyte-materials interactions in sensitive and/or selective nanomaterials and structure−property relationships of highly tunable nanostructures. This lack of fundamental understanding will hamper materials design and optimization for more versatile applications. Second, the biocompatibility of nanomaterials is intrinsically challenging to examine due to diverse morphologies and surface states, calling for concerted efforts from the community to standardize the related materials and processes. This standardization is not only important for human-interfacing devices, but also for workers handling nanomaterials. Moreover, the environmental impact of nanomaterials is a complex issue concerning materials and device disposal. Nanomaterials recycling should be considered in design. Regulations and legal frameworks are currently largely missing in nanomaterials safety. Third, the mechanical fragility of nanomaterials impedes their practical application. More robust materials should be fabricated, and more user-friendly protocols should be devised. Fourth, high-quality syntheses and processing, high-resolution patterning, and device integration are current issues in the manufacturing of nanomaterial-based devices. Ink formulation offers a viable route to the wide adoption of nanomaterials in printed electronics. Further improvements in functional performance, yield, resolution, and mechanical robustness are needed.

From laboratories to end-users, there are daunting challenges facing flexible sensors. Identification of killer applications entails extensive surveys of real-life problems, close discussions with potential customers, assessments of competitiveness with conventional sensors, and evaluations of technology readiness levels, among many other considerations. Subsequent sensor development should adopt application-specific designs. Tools and processes that facilitate rapid prototyping help shorten prototype-to-product times. Importantly, investment in pilot-scale production and testing facilities will be instrumental for translational efforts. Further expanding manufacturing capabilities to industrial scales is essential for commercialization. Special concerns relate to printed electronics, functional polymer processing, nanomaterial production and processing, and system integration. Although scientific and engineering efforts from the research community have proposed many promising solutions to these problems, their industrial relevance may be questionable given the limited interactions between research laboratories and industrial facilities. Therefore, support for access to these facilities and the development of new manufacturing capabilities should be a priority of research governing bodies and funding agencies. Finally, regulations addressing user safety, data privacy, ethics, quality assurance, worker safety, and environmental impact need to be developed to support the sector of flexible sensor technology.

For sustainable growth of this sector, long-term issues in environmental sustainability, industrial standardization, user acceptance and engagement, equitable deployment, and talent

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pipelines should be addressed. Future flexible sensing systems are expected to be intelligent, built on the basis of ongoing progress in artificial intelligence, edge computing, and neuromorphic computing.

Technology Roadmap. The above discussions break down the complex landscape of sensor types, performance metrics, form factors, system components, manufacturing, and commercialization of flexible sensor technology, focusing on challenges in different aspects of system performance and various stages of technology development. To put forward a cohesive vision of the development trajectory, here we propose a comprehensive, unified technology roadmap for flexible sensors. This roadmap is designed to connect the dots in different areas of research towards common and long-term goals and to promote disruptive, nonlinear technological advances for a ubiquitous flexible sensor future. The key to realizing these goals will be a dual strategy that elevates sensor performance, while simultaneously digging into the 'important problems' not well addressed by current solutions.

We sketch out a broad flexible sensor developmental narrative in six areas—dimensional scaling, functional performance (electrical performance as a representative), mechanical compliance, form factors, peripheral functions, and carbon footprint—to provide direction and extent of development for flexible sensors to head towards realistic deployment and to stay on a fast-growing trajectory (Figure 17). The narrative provides no timelines or progress guarantees but identifies critical steps, grounded in the current progress of flexible sensors combined with scenarios of state-of-the-art rigid sensors. Such a narrative is expected to provide guidance for multidisciplinary and cross-value-chain development strategies.

Dimensional Scaling. Scaling in terms of feature size reduction and array size increment will enable applications requiring high spatiotemporal resolution or large-area coverage. The feature size offered by printed electronics will continue evolving while microfabrication of emerging materials such as functional polymers might eventually achieve feature sizes comparable to rigid microelectronics. Areal scaling will target robotics, vehicles, and buildings.

Electrical Performance. Performance including conductivity, carrier mobility, and dielectric properties is the foundation of electronic (and ionic) sensors. These properties are currently compromised by the flexible form factor. Ongoing efforts in the rational design of materials and devices are heading towards performance comparable to rigid counterparts. Other functional performance, such as optoelectronic, electrochemical, (electro)-magnetic, thermal, and optical properties, will improve for various sensing modalities.

Mechanical Compliance. This represents a major advancement of flexible sensors over rigid sensors. Beyond being bendable, soft and stretchable devices are the future for more compatible integration with biological systems, primarily targeting human-centric applications. The ultimate goal will be achieving mechanical properties similar to human tissues, including other aspects such as viscoelasticity, strain-hardening, and self-healing.

Form Factors. Form factors of flexible sensing systems will be highly diverse. The near-term achievable form factors might be textiles or clothing-integrated systems and flexible hybrid systems. In clothing-integrated systems, interconnection and wireless communication modules are likely the first components, besides sensors, to be manufactured on fabrics or in fibers; other components will still be of a rigid form factor, and the components will be spatially separated. Flexible hybrid integration will produce compact systems that enable wearable skin patches. More challenging form factors such as tattoos, implants, and tissue-hybrids will require entirely soft or miniaturized devices, and their system integration will likely be through wireless communication.

Peripheral Functions. They extend the functionality of flexible sensors, enabling more sophisticated and diverse uses. Autonomous wireless sensor networks that require minimal maintenance after installation will be integral to the IoT and intelligent machines. Feedback mechanisms including electrical, visual,[967] auditory, haptic[895] and even olfactory stimulations will provide natural and immersive experience in human-machine interactions and the metaverse.[968] Intelligent sensors that emulate the human sensory systems represent an unbounded scientific pursuit to replicate and extend natural capabilities, and the potential applications are unimaginable.

Carbon Footprint. The carbon footprint of flexible sensors and systems greatly affects the sustainability of the sector. Near-term reductions in carbon footprint are likely through more efficient manufacturing consuming less material and energy, as well as dematerialization through lighter and thinner form factors.[29] Lifetime extension should focus on mechanical and functional durability. More sustainable ways of materials sourcing will entail the use of more abundant elements and environmentally benign extraction processes. Recovering materials from waste and upcycling waste into valuable products will be essential for a circular economy. Fully degradable devices that can be disposed of without harming ecosystems will be especially beneficial to single-use applications.

There are and will be numerous challenges as we navigate this roadmap. Yet, we are optimistic that the benefits of flexible sensors will outweigh the challenges. In drafting this forward-looking Review, we call for action from the community to address the bottlenecks impeding the maturation of flexible sensor technologies and propose groundbreaking concepts that will accelerate the development and commercialization of flexible sensors. We hope to inspire more scientists, engineers, innovators, and entrepreneurs with diverse backgrounds to participate in and contribute to this exciting field—multidisciplinary collaboration is the key to breakthroughs in a disruptive technology like flexible sensors.

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Notes

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Bending curvature, the inverse of bending radius; **Bioaffinity**, the molecular interactions between a bioreceptor and the analyte that give rise to specific binding. Bioaffinity biosensors use such molecular binding (of molecular components such as antibodies, proteins, nucleic acids, aptamers, molecularly imprinted polymers) for sensing[1075,1076]; **Bioreceptor**, a biologically derived material (*e.g.*, enzymes, aptamers, DNA, antibodies, cells) or biomimetic component (*e.g.*, molecularly imprinted polymers, nanozymes) that specifically recognizes the analyte.[1077,1078] Bioreceptors are also known as biological recognition elements or biorecognition elements[1077,1079]; **Biorecognition**, the process of signal generation (in the form of light, heat, pH, charge or mass change, *etc.*) upon interaction of the bioreceptor with the analyte[1077]; **Crosstalk**, interference on sensor output from neighboring sensor pixels in an array or other sensing modes in a multimodal sensor[1080]; **Drift**, a unidirectional change in signal that results in the average value changing monotonically (though not necessarily linearly) with time[99]; **Elastic range**, the strain and stress ranges within which deformation can be immediately and completely recovered upon unloading[1081]; **Heterogeneous integration**, the integration of separately manufactured components into a higher-level assembly that, in the aggregate, provides enhanced functionality and improved operating characteristics. In this definition, components should be taken to mean any units, whether individual dies, MEMS devices, passive components, and assembled packages or subsystems, that are integrated into a single package[1082]; **Immunosensor/immunoassay**, a sensor or assay based on antibody-antigen interactions[1075,1076]; **Latency**, in sensor signal readout, latency is the delay in time between sensor signal generation and the receival of that signal from readout electronics. In networking, latency describes the delay in time it takes a data packet to travel from one network node to another; **Linearity**, the quality of having a linear correlation between sensor output signal and stimulus intensity. This is reflected in a straight line of the response-*vs*-sensing range curve; **Mechanical metamaterials**, artificial structures with unusual mechanical properties defined by rationally designed structures of precise geometrical arrangements rather than their composition[1083,1084]; **Multimodal sensing**, detection of more than one type of stimulus by a sensing device/system. Detection of multiple chemical species is normally not referred to as multimodal sensing[51]; **Multiplexed sensing**, simultaneous detection of signals from multiple channels (sensing units) of an integrated sensing device. Often used to describe the simultaneous detection of multiple analytes by a biosensor[51,1085]; **Reliability**, the degree to which an individual sensor repeatedly yields the same signal for the same stimuli under the variety of ambient conditions expected for a particular sensor application[64,99]; **Repeatability**, the degree to which an individual sensor repeatedly yields the same signal for the same stimuli under the same operating conditions. Repeatability necessarily depends on stability[99]; **Response time**, the time interval between the stimulus and the sensor response.[1086] When the sensor signal gradually increases to a stable value corresponding to the intensity of the stimulus, usually a percentage of maximum is indicated to define the response time; **Selectivity**, the ability of a sensor to discriminate between the analyte/stimulus of interest and possible interferences[99]; **Sensitivity**, for a reversible sensor, sensitivity is defined as the change in sensor output signal obtained for an incremental change in the stimulus, *i.e.*, the slope of the response-vs-sensing range curve. It is often confused with limit of detection (LOD), *i.e.*, the lowest concentration of an analyte or the smallest value of a stimulus that can, with some level of statistical confidence, be differentiated from zero[99]; **Sensor hysteresis**, the degree of difference between the response curves when going up and down the sensing range; **Somatosensory system**, the network of neural structures in the brain and body that produces the perception of touch (haptic perception), temperature (thermoception), body position (proprioception), movement, and pain; **Stability**, the ability of a sensor to maintain accurate measurement in the presence of possible environmental variation and in both short term and long term relative to the specified service life[99]; **Technology readiness levels (TRLs)**, a systemic qualitative assessment system used to estimate the maturity level of a particular technology, and to compare the maturity between different types of technology[869,1087]; **Time division multiple access**, a channel access method that divides

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signals into different time slots, used to facilitate channel sharing without interference. In array signal readout, this dictates that sensor pixels are read in rapid succession.

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