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Bridging the Gap—Thermofluidic Designs for Precision Bioelectronics

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Bioelectronics, the merging of biology and electronics, can monitor and modulate biological behaviors across length and time scales with unprecedented capability. Current bioelectronics research largely focuses on devices' mechanical properties and electronic designs. However, the thermofluidic control is often overlooked, which is noteworthy given the discipline's importance in almost all bioelectronics processes. It is believed that integrating thermofluidic designs into bioelectronics is essential to align device precision with the complexity of biofluids and biological structures. This perspective serves as a mini roadmap for researchers in both fields to introduce key principles, applications, and challenges in both bioelectronics and thermofluids domains. Important interdisciplinary opportunities for the development of future healthcare devices and precise bioelectronics will also be discussed.

1. Introduction

The convergence of biology and electronics has paved the way for recent bioelectronics. These devices are designed to interface with biology and detect biological signal accurately. Bioelectronics can also be used to precisely modulate a plethora of complex biological processes, an advancement that has revolutionized various aspects of biomedical science and technology.[1] Given the inherent complexity of bioelectronics, their design requires multidisciplinary efforts, including mechanical, electrical, chemical, and heat and mass design considerations.[2]

Current bioelectronics research is predominantly focused on new materials design that enables novel bio-mechanical and bio-electrical interfaces. The fascination with the bio-electrical aspect dates to Luigi Galvani's groundbreaking frog experiment in the 18th century. Galvani discovered that when he stimulated a frog's leg with an electrical spark, the leg's muscles would twitch. He concluded that this twitching was caused by the electricity in the animal. Galvani's work became the foundation of further research into the relationship between electricity and biology, ultimately leading to important discoveries in neuroscience and physiology.[3–6] More recently, the attention has shifted toward the size and mechanical properties of these devices. The development of miniature flexible electronics can now adapt to the dynamic biological environment while maintaining the functional integrity of rigid electronic components.[7] Many materials' designs have enabled miniature devices for a variety of in vivo applications, including wearable bioelectronics.

Despite this rapid advancement, the thermofluidic aspect of biosensing and biomodulation has been overlooked. Current thermofluidic research studies the multi-physical processes where fluids flow and other energy processes occur simultaneously, such as phase-change, wettability, liquid transportation, and other complex solid–liquid interactions. One way to demonstrate this is by examining the number of papers published in the past ten years (up to October 2023) that contain keywords related to both "bioelectronics" and other disciplines. In comparison to manuscripts related to "materials" (4158) and "mechanics" (1118), we observed a significantly smaller number of papers within the domain of thermofluids, including "heat transfer" (43), "rheology" (12), and "thermofluid" (only 2). Since many biological samples are fundamentally complex fluids, neglecting thermofluidic control in bioelectronics appears unjustified.

Some recent advances in miniature bioelectronics have underscored the integral role of thermofluidic designs. This includes 1) new methods to construct bio-interfaces, which involve engineering complex solids and fluids; 2) devices for recording biological information, where the heat and mass flow of analytes is crucial to the recording and sensing capability; 3) devices for

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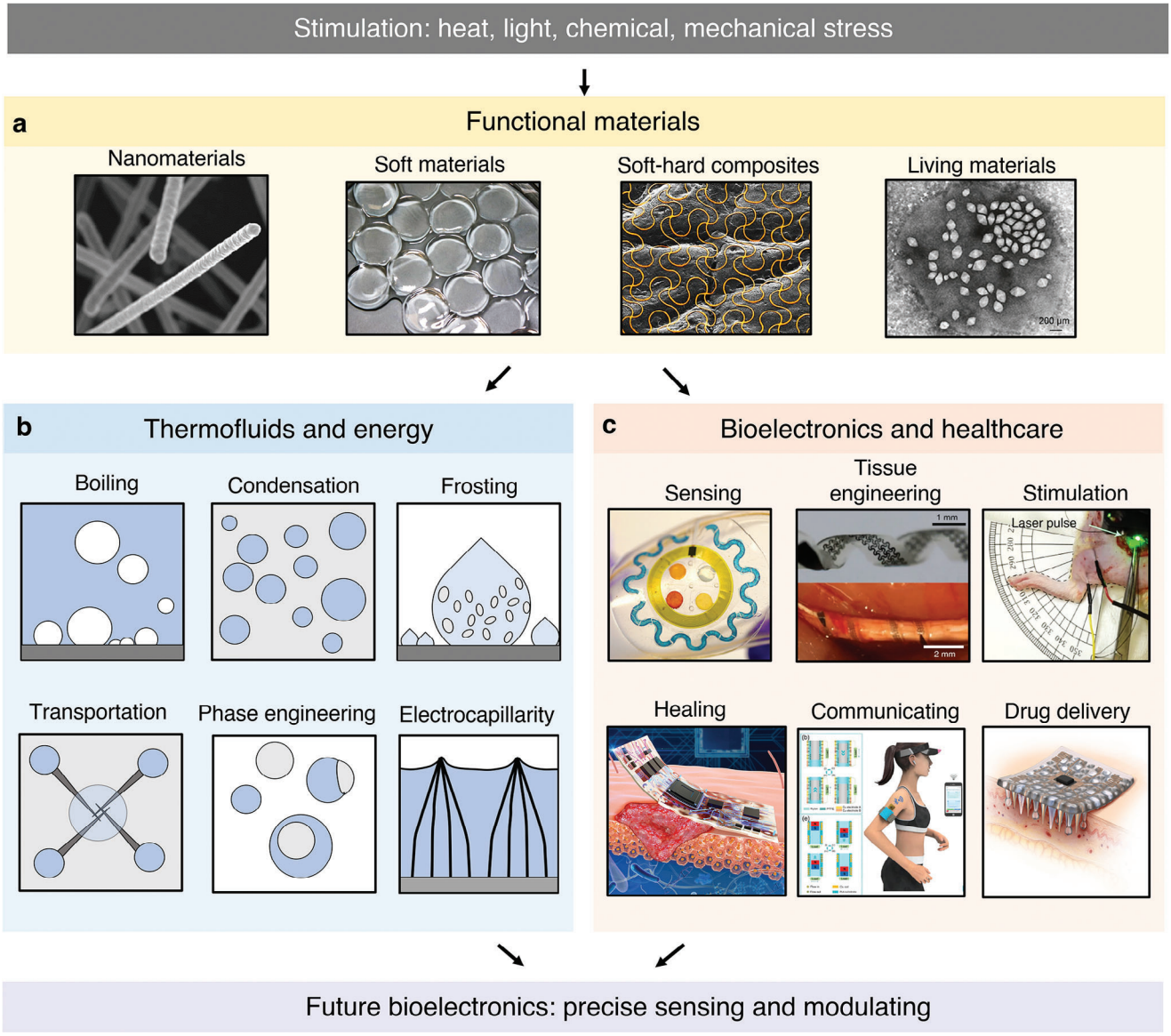

Figure 1. Integrating thermofluids and bioelectronics for future bioelectronics. a) New functional materials developed[8–11] that enable the developments in both b) thermofluidic engineering including phase-change phenomena, fluid transportation, and the formation of delicate structures using capillarity, and c) bioelectronics,[7,12–17] including devices used for wound healing, drug delivery, bio-stimulation, and bio-recording at different length scales. Reproduced with permission. Copyright 2016, American Association for the Advancement of Science[7]; Copyright 2022,[17] 2023[8] Wiley; Copyright 2015,[17] 2022,[9] 2023[16] American Chemical Society. Copyright 2019,[11] 2020,[14] 2021,[10] 2022[15] Springer Nature; Copyright 2022, Wiley.[13]

stimulating biological targets at both cellular and tissue level, including the control of biofluids for precise electric stimulation and utilizing phase-change heat transfer for thermal regulation. It becomes obvious that the convergence of thermofluids and bioelectronics could open new opportunities in both fields, leading to the development of biomedical devices that are more effective, sensitive, and adaptable to the ever-changing dynamics of complex biological environment.

This perspective paper serves as a mini roadmap for researchers in both fields of bioelectronics and thermofluids to bridge the two historically disconnected domains, which is outlined in **Figure 1**. We will first present a brief overview of bioelectronic devices to be used for both bio-sensing and bio-modulating. We will then introduce advancements in the design of functional surfaces that can modulate complex thermofluidic processes, including liquid transportation, wettability, and phase transitions. The third part of the paper discusses the intersection of thermofluidic principles in bioelectronic devices, focusing on both current designs and future possibilities. We want to emphasize that there are many impactful work in both fields, so it is impossible for this short perspective paper to include all the exciting progress. Instead, we will concentrate on a limited number of representative works to illustrate our point.

2. Major Progresses and Applications of Bioelectronics Devices

Two major applications of using current bioelectronics are 1) biosensing, which integrates multiple sensors onto the flexible platform, and 2) bio-modulation, which equips electrodes, drug delivery systems, of other phytochemical stimulation setups on the flexible electronics. We will first briefly discuss the basic working principles and applications of these two kinds of devices.

2.1. Biosensing at Different Length Scales

The electrical and chemical signals happening in biological processes, from cells to tissues to organ systems to the entire body, leave traces for advanced health monitoring. By reading these traces using advanced electronic components, bioelectronic devices can provide real-time, continuous health monitoring, enabling early detection of potential health issues and allowing for immediate interventions. Thermofluidic techniques are important for constructing stable and controlled biofluidic environment that enables reliable sensing processes. Critical aspects to be considered include analyte diffusion, wettability design, phase separation of biofluids, and the water-up-taking behavior of complex fluids like hydrogels, which are frequently used in electrochemical sensors and will be discussed in section 3.

On the cellular level, the separation of charge across a cell's plasma membrane, from ions such as sodium, potassium, and chloride, causes a potential difference. By studying cells' potential and the patterns of action potentials, one can gain fundamental insights into various biophysical processes including neuronal communication, muscle contraction, and cardiac function.[18] Nanomaterials like nanotubes and nanowires have been explored for ultrasensitive detection of cellular biophysics.[1,19–21] For example, nanoscale field effect transistors have been developed as an active probe size of only tens of nanometers (**Figure 2**a). Coating the tip with a phospholipid bilayer allowed the probe to be inserted through the membranes of beating cardiac cells, where it could sense the temporal changes in cell potential.[22]

Advances made in biosensing at the cellular level have resulted in various tissue-sized materials that record tissue-level activities,[1,23] such as electrophysiological studies,[24] ultra-sound imaging,[25,26] nerve activity,[27] electronics skin, and brain–machine interfaces.[10,28] The use of flexible and miniature bioelectronics often provides many advantages against the traditional bulky, unhygienic electronic hardwares that require complicated and risky surgeries to install.[29] For example, devices that can interface with neurons in the brain can deliver input and output for neuromodulation,[28] possessing great potential for treating neural disorders and loss of function (Figure 2b).[28,30]

Wearable electronics are even larger devices that can detect human-body level metabolism and physical conditions. Integrating biosensors into the system enables real-time detection of biomarkers in various biofluids, such as sweat, urine, tears, and blood (Figure 2c). For example, detecting sweat could help monitor inflammatory processes and immune responses in common chronic illnesses such as stroke and heart disease.[31] The benefit of using such wearable biosensors is that they enable a non-invasive way to monitor these biomarkers: the device extracts these biofluids on-demand and uses a microfluidic module to capture and detect useful biomarkers like glucose and proteins. Epidermal electronics can also measure the on-skin physical properties such as temperature, water content, and thermal properties (Figure 2d), which will be further discussed in section 3 and other review papers.[32]

2.2. Bioelectronic Devices for Biomodulation

Biological systems respond to and communicate through biophysical cues, such as electrical, thermal, and mechanical signals. Bioelectronics can achieve biomodulation by artificially creating these signals to alter biological behaviors across different time and length scales. When bioelectronic devices directly interface biofluids, precise control on solid–liquid interactions is critical.

In principle, many energy materials used in electronics, photonics, and energy conversions, can also be used in biological systems to provide physical cues for biomodulation. Currently, a variety of new materials systems have been introduced to produce electrical signals that stimulate biological systems, including metal conductors, conductive polymer systems, semiconductor materials, as well as soft–hard composites designed to form biocompatible interfaces with target cells or tissues. Hydrogels are also becoming an important materials system for biomodulation, thus a thermofluidic view to control hydrogel behaviors, such as temperature regulation, rheology control, and precise heat and mass transfer designs, can be applied to biomodulation as well. All material systems have advantages and disadvantages, which will be further discussed and have been extensively reviewed elsewhere.[37,38]

Thermal regulation is adjacent but an important part of photostimulation. Upon light illumination, heat can be released to stimulate or damage cells or tissues.[39] Therefore heat transfer designs should also be integrated into the photo-stimulators. For instance, heat sinks can be miniaturized and integrated into silicon bio-interfaces, dissipating the heat to the tissue's surrounding vasculature. Since blood constantly flows, it could carry the heat away from the tissue, much like a liquid cooling system.[40] In section 3, we will also discuss microfluidic systems that actively regulate the thermal properties of skin and body.

3. Functional Surfaces for Thermofluidic Control

Historically, the field of thermofluids studies the synergetic interactions between heat transfer and fluid flow, aiming to enhance the performance of thermal energy devices, such as condensers, boilers, and engines. In recent years, the scope of thermofluidic research has broadened significantly and studies a wider range of multi-physical processes. This includes processes when fluid flow and thermodynamics couples with various physical cues such as heat transfer, mechanical force, and molecular interactions between solids and liquids. Recent developments in functional materials and surfaces have shown promising capability to precisely control wettability, droplet transportation, and liquid phase transitions (**Figure 3**). Precisely modulating these thermofluidic behaviors has made substantial impacts on energy systems, environmental science, and bioengineering.

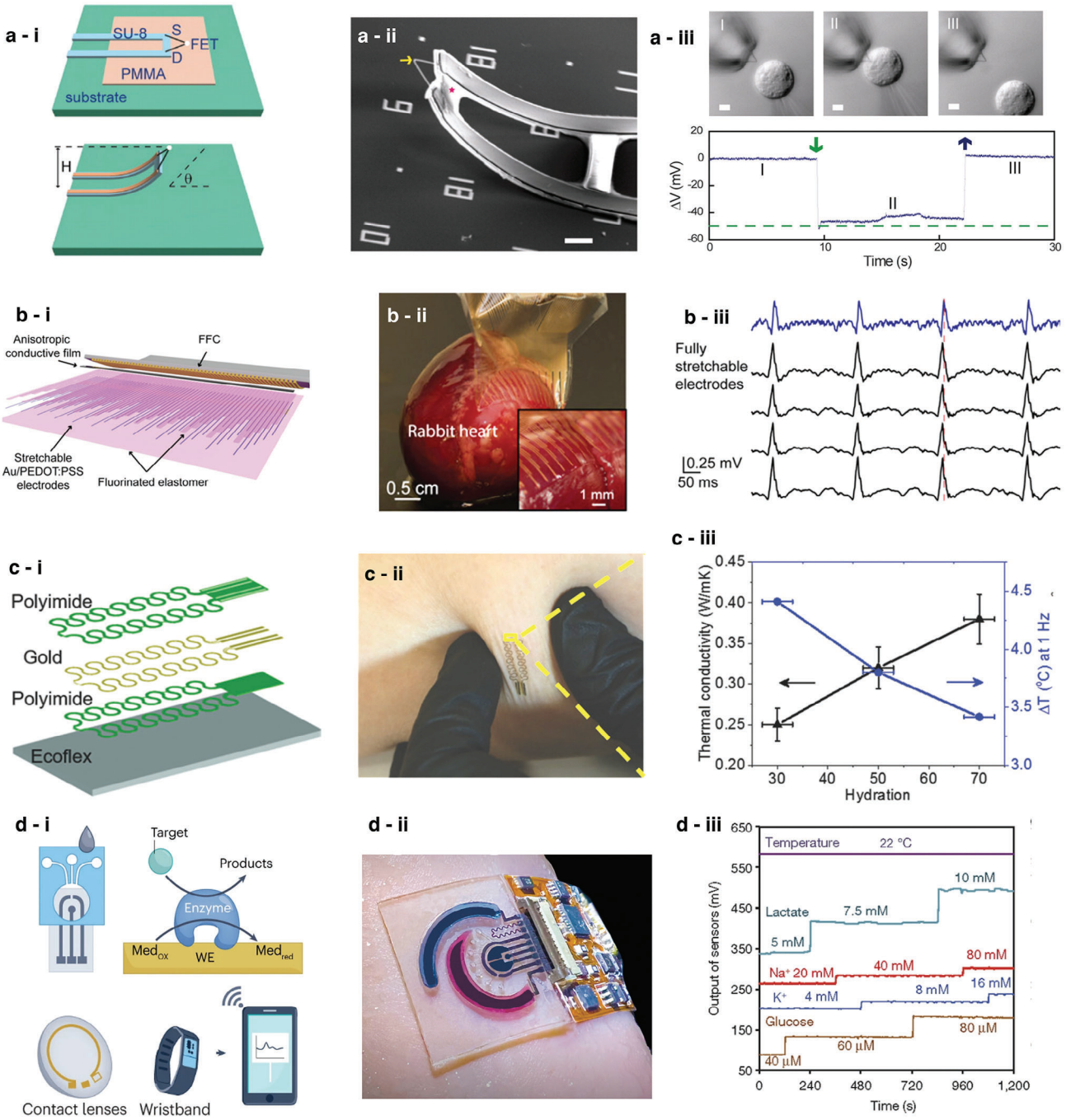

Figure 2. Bioelectronics for sensing across different length scales. a) Cellular-level probing; (a-i) shows design schematics of flexible, nanoscale field-effect transistors; (a-ii) depicts an image of the device mentioned in (a-i); (a-iii) features a cardiac muscle cell approaching a nanowire probe kinked 60° and the corresponding electrical recording. Reproduced with permission.[22] Copyright 2010, AAAS. b) Tissue-level recording; (b-i) depicts the structure of an intrinsically stretchable electrode array for in vivo electrophysiological mapping of the heart; (b-ii) shows the electrode array conforming ex vivo to a rabbit's heart via surface tension; (b-iii) is an ECG chart with readings (blue) from the electrode array's electrograms on the heart's surface and from surface contact leads (black). Reproduced with permission.[33] Copyright 2020, PNAS. c) Wearable chips and microfluidic designs for thermophysical measurements; (c-i) illustrates the various layers in 3ω sensors to thermally characterize human skin; (c-ii) is a serpentine 3ω sensor printed onto a silicone substrate, applied to the forearm; (c-iii) is the calculated thermal conductivity from data from the sensor. Reproduced with permission.[34] Copyright 2017, Wiley. d) Wearable chips for chemical monitoring. Reproduced with permission.[31,34–36] Copyright 2016, Springer Nature; Copyright 2017, Wiley; Copyright 2021, Springer Nature; Copyright 2022, Springer Nature.

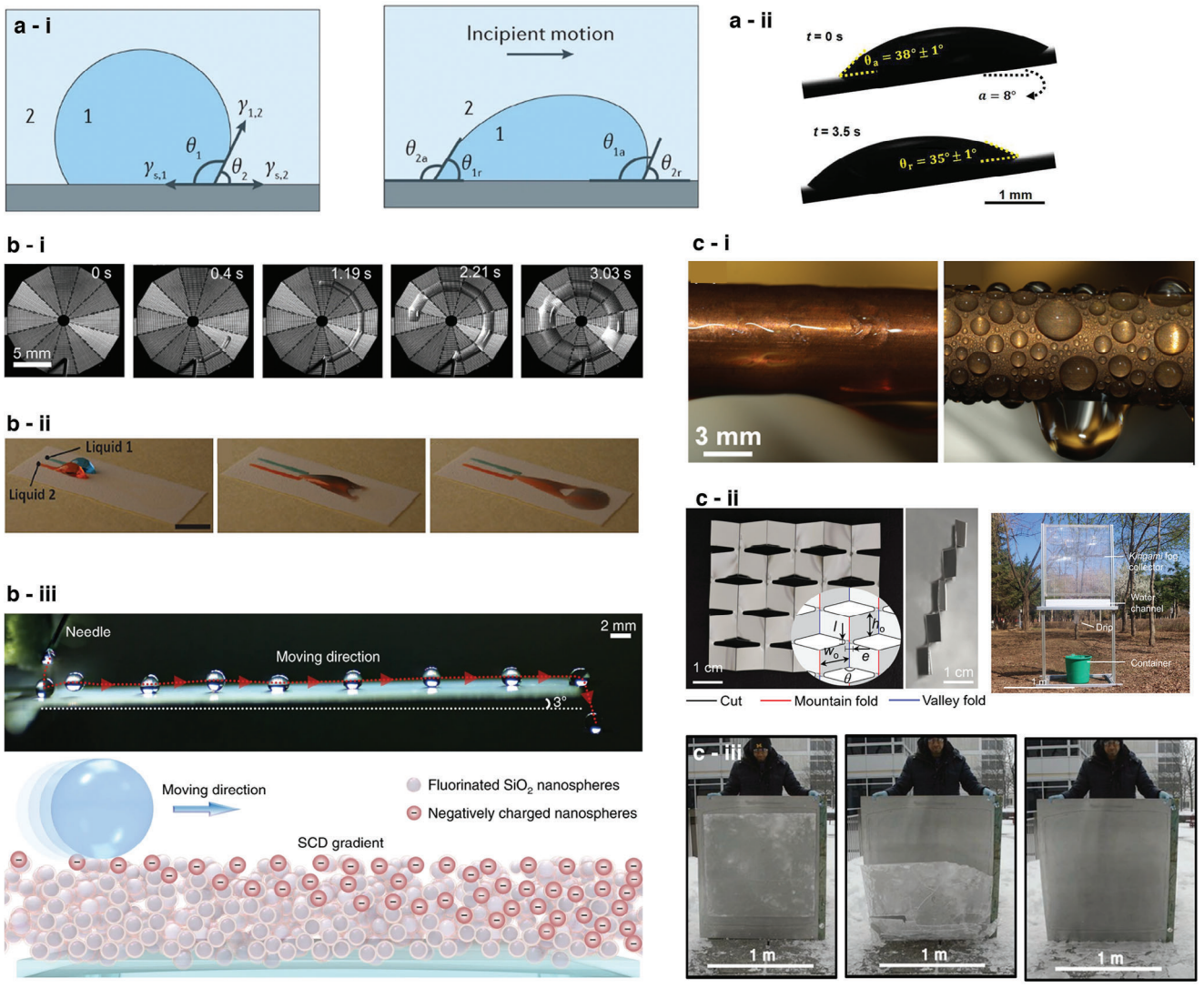

Figure 3. Thermofluidic designs that modulate complicated fluidic behaviors. a) Fundamentals of fluid–surface interaction. Reproduced with permission.[67,68] a-i) Wetting hysteresis occurs when a droplet begins to move.[36] a-ii) Water droplet sliding across a surface coated with polyethylene glycol.[37] Copyright 2016, Springer Nature; Copyright 2020, American Association for the Advancement of Science. b) Surface designs for droplet transportation.[43,69] b-i) Droplet's self-propulsion on an annular path.[20] b-ii) Paper-based microfluidic reactor that transport two streams of fluids into a central reaction pad.[38] b-iii) Water droplet actively climbs a 3° slope with a surface charge density gradient.[38] Reproduced with permission. Copyright 2022, American Chemical Society. c) Phase change engineering to be used in heat transfer (c-i),[51] water harvesting (c-ii),[70] and anti-icing (c-iii).[70,71] Reproduced with permission. Copyright 2013, American Chemical Society; Copyright 2021, Springer Nature; Copyright 2019, American Association for the Advancement of Science.

3.1. Fundamental Concepts on Wettability

Engineering surface wettability is an important approach to tune the interactions between the surface and the liquid sitting on it. Depending on the droplet's apparent contact angle at the liquid–solid–air three-phase line (θ, which is shown in Figure 3a), surfaces can be characterized into hydrophobic surfaces ($\theta > 90°$) that are non-wetting, and hydrophilic surfaces ($\theta < 90°$) that strongly interact with water. The most effective way to control surface wettability is to develop coating materials with different water-affinity. Wettability can also be augmented by introducing surface roughness, which is quantitatively outlined by the Wenzel equation.[41,42] Surfaces with carefully designed wettability can control the transportation and phase-change of the contacted liquid effectively, which is their core value in many applications for energy or biomedical devices (Figure 3b).[43] For this reason, many recent thermofluidic innovations are driven by new materials having novel chemistry,[44–46] size,[47] geometry,[48,49] and surface morphology[50–52] that can be used to tune surface wettability.

While the apparent contact angle measured when a droplet sits on a solid gives a rough idea about surface wettability, precise transportation control needs to detail the difference between the contact angle at the droplet's moving front (θ_a) and back (θ_r). This introduces the important concept of "contact angle hysteresis" ($\theta_a - \theta_r$), which still remains partially understood.[53,54] On an ideal

homogeneous surface, there is no hysteresis between the two contact angles, and the liquid sitting on it can move freely without resistance. This is demonstrated by many oil-like surfaces yielding high water mobility with low contact angle hysteresis, but not necessarily requiring high water-repellency (Figure 3b).[46] In practice, surface defects and contaminants can pin the droplet at its contact line, resulting in a decreased receding angle and leading to contact angle hysteresis.[55–57] This hysteresis acts as a resistance force that hinders the droplet's mobility and requires special care for microfluidic devices and bioassays.

3.2. Active Fluid Control

In addition to passive designs for fluid transportation (like wettability designs), many recent efforts have focused on actively controlling fluid behaviors using light, heat, and electric and magnetic fields. Electrowetting involves applying an external electric field to a droplet resting on a surface. The electric field modifies the wetting properties of the droplet, which changes its shape and allows it to move. This technique is commonly used in microfluidic devices and digital microfluidics.[58–60] Optoelectrowetting combines both light and electric fields to manipulate droplets. For optoelectrowetting, a photosensitive surface is often used, and when light is shined on this surface in the presence of an applied voltage, the wetting properties change, allowing the movement of droplets. Moreover, many recently developed surfaces change wettability upon light illumination does not even necessarily involve applied voltage.[61–64]

3.3. Phase-Change Control

The phase change of biofluids has important implications because multi-phase interactions are ubiquitous in intracellular environments and biosensing processes. Also, phase-change heat transfer processes are important in many biomedical devices. The most well-known example is cryosurgery, which has been developed for decades using extreme cold to freeze and destroy diseased tissues and cells (such as cancer cells). The phase-transition of argon or nitrogen is critical for rapid removal of heat and causes yet another rapid phase transition of water in surrounding tissues. Controlling the formation of ice crystals in tissues can either be used to rupture and kill the cells, or preserve the tissues for transportation.[65] For bioimaging, microbubbles can be generated and used as ultrasound contrast agents. The generation and regulation of microbubbles from aqueous itself is a complex thermofluidic phase change process. For biosensing, the condensation of human-exhaled aerosols forms exhaled breath condensate, which has attracted increasing attention, as it contains biomarkers in blood and can be used for non-invasive disease monitoring.[66]

Recent advances in thermofluidics have shown promising results to effectively modulate multiphase transitions between gas, liquid, and solid (Figure 3c). Phase-change heat transfer processes such as condensation and boiling can be boosted by functional surfaces.[72,73] Condensation on durable superhydrophobic surfaces can promote droplet formation and removal, resulting in faster condensation, which benefits both the energy system, atmospheric water harvest, and human exhaled breath collection.[51,52,67,70,74–76] In desalination processes, like solar distillation, functional surfaces can enhance the phase change from liquid to vapor and back again.[70,77,78] Functional surfaces can also delay or promote ice formation. Many icephobic surfaces have been introduced to prevent ice from accumulating on wind turbines and aircrafts.[79,80] Phase-change designs are also employed for power electronics to dissipate heat, which is important for in vivo bioelectronic devices that require compact size and high energy consumption.[81–83]

3.4. Superwetting Chips for Biofluids Control

The most straightforward biological application of precise fluid transportation is probably superwetting chips, which are wafer platforms engineered to show spatially heterogeneous wettability (**Figure 4**a). Superwetting chips can precisely control the flow of fluids, allowing small volumes of fluids to be manipulated, mixed, and analyzed efficiently[43] Thus, the technology acts as a miniature platform that integrates different bioassay functions onto a single chip. The unique surface properties of these chips enable them to quickly process biofluid samples like blood, saliva, or urine.[84] The integration of superwetting chips with body fluids and biosensors can quickly detect and quantify the presence of biomarkers or pathogens in body fluids, allowing rapid disease monitoring and detection when treatment is most effective. Sensitive chemical sensing can also be achieved by evaporation-based enrichment that enhances sample concentration by in situ evaporation of water or other solvents (Figure 4b). Note that for chemical detection, immobilizing receptors that react with the analytes can be difficult on a superhydrophobic surface due to the weak interaction between the chip surface and solutions containing chemical crosslinkers for receptor immobilization. Surfaces with patterned wettability should be designed so chips can be selectively treated with bio-receptors, where only the sensing area receives superwetting properties. The designs of biphilic surfaces are extensively reviewed in many recent papers.[43,85]

The controlled and predictable fluid behavior on superwetting chips can also be used to create micro-environments for cell culture and tissue engineering in both 2D[1,86–89] and 3D configurations[90,91] (Figure 4a). This can lead to more controllable and precise results compared to traditional petri dish methods. Superwetting chips can also help test how drugs are released in the body, which is useful for targeted drug delivery and personalized medicine.[92,93] The applications of cell-based assay in drug evaluation have also been widely explored to guide drug screening.[94,95] Other than being used alone, superwetting surfaces make key components in many implantable biomedical devices for anti-bacterial and anti-fouling applications.[96]

A major challenge when these superwetting surfaces interface with biofluids is their long-term stability and robustness[97,98] (Figure 4c,d). The functional coatings designed on the superwetting chips can degrade due to the wear and tear.[99] Most engineering surface has poor chemical resistance and biocompatibility[100,101] especially when used in vivo. The long-term storage is another challenge, since airborne volatile organic compounds (VOCs) can adsorb on the chips' hydrophilic surface and significantly change surface wettability.[55] Perhaps the

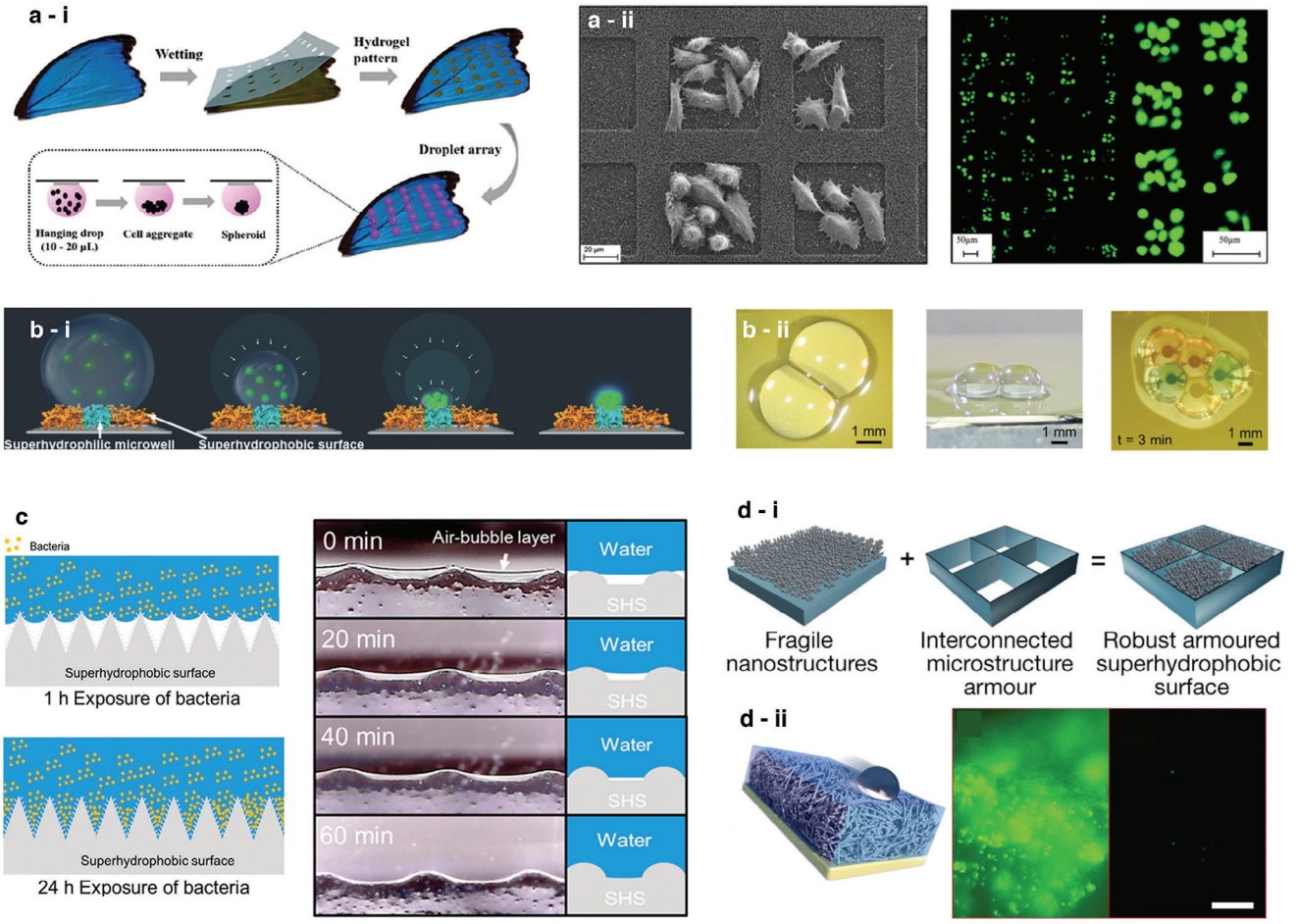

Figure 4. Applications of superwetting chips in bioengineering. a) 2D and 3D cell culturing.[84,86] a-i) Cell spheroids form on the superhyrophobic butterfly wing spotted with hydrophilic hydrogel.[55] a-ii) Mammalian epithelial cells trapped within superhydrophilic Silicon Nanowire patterns.[56] a-iii) Fluorescence image of cells incubated on biphilic surface with superhydrophilic patterns.[56] Copyright 2021, Wiley; Copyright 2011, Royal Society of Chemistry. b) Biological assays that have superior sensitivity[111] and air-stability.[112] b-i) Evaporation-enrichment effect with a superhydrophilic microwell on a superhydrophobic substrate.[82] b-ii) Non-coalescing droplets as bio-reactors on an oil-infused surface. Reproduced with permission. Copyright 2015, Wiley; Copyright 2014, *Proc. Natl. Acad. Sci. USA* c) Challenge in biofouling and surface longevity. The images showcase the short-lived anti-biofouling properties of superhydrophobic materials, with bacteria adhering to the surface shown.[107] Reproduced with permission. Copyright 2018, American Chemical Society. d) Materials designs for long-term usage when interfacing biofluids. d-i) Enhanced robustness in superhydrophobic surfaces by designing protective microstructures.[74] d-ii) Exceptional anti-biofouling performance of slippery, liquid-infused porous surfaces versus the poor performance of PTFE.[84] Reproduced with permission.[104,113] Copyright 2020, Springer Nature; Copyright 2012, *Proc. Natl. Acad. Sci. USA*.

most significant surface challenge for biomedical devices is biofouling where unwanted cells, proteins, or biomacromolecules adsorb on the surface, interfering with its functionality[102] Although fluorinated polymer coated medical devices could be a potential solution, fluoropolymers are reported to cause tissue inflammation.[103]

The mechanical robustness of hydrophobic surfaces is becoming less troublesome with new coatings having multi-layer structure,[49,104] self-healing chemistry,[44] and strong interfacial adhesion.[105] Long-term hydrophilicity that resists VOCs has also received more attention. Materials with carefully designed structures, such as electroplated porous metal, have shown stable wickability, which is beneficial for boiling applications.[106] Biofouling is a more challenging issue. Biomacromolecules have dynamic conformation and can achieve good adhesion with either hydrophilic surface (via hydrogen bonds) or hydrophobic surface (via hydrophobic force).[107] The conventional strategy is to use polyethylene glycol (PEG) coating that prevents bioadhesion by the formation of a hydrous layer.[108,109] However, roughly 10% of the global population can develop an immune response to PEG, so more biocompatible anti-fouling coatings are yet to be developed.[110] Despite the claim that superhydrophobic surfaces can effectively prevent biofouling, such an effect is only temporary (Figure 4c).[107] "Dynamic coatings" that have molecular mobility, such as oil-infused layers, showed superior anti-biofouling performance (Figure 4d). But oil-infused layers are usually too thick for miniature bioelectronics devices like nanoparticles. A promising and systematic approach to addressing biofouling is the recently developed "nano-vitrimers" materials, which are ultra-thin, dynamic, and self-healing.[44]

3.5. Molecular Design Principles for Precise Solid–Liquid Interactions

One important aspect in designing thermofluidic behaviors is the control of non-covalent solid–liquid interactions (such as biofluids–bioelectronic device interactions). This topic is neither directly related to bioelectronics nor thermofluidics, but it guides the understanding and creation of functional surfaces for both applications. Both natural and artificial biofluids contain many subcomponents with a spectrum of size, polarity, and dynamics. Through complex interactions, distinct phases will form and complicate the biofluids that interface electronic devices.[114]

Although the solid–liquid interaction is a quantum mechanical behavior that happens on the surface of materials, classical methods have been developed to simplify the process and use empirical "surface free energy" as the bridge that connects molecular interactions and macroscopic wettability. Surface free energy is defined as the energy associated with the expansion of surface area, arising fundamentally from atomic interfacial interactions that alter the chemical potential of the system.[115] Fowkes proposed that the surface free energy of a solid, which is often noted as γ_s and has a unit of energy per area, can be divided into polar component (γ_s^p) and dispersive component (γ_s^d).[116,117] These two empirical surface parameters can then be used quantitatively to predict adhesion, cohesion, wetting, and complex multi-phase interactions as simple as assembling Lego bricks. Young's equation relates to the moving droplet's contact angle with the surface free energies of both the solid and liquid phase, allowing experimental estimation of γ_s.[118] Many other models have refined the decomposition of γ_s. Note that the measurement of γ_s using contact angle is only applied to non-polar materials that yield a finite value of contact angle. Many new methods have been proposed for directly measuring surface energies, making precise predictions of multiphase interactions at bio-interfaces possible.[115,119–121]

Computation simulation is an important and wide topic that is beyond the scope of this perspective, and many advances of using simulation for surface designing and understanding have been reviewed elsewhere.[122] In general, precisely predicting the multibody interaction at a surface is difficult. The empirical force field approach uses existing liquid model to understand intermolecular interactions, which allows fast computation, but might lack insights about detailed electronic interactions. *Ab initial* methods or first-principle approaches can be accurate but cumbersome and computationally intensive. Recent developments in machine-learning processes can combine the merits of two approaches. For example, the "deep-potential molecular dynamics" method uses DFT results as training sets to obtain semi-empirical potential fields of molecules. The training sets then can generate the simulation results of a large and complex system quickly, which can illuminate more complex multi-phased thermos-bio-fluidic processes.[123,124]

4. Bridging Bioelectronics and Thermofluids: Current Efforts and Future Possibilities

Below, we will discuss some current bioelectronic designs that benefit from the integration of thermofluidic principles, including complex fluids for the construction of bio-interfaces, stable biosensing devices, and precise bio-modulating methods. We will also include an outlook to guide thermofluidic designs for future precision bioelectronics. All the interdisciplinary research are also briefly highlighted in **Table 1**.

4.1. Compliant Materials and Complex Fluids for Constructing Bio-Interfaces

As biology and electronic devices mechanically mismatch, developing electronic systems that mimic the stiffness and stretchability of soft tissues is an important goal. Metals and semiconductors, being the most used electronic components, are inherently rigid and not easily bent. Pioneering work in this field (done by Dr. John Rogers, Yonggang Huang, and many others) involves altering the geometry of metallic electronic components into thin films and strips, resulting in significantly reduced bending stiffness. This modification allows them to deform easily and greatly enhances their resistance to brittleness.[2,125] Research in this field has been extensively reviewed elsewhere.[2,125]

Complex solids and liquids are also promising materials to achieve satisfying mechanical properties close to biological systems, which are extensively introduced in many existing review papers.[126–128] Complex fluids are also receiving more attention in the field of thermofluids these years. Compared to simple Newtonian liquids, the rich and complex rheology of such complex fluids makes them unique material systems for enhanced water harvesting and heat transfer performance.[129,130] As useful bio-interfacial materials, complex fluids and hydrogels can embed drugs, electronic components, or living components. Such materials are often termed "tissue-like materials" or "living materials" (**Figure 5**c).[20,131] Hydrogels, are networks of hydrophilic polymer chains[132] and can be made intrinsically conductive for bioelectronics, thus potentially improving upon the existing conductors that may not be so compressible and fatigue-resistant.[133] Materials' resilience from bendability and stretchability also enhances stable performance that bears human movements and exercises. Otherwise, rigid devices may not just break, but also damage and inflame surrounding tissue.[134]

Thermofluidic approaches for controlling hydrogel behavior are critical to the performance of either bio-recording or bio-modulating. Important thermofluidic aspects include temperature regulation, rheology control, and precise heat and mass transfer designs. More specifically, these designs should include modeling the rheological behaviors including shear-thinning, extensional thickening, and viscoelasticity observed in standard in vitro models. Additionally, it should address heat and mass transfer processes, including heat conduction (through-skin heat transfer), radiation (heat transfer between the environment and biological systems), convection (heat transfer involving the movement of biofluids), diffusion (inter or intra-cellular transfer), and mass convection (mass transfer processes that become significant in scenarios such as sweat evaporation or blood flow).

All these thermofluidic considerations can enhance the performance of hydrogel as bio-interfacial material for applications like wound healing. Several tissue-like materials have been created to treat wounds with sophistication. An example is smart bandages, which often can modulate the wound environment to speed healing and prevent infection. One type of smart, flexible bandage

Table 1. Proposed promising research topics that intersect thermofluids and bioelectronics.

		Surface liquid behaviors		Thermodynamics and phase transition		Heat and mass transfer	
		Wettability	Adhesion	Liquid–Liquid transition	Solid–Liquid–Gas transition	Heat transfer	Mass transfer
Bio-interface	Complex fluids	Bio-adhesion control				Hydrogel drying dynamics and stability	
Bio-recording	Tissue level	Biofouling	Underwater adhesion				
	Cellular level		Biofilm morphology	Intracellular phase change			Ion transfer kinetics
	Point-of-care	Fluid guiding		Enhancing the detection limit of dilute airborne biomarkers			Sensor physiochemical stability
Bio-stimulation	Electrical	Impedance optimizations	Biofouling	Intracellular phase change	Bubble-based acoustic modulation	Photothermal stimulation	Ion transfer kinetics
	Thermal					Passive cooling;	Precise thermal modeling;
						Artificial skin design;	Temperature mapping on complex morphology;
						Cryotherapy and tissue preservation	Thermal therapy

could regulate temperature near a wound with a heater cast above alginate hydrogel.[135] Embedded in this hydrogel were also drug carriers for a controlled release of antibiotics. As the viscoelasticity of hydrogels is usually sensitive to temperature (especially near the gel point), a promising way to optimize drug release is precise control of hydrogel heat and mass transfer dynamics. Creating appropriate temperatures in the wound environment also plays an important role in healing due to its important role in blood flow, enzyme activities, bacterial growth, and inflammation control.[136] Therefore, thermal regulation of hydrogels could synergistically enhance the wound-healing process.

It is also important to use thermofluidic knowledge to adjust the hydrogel's interactions with water, including how it absorbs, stores, and releases water.[8,137–139] A major application challenge of using hydrogels is that they often dry out when exposed to the environment, such as during wound dressing process. To prevent evaporation and manage heat transfer, the hydrogel can be bound to a water-impervious elastomer.[140] Fundamental aspects of hydrogel heat and mass transfer need more extensive studies in addition to recent progresses.[8,137–139]

4.2. Thermofluidic Designs for Biosensing

The precise control of analyte flow, heat-mass transfer, as well as phytochemical reactions of biomarkers all play a critical role in sensing biological analytes. This section briefly uses enzyme-based, electrochemical glucose sensor as an example to discuss the opportunities and challenges in thermofluids. Most global biosensors are glucose sensors, which are being used by around 500 million patients globally. After decades of development, it is still challenging to achieve satisfying long-term stability and sensitivity simultaneously.

Enzyme-based sensors use a specific biochemical reaction mediated by enzymes to detect chemical compounds, usually by electrical means.[141] Specifically, when the target analyte encounters an immobilized enzyme, a specific biochemical redox reaction takes place. The charge transfer coming from the reaction will be turned into a readable electrical signal, to be either a current (in an amperometric sensor), a potential difference (in a potentiometric sensor), or a change in conductance or impedance (in a conductometric sensor). In an ideal situation, this electrical signal is directly proportional to the analyte concentration.[141] More detailed introductions and recent advancements of electrochemical biosensors are also introduced elsewhere.[142]

The first step in creating an enzyme-based electrochemical sensor is to immobilize and fix the enzyme on the sensor surface.[143] For a typical three-electrode sensor configuration that contains a working electrode, counter electrode, and reference electrode, the enzyme is typically immobilized on the surface of the sensor's working electrode where the potential is controlled. Enzymes immobilization can be achieved by physical adsorption, covalent bonding, cross-linking, or entrapment in a polymer matrix.[144]

Despite the straightforward physical picture, the performance of an actual biosensor is far from equilibrium when one considers the complex flow and mass transfer processes during the measurement. The diffusion of the analyte depends on the concentration gradient and diffusion coefficient, but the

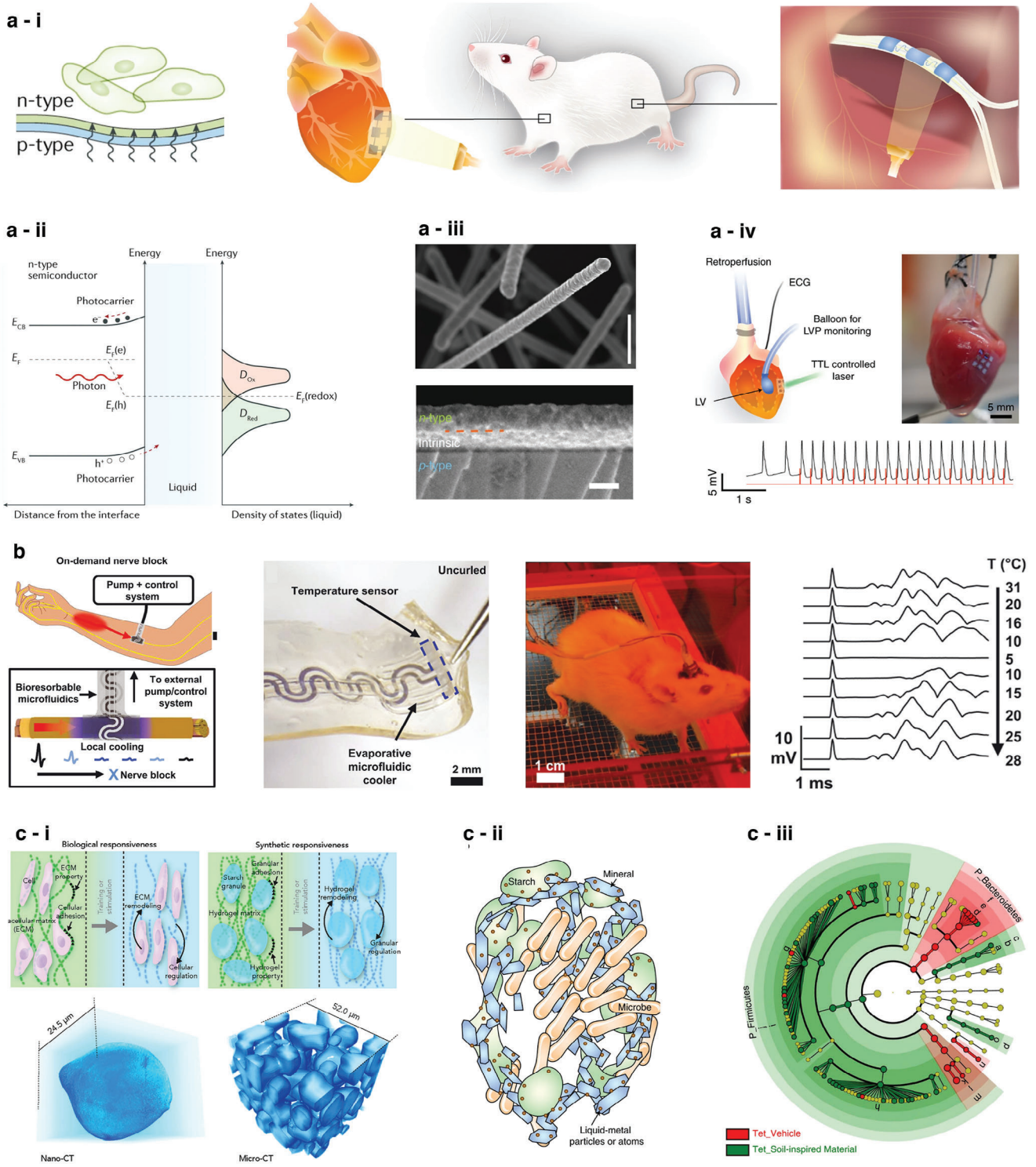

Figure 5. Bioelectronics for biomodulation. a) Semiconductor-biology interfaces for photo stimulations.[11,14] a-i) Semiconductor interfacing with biological tissue and being optoelectronically activated to stimulate nerve and heart tissue.[15] a-ii) The mechanism of porosity-based semiconductors.[15] a-iii) Nanoscale silicon nanowires for cellular-intracellular biomodulation.[11] Reproduced with permission. Copyright 2019, Springer Nature; Copyright 2022, Springer Nature. b) Thermofluidic-based nerve modulation. Each panel showcases the concepts, materials, and tests of a local cooling device to block nerve conduction.[150] Reproduced with permission. Copyright 2022, Science. c) Complex fluids and soft matter as bio-interfaces for microbial modulation.[151,152] c-i) Hydrogel made from starch granules that mimic biological tissue.[130] c-ii) illustrates how a microbial system and soil-inspired material interact in a chemical system for microbial modulation.[131] c-iii) depicts a taxa analysis of the soil featured in (c-ii) and how the soil-inspired material increases bacterial diversity.[131] Reproduced with permission. Copyright 2020, Cell Press; Copyright 2023, Springer Nature.

environment is dynamic.[145] Enzyme immobilization is often achieved using hydrogel matrix, which swells easily upon contact with the biofluids.[143] The reaction of the analyte with the enzyme is apparently affected by the diffusion of both the enzyme, analyte, and swelling of hydrogels. After the reaction, the product(s) of the reaction need to diffuse away from the sensor surface, especially when bubbles are formed. If they accumulate on the surface, they can severely interfere with further reactions.

Temperature control is another aspect worth considering. Biosensors often rely on enzymes that exhibit optimal activity at specific temperatures. Although the test of biosensors is often performed in a well-controlled laboratory, temperature fluctuation can occur when wearable biosensors are exposed to the ambient environment, causing deviations from the enzyme's optimal working temperature. These deviations can come from weather variations or human factors, such as skin inflammation that leads to elevated temperatures. Without proper temperature regulation, it is expected that the enzyme activity and biosensor performance can be affected by the environment.[143]

Due to all the mentioned instabilities in enzyme-based sensors, most commercial blood glucose meters heavily depend on disposable testing strips, which can only be used once to ensure the consistency of detection. This highlights that precise control in the flow, mass heat-mass transfer, and hydrogel hydrodynamics are critical in developing biosensors with spontaneous high sensitivity and long-term stability.

4.3. Electro-Thermo-Mechanical Bio-Modulation at Cellular Level

To increase the precision in bio-modulating, semiconductor materials have been made into precise tools to introduce localized physical stimuli with high spatiotemporal resolution (Figure 5a). Inorganic semiconductors display many relevant electrical and optical properties, and they can be fabricated into a broad spectrum of electronic and photonic devices. Recent progress in fabricating flexible circuits made semiconductor materials, such as silicon, suitable for biomodulation. As the most used material for solar cells, silicon has been extensively developed for photostimulation. With light from a laser, silicon-based biointerfaces can stimulate rat hearts ex vivo and sciatic nerves in vivo. At a smaller length scale, silicon photodiodes can stimulate nerve cells in mammalian spine tissue with near-infrared light.[146] Since the photodiodes can provide real-time, targeted control of living cells, it demonstrates minimally invasive bio-interfacing that can treat poorly functioning signaling in the carbon nanotubes. New surfaces and coatings on such nanomaterials can change the impedance or even materials' band-structures that optimizes the performance of stimulation. For example, introducing an ≈100 nm-thick porous silicon on regular silicon wafer can significantly change silicon band structure and enhance the performance of photo-electricity generation by light illumination.[14] As surface nanostructures and coatings are also major topics in current thermofluidic research, interdisciplinary efforts might result in advanced thermal coatings that simultaneously show enhanced bio-modulation performance.

Silicon photodiodes with a P-type core/intrinsic shell/N-type shell can also create chemical and mechanical stimulation by producing hydrogen peroxide when stimulated by light.[147] Since low hydrogen peroxide is linked with many diseases,[148] silicon-based materials can treat such conditions by chemically producing H_2O_2 in vivo. The H_2O_2 can also be produced into microbubbles to be further stimulated by acoustic methods, also used for bio-mechanical modulation.[149] This topic is closely related to thermofluidic research on liquid–gas phase transitions, boiling research, and bubble dynamics, all of which can contribute to precise control of bubble generation and cavity management.

4.4. Thermofluidic Systems for Bio-Thermal Regulation

Thermofluidic techniques have proven effective for tissue-level modulation, with one crucial aspect being the design of microfluidic systems. Many biological structures are not inherently designed to exhibit significant temperature variations. In the context of surface-level cooling, the evaporation of sweat plays a critical role as a primary passive mechanism for heat dissipation. The latent heat absorbed from the human body during evaporation efficiently removes excess heat. However, biological systems establish a homogeneous temperature environment for stable physiological performance. Therefore, the use of microfluidic devices represents a valuable opportunity for actively controlling heat flow and temperature both inside and outside the human body. Flexible microchannels can be employed to carry fluids that regulate temperature, deliver cold, and administer therapeutic drugs, thus facilitating the modulation of nerve behavior in tissues and organs such as the gut and brain, which is outlined in **Table 2**.[153,154]

Specifically, the regulation of neurons has many research and clinical uses.[153] One example is to use microfluidic designs for neuron cooing, which can slow neuron activity without altering their fundamental behavior, offering a safer alternative to silencing (Figure 5b).[155] Slowed neuronal activity allows researchers to observe and analyze neural dynamics at a more manageable speed. Cooling also allows reversible "lesions," which temporarily deactivate specific brain regions, enabling researchers to identify the function of those regions without causing permanent damage. This is an improvement from the earlier days of neuroscience when researchers had to cause permanent lesions to the brain.[155] Yet since neural cooling offers an easier way to analyze parts of the brain, it has potential for patient-specific use, such as for language mapping during awake craniotomy where neuron cooling may perform better than electrical stimulation.[156]

Neuron cooling can also manage pain. An important technological goal is to develop miniatures for bio-cooling and heating. Recent work showed an implantable yet minimally invasive and microfluidic cooler that can temporarily block nerve conduction, which can replace opioids for treating pain.[150] The device comprises water-soluble materials, so the cooling system dissolves after the healing process, eliminating the need to remove it surgically. The techniques have also been recently extended to the skin and human body for effective thermal regulation.[157,158]

Thermofluidic techniques have also been employed for tissues or skin-level heat management. Many designs exist to modify bioelectronic devices to have a thermoregulatory component.[157,158] For instance, physiological sensors attached to the skin that continuously monitor health can cause injuries if they overheat.[104] Recently a new mechanism was introduced that uses thin,

Table 2. An overview of thermofluidic systems for bio-thermal regulation.

Feature	Materials	Design	Scale	Function	Purpose
Neuron cooling	Biocompatible polymers	Microfluidic designs	Tissue-level	Slows neuron activity	Analyzing neural dynamics, creating reversible "lesions," language mapping during awake craniotomy
Pain management	Water-soluble materials	Implantable microfluidic cooler	Microscale	Temporarily blocks nerve conduction	Replacing opioids for pain treatment, dissolves post-healing to eliminate surgical removal
Skin thermal regulation	Biocompatible polymers	Various thermoregulatory components, for heat dissipation, insulation, and active cooling and heating	Tissue or skin level	Regulates skin temperature	Preventing overheating injuries, includes passive cooling, switchable thermal barriers, and resistive heaters
Bioelectronic device insulation	Silicone, thermoplastic elastomers, or other biocompatible polymers	Thin, flexible bladders filled with a fluid	Tissue or skin level	Prevents device overheating	Detaching device from skin upon overheating to prevent injuries

flexible bladders to insulate the skin and detach the bioelectronics device from the skin when it overheats.[104] Similar thermal designs can be applied to many devices that integrate with the skin, and these designs include passive cooling, actively switchable thermal barriers, and thin resistive heaters.[103]

4.5. Outlook: Accurate Biosensing of Airborne Biomarkers

Recent advances in wearable biosensors provide a new endeavor toward non-invasive, point-of-care healthcare solutions. Specifically, many existing works have been able to monitor biomarkers from accessible biofluids such as blood, urine, and sweat. However, what is less mentioned in the literature is the detection of dilute airborne biomarkers. Through the gas exchange happening in alveoli between the blood stream and lung, important blood-borne biomarkers can also be found through exhaled breath (**Figure 6**a-i). On average per day, we breathe around 20 000 times, and a small fraction of the exhaled air consists of biomolecules that contain valuable clues about the body's metabolism (Figure 6a-ii).[159] Developing portable biosensors that can effectively capture and sense those airborne biomarkers can revolutionize bioelectronics, which would also allow non-invasive monitoring of public health. However, the challenge in the field is that the biomarkers are often diluted to a part-per-billion level. To achieve a higher detection limit, developing new sensing materials has been the go-to method. For example, the use of novel 2D materials like graphene and MXenes, or adopting transistor-based sensor designs, can amplify the signal current. But obviously the thermofluidic effort is equally important to transfer the phase of biomarkers from airborne states into highly concentrated, detectable solid or liquid. Integrating thermofluidic designs that optimize analyte behavior and bioelectronics sensor design can enhance the detection limit of current sensors.[160] Currently, most breath analyzers are closed systems that require close contact with the human body. Exhaled breath is often condensed within internal metallic tubes, which are cooled by dry ice or conventional ice. To minimize invasiveness, especially for infant healthcare and various scenarios, thermofluidic efforts are needed to capture airborne biomarkers from open air and integrate them with bioelectronic devices for real-time and continuous detection. For comprehensive information on the current market and device development of breath analyzers, readers are referred to existing literature.[159]

4.6. Outlook: Understanding the Thermodynamics and Kinetics of Complex Biofluidic Behaviors

Despite how much of the thermofluidics field's efforts have focused on working with single water phase, biofluids contain many subcomponents with a spectrum of size, polarity, and dynamics. Through complex interactions, distinct phases form and complicate the biofluids that interface electronic devices.[114] One important aspect in biomodulation is the precise control of the dynamics of complex, multicomponent biofluids with the effort from the thermofluidic field. Understanding phase separation can provide insights into the dynamic behavior of cellular components in different conditions.

Some notable scenarios include intracellular condensates and biofouling. In cellular biology, liquid–liquid phase separation drives the behavior of many important organelles, such as nucleoli, P granules, and stress granules (Figure 6b).[161] These organelles are essentially droplets of proteins and RNA that separate out from the cytoplasm or nucleoplasm, similar to oil droplets in water.[162] As the functionality of proteins heavily depends on the integrity of their structure, the abnormal phase separation can lead to protein aggregation and further result in several neurodegenerative diseases like Alzheimer's and Parkinson's. For instance, the aggregation of amyloid-beta peptides in Alzheimer's is believed to be a phase separation process.[163] Understanding this process can help develop strategies to intervene or control these diseases.[164] Future bioelectronics devices, designed with phase separation in mind, could modulate the phase separation and reverse protein aggregation or deliver drugs precisely during the process, which has already been demonstrated in in vitro system with electric field.[165]

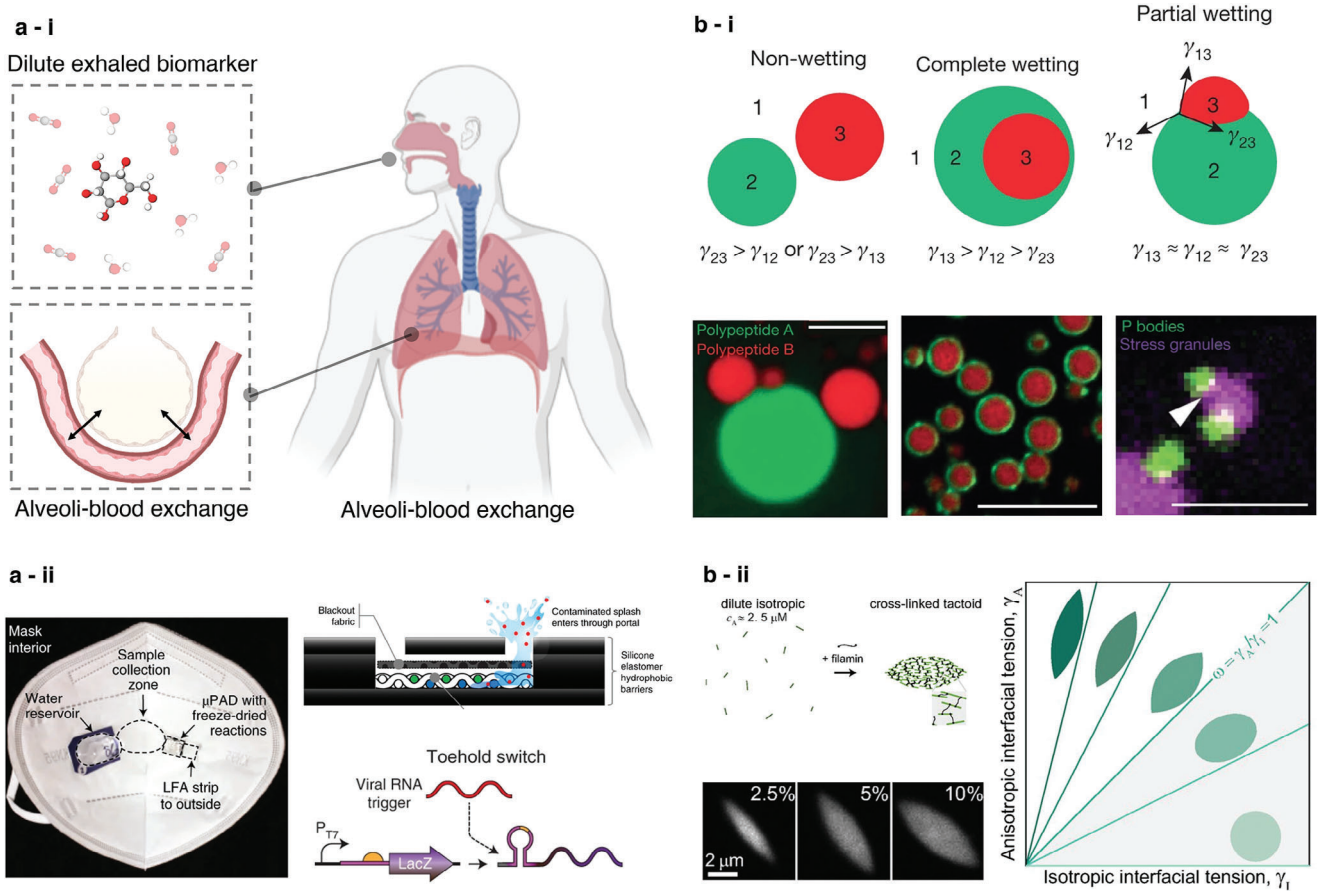

Figure 6. Future precision bioelectronics, where (a) presents a concept for a device detecting airborne biomarkers and (b) shows concepts involved in adjusting designs for bioelectronics when considering thermofluidics. a) Synergistic design of bioelectronics and thermofluids for sensitive biosensing.[171] a-i) The concept of utilizing breath analysis to detect important biomarkers originated from blood stream, which is also discussed in other work.[171] The figure is generated by illustration software "BioRender." a-ii) A representative mask device used to collect exhaled biomarkers. Reproduced with permission. Copyright 2021, Springer Nature. b) Precise biomodulation via rationalized manipulation of multiphase biofluids.[172,173] b-i) shows how varying interfacial tensions create different wetting outcomes.[153] b-ii) Liquid behavior of cross-linked actin bundles with various filamin concentrations.[154] Reproduced with permission. Copyright 2022, Springer Nature; Copyright 2017, PNAS.

Biofouling is another major challenge caused by the complex behaviors of biomacromolecules, which diminishes the long-term stability of bioelectronics due to proteins and other biomacromolecules adhering to device surfaces. Perhaps the most noticeable cases are nanomaterials for bioelectronics, such as nanoparticles, silicon nanowires, and carbon nanotubes, which are small and have high surface–volume ratios. For example, therapeutic nanoparticles require extended circulation time in the bloodstream. The rapid protein fouling on these nanoparticles makes them easy targets for the human immune system, often leading to their destruction before the drug delivery sites.[166–168] Understanding the multiphase interaction process is fundamental to learning how cells compartmentalize their components and functions without needing a membrane. However, the task is difficult even for the most advanced molecular simulation techniques such as deep potential molecular dynamics.[169]

It should also be noted that reliable experimental approaches to probe and understand multiphase droplet behavior need further developments. Analytic chemistry techniques, such as liquid/gas chromatography, mass spectrometry, Raman, and infrared spectroscopy are all options for observation, but it is difficult to use the right sampling technique to connect the phase dynamics and instrument detection at the right timescale. But perhaps the most immediate research in this area is to use advanced optical methods for cellular biology, such as fluorescence, to study artificial binary or multiphase droplets and convert the knowledge into the biological environment.[165,170]

4.7. Outlook: Miniature Devices Design

As human body needs to maintain homeostasis, thermofluidic biomodulation is a promising approach for neuromodulation and wound healing, which involve heat management processes. Recent work has demonstrated the use of programmable thermal therapy, which involves delivering controlled heat to the skin surface at a desired temperature and duration, and can feature active thermoregulation, virtual social interactions, and sensory expansion.[157] Like the need for heating, cooling can also relieve pain and aid wounds. In contrast to traditional analgesic

medications that dull the pain receptors, miniaturized coolers can also be applied to the wound or pain-causing locations. Cooling by such miniaturized device can temporarily block nerve conduction using a liquid-to-gas phase transition as the cooling mechanism, as demonstrated by recent work.[150] By integrating a thermal thin-film sensor that monitors the temperature in real time, a closed-loop control is also achieved.

However, it is still challenging to develop wireless devices for the heating or cooling of biological tissues in vivo. Heating is an easier challenge using a miniature device with embedded batteries, but cooling is much more difficult. Active cooling devices that take away the heat from a location require heat-dissipating designs, as dictated by the second law of thermodynamics. While recent work showed promising results of in vivo cooling by a microfluidic channel carrying coolant, heat dissipation is still performed in vitro.[150] Passive cooling materials, or strategies for dissipating the heat inside the body, are not fully developed and require efforts from thermofluids research for in vivo cooling technologies.

In addition to thermofluidic modulating, the monitoring of human thermofluidic properties is also important. For example, thermal sensing methods offer versatile measurements of skin health and can monitor skin disorders. Skin temperature can be used to indicate core body temperature, hydration status, microvascular perfusion, and flow rates of blood and cerebrospinal fluid. Advanced thermal measurement techniques have been adopted for such applications, such as using the 3ω method that characterizes thin film thermal properties for skin measurement.

As outlined by a recent review on this topic,[32] a challenging aspect of future work is creating access to probe the temperature and fluid flow of deeper tissues with as little invasiveness as possible. Integrating injectable fiber with time-domain thermal reflectance is a promising direction, but more work needs to be made on miniature device design.[174]

5. Conclusion

This perspective briefly discusses both progress and challenges in the fields of thermofluids and bioelectronics, aiming to bridge these two fields and identify promising future directions for the development of next-generation healthcare devices. The development of new materials now enables precise control over fluid properties, such as transport, wettability, and phase-change behaviors. This precision in fluid control is important for contemporary bioelectronics, in terms of both biosensing and biomodulation. Combining the transferable skills of researchers in both thermofluids and bioelectronics can create various opportunities, from advanced complex fluids for bio-interfaces, to more reliable biosensing platforms and more precise bio-modulation methods.

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Conflict of Interest

The authors declare no conflict of interest.

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