



Real-time on-body sweat sensing: Electrochemical insights, progress, and prospects

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ABSTRACT

Among various biofluids, human sweat has attracted increasing interest because it can be readily accessed non-invasively at the skin surface and contains a wide range of metabolites, biomarkers, and electroactive species that convey valuable physiological information related to human health. Electrochemical-based sweat monitoring techniques are particularly well-suited due to their inherent sensitivity, low power consumption, ease of miniaturization and compatibility with wearable platforms. Accordingly, significant advances have been reported in electrochemical sweat sensors integrated with nanostructured electrodes, microfluidics, and flexible wearable platforms. However, the analytical relevance of many reported systems remains limited, as sensor performance is frequently evaluated using artificial or collected sweat, conditions that fail to capture the dynamic, non-equilibrium conditions. To emphasize the significance of on-body sweat sensing, this review critically examines electrochemical sweat sensors that operate directly on the human body and perform real-time measurements in native sweat. Representative studies targeting stress and neurochemical markers, metabolic analytes, and small molecules are analyzed, with particular emphasis on analytical performance under physiological sweating conditions rather than device architecture alone. Across different analyte classes, recurring challenges are identified, including sweat-rate-dependent dilution and accumulation effects, pH-induced signal modulation, matrix interference, calibration instability, electrode-skin interface degradation, and pronounced inter-individual variability. By integrating these cross-cutting limitations, this review highlights that reliable sweat electrochemistry is fundamentally constrained by signal interpretation within a dynamic biological matrix, rather than by detection sensitivity alone. Ultimately, this review outlines key directions necessary for advancing wearable sweat electrochemistry toward robust, reliable, and physiologically meaningful applications.

1. Introduction

Human sweat is a complex biofluid secreted by eccrine glands that contains electrolytes, metabolites, stress-related compounds, and other small molecules. Its composition reflects an interplay between systemic physiology, glandular transport, and skin-surface interactions [1,2]. Unlike blood or interstitial fluid, sweat is produced locally and intermittently, and its composition is strongly influenced by sweat rate, sampling location, hydration status, and environmental conditions. These characteristics make sweat analytically distinct, as measured concentrations do not directly correspond to circulating levels but instead encode physiological information shaped by secretion dynamics and surface transport processes [3,4]. Despite these complexities, sweat

offers a unique opportunity for non-invasive and continuous monitoring, particularly when accessed directly on the body in real-time. Consequently, meaningful sweat analysis requires sensing strategies capable of operating under dynamic, non-equilibrium conditions rather than static sampling paradigms [5,6].

Electrochemical techniques are particularly well suited to address these challenges, as they transduce chemical activity into electrical signals in real-time through well-defined charge-transfer and redox processes [7–9]. Electrochemical sensors are widely adopted due to their high sensitivity, scalability, and system-level simplicity, enabling quantitative detection without the need for bulky components. Their operation under ambient conditions, low power requirements, and compatibility with miniaturized electronics make electrochemical

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sensors particularly well-suited for continuous and distributed monitoring [10–12]. Moreover, electrochemical platforms offer broad adaptability through surface functionalization. Selectivity can be engineered using ion-selective membranes, enzymes, molecularly imprinted polymers (MIPs) and emerging functional materials such as nanostructured catalysts and conductive composites [13,14]. The rapid signal generation mechanisms, whether based on potential shifts, current responses, or impedance changes, support real-time analysis with high temporal resolution. In addition, electrochemical sensors can be fabricated using scalable, cost-effective methods such as printing and thin-film processing, facilitating integration into compact, portable, and multiplexed sensing systems [15,16]. Collectively, these attributes make electrochemical sensing inherently compatible with wearable formats that require continuous operation, mechanical flexibility, and minimal energy consumption [17].

Importantly, electrochemical responses in sweat are strongly influenced by local physicochemical conditions, such as pH, ionic strength, and matrix composition, which can modify signal output independently of analyte concentration. As a result, sweat sensing requires careful interpretation of the measured signals in addition to detection [18]. In recent years, there has been rapid growth in wearable sweat sensors integrated into flexible substrates, microfluidic patches, and conformal wearable platforms [19,20]. However, wearable form factors alone do not ensure physiological relevance, as a substantial fraction of reported studies continue to rely on artificial sweat formulations or sweat collected off-body before analysis. Such approaches fail to capture the dynamic conditions encountered during real-time, on-body operation. These include temporal fluctuations in sweat rate, evolving pH, variable skin-sensor contact, and continuous exposure to complex biological matrices [21]. Consequently, performance metrics derived from artificial or collected sweat often overestimate analytical robustness in practical use. This discrepancy arises because on-body electrochemical sweat sensing operates in a fundamentally different analytical regime. Under these conditions, the measured signal reflects a convolution of analyte concentration, sweat secretion dynamics, transport delays, matrix interference, and inter-individual variability [22]. These factors profoundly influence calibration accuracy, selectivity, and signal stability, particularly during prolonged wear or physical activity. As a result, the primary challenge of wearable sweat sensing shifts from analyte detectability to signal interpretability. Under real-time conditions, electrochemical responses are governed not only by the presence of target species, but also by evolving physicochemical and transport processes at the skin-sensor interface [23]. Variations in sweat rate, local pH, ionic strength, and evaporation can further induce signal drift, transient offsets, or apparent concentration changes that are decoupled from underlying physiological trends. Accordingly, conventional performance metrics obtained under controlled laboratory conditions, such as sensitivity or limit of detection, provide an incomplete representation of sensor behavior during continuous monitoring [24]. Meaningful interpretation of sweat electrochemical data, therefore, requires analytical frameworks that explicitly account for contextual dynamics and interface evolution, rather than treating sweat as a static electrolyte or assuming direct correspondence with systemic biomarker levels.

Real-time on-body sweat sensing represents a shift from static biochemical measurement toward a continuous, system-level monitoring of human physiology. In this paradigm, sweat is no longer treated as a passive biofluid but as a dynamic carrier of time-resolved chemical information. This information is shaped by secretion (including both active and passive sweat), transport, and surface interactions at the skin surface [25,26]. Electrochemical sensors, often integrated with microfluidic architectures or absorbent sampling layers and positioned directly at the skin interface, play a central role in this transformation by transducing transient molecular events in sweat into electrical signals that can be processed and interpreted in real-time. When coupled with wireless electronics and data analytics, these signals extend beyond localized measurements, enabling longitudinal monitoring and seamless

integration with digital health infrastructures [27,28]. This end-to-end framework positions sweat sensing within a broader closed information loop, in which biochemical activity at the skin surface informs physiological assessment, personalized feedback, and the future development of closed-loop diagnostic or therapeutic strategies [29]. This progression from sweat secretion to closed-loop interpretation is schematically illustrated in Fig. 1.

Although numerous reviews have surveyed wearable electrochemical sweat sensors [30], existing literature largely treats sweat as a uniform analytical medium. This includes studies based on artificial formulations, collected or spiked samples, and native human sweat, often without clearly distinguishing the mode of sweat generation or the analytical context of measurement [31–34]. As a result, the specific analytical implications of measuring sweat directly on the body, where secretion is dynamic, heterogeneous, and physiologically coupled, have received limited focused discussion [35]. In this review, we specifically emphasize electrochemical sensors that operate on the human body and interrogate native sweat in real-time. This approach enables isolation of analytical behaviors and challenges that arise uniquely from on-body sweat generation and continuous measurement. Representative works targeting stress and neurochemical markers, metabolic indicators, and small molecules are examined to extract analytical insights rather than to catalog device architectures. Particular emphasis is placed on cross-cutting challenges that recur across analytes, including pH-dependent signal modulation, sweat-rate-induced dilution and accumulation effects, matrix interference, and inter-individual variability. By synthesizing these shared constraints, this review aims to clarify the analytical boundaries of wearable sweat electrochemistry and to outline directions necessary for advancing reliable and interpretable real-time sweat sensing. To frame these discussions, the following section first establishes human sweat as a dynamic, non-equilibrium electrochemical matrix, highlighting the physicochemical and transport phenomena that fundamentally differentiate on-body sweat sensing from conventional electrochemical analysis.

2. Human sweat as a dynamic analytical matrix

Human sweat is a dilute, compositionally complex, and dynamically regulated biofluid that serves as an accessible window into physiological and metabolic processes. Secreted primarily by eccrine glands, sweat consists predominantly of water containing dissolved inorganic ions, metabolites, and small organic species. Their measured concentrations reflect the convolution of systemic physiology, glandular transport, and surface-level processes rather than direct equilibrium with blood [36, 37]. In general, sweat is produced through multiple secretion pathways, including passive secretion under resting conditions, thermally or exercise-induced active sweating, and emotionally triggered sweating. Chemically or electrically stimulated sweat, generated using iontophoresis or pharmacological agents, represents another controlled mode of secretion [38]. Each secretion mode is governed by distinct physiological mechanisms and yields sweat with different secretion rates, volumes, and compositional profiles, thereby introducing analytical variability at the point of sampling [39]. Actively secreted sweat reflects dynamic thermoregulatory and metabolic processes and is strongly time dependent, whereas passively obtained sweat is often sparse, intermittent, and more susceptible to surface accumulation and evaporation. In contrast, stimulated sweat, while enabling controlled and localized secretion, may deviate from natural sweating dynamics due to altered gland activation pathways and transport kinetics, complicating physiological interpretation [40].

Unlike blood or interstitial fluid, sweat composition is not tightly regulated by homeostatic mechanisms; instead, it evolves continuously in response to thermoregulation, physical activity, hydration status, and environmental exposure [41]. This intrinsic variability establishes sweat as a time-dependent, non-equilibrium analytical matrix. Static or end-point measurements provide limited physiological insight. Human

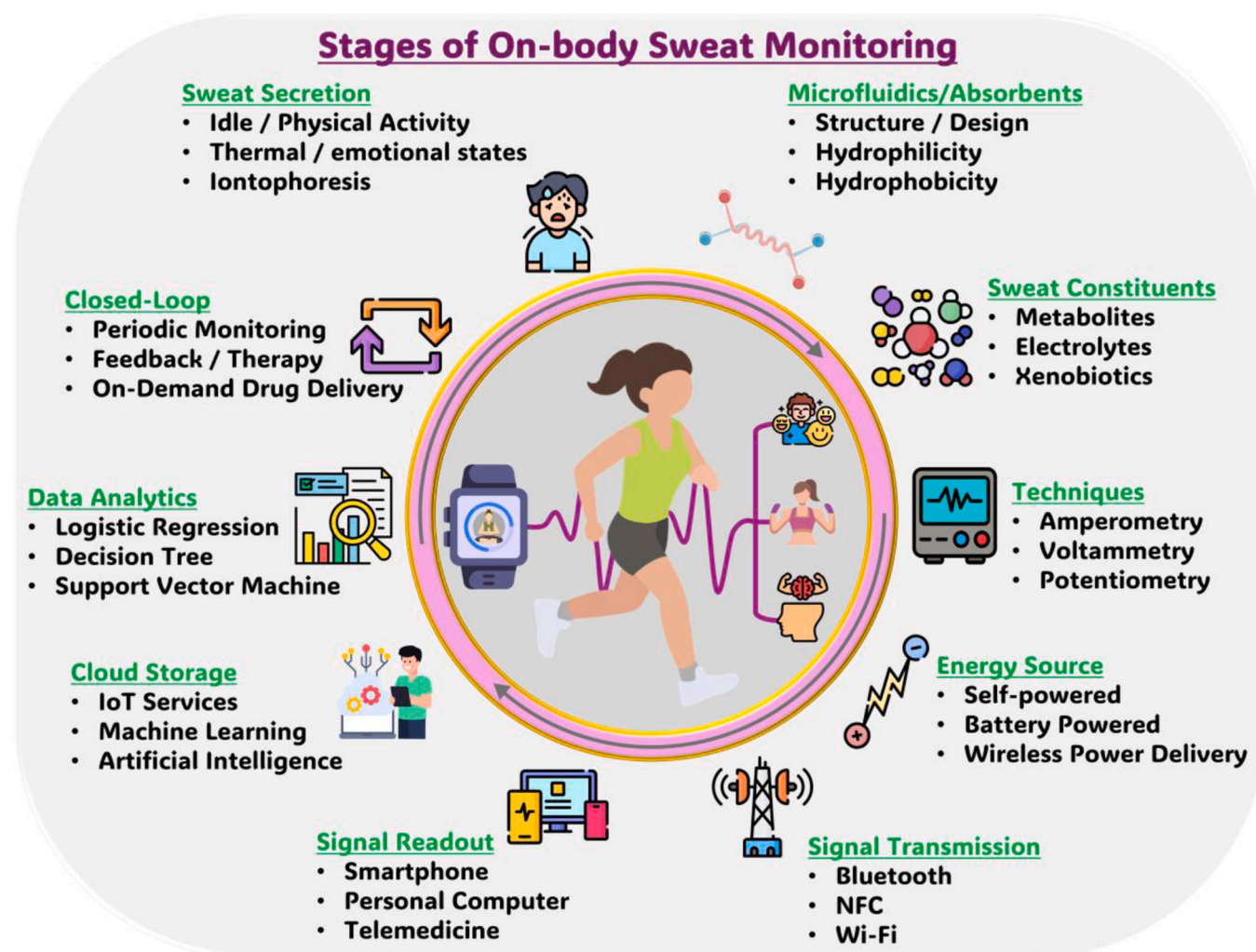


Fig. 1. Framework illustrating the stages of on-body sweat monitoring, from sweat secretion and electrochemical sensing to wireless data transmission and cloud integration, highlighting future closed-loop diagnostic and therapeutic opportunities. The icons used in this figure were adapted from www.flaticon.com.

sweat contains a diverse range of inorganic ions, metabolites, hormones, and small organic molecules spanning several orders of magnitude in concentration. Major electrolytes such as sodium and chloride are typically present at millimolar levels, while potassium and ammonium occur at lower millimolar to sub-millimolar concentrations, with values strongly modulated by sweat rate and ductal reabsorption [42]. Many common metabolites such as glucose, urea, and lactate are present in biological fluids at millimolar concentrations, whereas others like uric acid are typically found at sub-millimolar levels. In contrast, stress-related hormones and signaling molecules, such as cortisol, adrenaline, dopamine, and norepinephrine, are present at nanomolar or sub-nanomolar levels, which remain under active investigation [43–45]. Importantly, these concentration ranges are not fixed values but represent dynamic envelopes that shift with secretion mode, physical activity, hydration status, and local skin conditions. In real-time on-body measurements, apparent analyte levels further reflect temporal dilution, accumulation at low sweat rates, and evaporation-driven concentration changes at the skin surface. Consequently, sweat composition should be interpreted as a continuously evolving chemical profile rather than a static analytical target, reinforcing the need for time-resolved sensing strategies. During ductal transport, selective ion reabsorption renders electrolyte concentrations strongly dependent on secretion rate. As sweat flux increases, ion dilution occurs, whereas low sweat rates promote localized accumulation and evaporation-driven concentration changes [46]. Such rapid and bidirectional fluctuations in ionic strength

directly influence electrode interfacial behavior, underscoring the need for continuous, real-time electrochemical monitoring rather than discrete sampling approaches.

On the other hand, sweat pH further illustrates the importance of real-time analysis. Governed by a balance of lactate, bicarbonate, ammonia, and weak organic acids, sweat pH exhibits limited buffering capacity compared to conventional electrochemical electrolytes [47]. Transient changes in secretion rate, evaporation, or metabolic activity can induce rapid pH shifts that significantly affect enzymatic reaction kinetics, redox equilibria, and the surface charge states of electrode materials [48]. Capturing these transient variations requires sensors capable of dynamic response under on-body conditions, as averaged or post-collection measurements obscure temporal trends critical for physiological interpretation. Beyond inorganic species, sweat contains metabolites such as lactate, glucose, urea, and UA. Their observed levels arise from combined contributions of systemic circulation, local skin metabolism, and transport across the sweat gland and skin surface. Accordingly, sweat-blood relationships are often nonlinear, time-delayed and sweat rate dependent, particularly during exercise or thermal stress, when secretion dynamics evolve rapidly [49].

Similarly, environmental and physiological factors further reinforce the necessity of real-time analysis. Variations in sweat rate, skin temperature, and mechanical motion alter analyte transport to the sensing interface, while evaporation and skin contamination reshape the local chemical environment before detection [50,51]. These coupled

dynamics cannot be reproduced in artificial sweat formulations or resolved through collected sweat analysis. Both approaches lack temporal and spatial fidelity. Consequently, sensor performance assessed under static conditions often fails to predict behavior during prolonged on-body use. Collectively, these characteristics define human sweat as a dynamic and non-equilibrium electrochemical matrix, for which analytical reliability depends on time-resolved measurement and contextual interpretation rather than static concentration values. Continuous on-body sweat analysis, therefore, enables resolution of transient chemical events, compensation for physiological variability, and identification of meaningful trends that would otherwise be lost in collected or artificial systems [52]. Recognizing and accounting for the time-dependent nature of sweat chemistry is therefore fundamental to advancing electrochemical sweat sensors from laboratory demonstrations toward analytically robust and physiologically interpretable wearable platforms.

3. Electrochemical principles underpinning sweat sensing

Electrochemical sweat sensing depends on interfacial charge-transfer and mass-transport processes at the electrode-sweat interface, where chemical activity is transformed into measurable electrical signals [53]. Under wearable conditions, these processes are continuously influenced by sweat composition, secretion dynamics, and mechanical perturbation, making the electrochemical response inherently context dependent [54]. Therefore, the choice of electrochemical transduction strategy directly affects sensitivity, temporal resolution, long-term signal stability, susceptibility to drift, and robustness against interference during real-time on-body operations. Potentiometric, amperometric, voltammetric, and impedance-based transductions dominate sweat sensing, each imposing distinct analytical constraints under physiological conditions [55,56]. Potentiometric sensors are widely employed for sweat ion and pH monitoring due to their low power requirements and quasi-steady-state response. However, under native sweat conditions, potentiometric accuracy is strongly influenced by temperature fluctuations, dynamic ionic strength, membrane hydration kinetics, and reference electrode instability [57,58]. These influences are often minimized in artificial sweat studies but become prominent during prolonged on-body use, where signal drift and baseline instability limit quantitative reliability.

Amperometric and voltammetric techniques are extensively applied to metabolite sensing, including glucose and lactate, offering high sensitivity and rapid response. However, in real-time on-body deployment, these methods face converging challenges, including electroactive interference, oxygen dependence, progressive enzyme degradation, and electrode fouling [59]. Continuous exposure to native sweat, combined with repetitive mechanical deformation during wear, further amplifies baseline drift and signal instability, limitations that are often obscured under static laboratory measurements [60]. In contrast, electrochemical impedance spectroscopy is generally less suited for direct, continuous quantification of sweat analytes due to its relatively slow acquisition, sensitivity to non-specific interfacial changes, and complex data interpretation under dynamic conditions. As a result, impedance studies are primarily employed as diagnostic and monitoring tools rather than primary sensing modality, offering insight into interfacial resistance, double-layer capacitance, biofouling progression, electrode degradation, and changes in skin-sensor contact quality during prolonged wear [61,62]. Although impedance methods do not yield analyte-specific concentration readouts in real-time, their strength lies in elucidating signal degradation mechanisms and interface evolution in wearable systems, where electrochemical interfaces evolve continuously over time.

Electrochemical transduction offers several key advantages for wearable sweat sensing, particularly when compared with alternative detection modalities. These include high sensitivity, low detection limits, rapid response times, and direct compatibility with miniaturized,

low-power electronics, making electrochemical sensors especially suitable for continuous, real-time monitoring under dynamic physiological conditions [10,12]. However, in contrast to some optical-based methods, electrochemical systems can be more susceptible to long-term stability challenges and signal drift during prolonged on-body use. Factors such as surface fouling from biomolecules, enzymatic degradation in biorecognition layers, fluctuations in sweat ionic strength, and reference electrode instability may affect signal reliability over time. Nonetheless, these limitations are increasingly mitigated through advances in nanostructured materials, antifouling coatings, solid-state reference electrodes, and calibration-free or signal-correction strategies, thereby significantly improving operational stability and anti-interference performance. In comparison, colorimetric assays provide excellent operational simplicity and inherently low susceptibility to electrical noise, as they rely on visible color changes rather than electrical signals. This makes them relatively robust against certain types of electromagnetic interference. However, their major limitations lie in poor quantitative accuracy, low temporal resolution, and difficulty in enabling continuous monitoring, particularly under variable sweat rates and lighting conditions. Optical and fluorescence-based wearable sensors offer high molecular specificity and reduced chemical cross-interference, but their dependence on external light sources, photodetectors, and complex signal processing increases system complexity, power consumption, and susceptibility to environmental disturbances [63]. Similarly, surface-enhanced Raman spectroscopy (SERS) provides exceptional molecular fingerprinting capability and minimal electrochemical interference; however, its reliance on stable plasmonic substrates, sensitivity to motion artifacts, and challenges in maintaining consistent signal enhancement under fluctuating sweat compositions limit its long-term reliability and practical integration into flexible, wearable formats. Overall, while alternative modalities such as colorimetric, optical, and SERS-based approaches offer advantages in simplicity or molecular specificity, they are generally less suited for continuous, real-time, and low-power wearable applications. Electrochemical sensing, despite its inherent challenges in long-term stability and interference, remains the most practical and scalable approach for wearable sweat analysis. Importantly, ongoing progress in materials engineering, device architecture, and signal processing is steadily closing these gaps, reinforcing the position of electrochemical techniques as the leading platform for robust, continuous sweat monitoring.

Within this analytical framework, electrode materials shape real-time on-body sweat sensor performance less through intrinsic sensitivity alone and more through how their surfaces evolve under continuous exposure to native sweat. Functional materials such as MXenes, metal organic frameworks (MOFs), covalent organic frameworks (COFs), and their hybrids are increasingly employed to enhance electroactive surface area, regulate analyte transport, and tailor interfacial chemistry [64,65]. While these attributes improve initial signal response and enable low-concentration detection, they also increase susceptibility to biofouling, structural instability, and time-dependent drift. The high porosity and chemical reactivity characteristic of these materials facilitate the adsorption of proteins, lipids, and salts from sweat, often leading to attenuation of charge-transfer kinetics during prolonged wear [66]. In addition, concerns related to oxidative instability (particularly for MXenes), framework degradation or metal ion leaching (in MOFs), and uncertain skin compatibility under extended contact complicate their translation to reliable on-body operation [67]. Carbon-based materials share similar trade-offs, where their high surface area and flexibility enhance signal magnitude but also accelerate adsorption-driven fouling. In contrast, noble metals and metal oxides provide superior electrochemical stability but exhibit reduced mechanical compliance, increasing vulnerability to motion-induced contact artifacts [68,69]. In enzyme-mediated systems, these material-dependent effects are further coupled with enzyme retention, microenvironmental pH, oxygen accessibility, and denaturation kinetics, collectively governing signal longevity rather than peak response [70]. Accordingly, in real-time

on-body sweat sensing, electrode materials primarily determine rates of fouling, enzymatic degradation, interfacial drift, and mechanical robustness, not absolute detection limits [71]. Analytical reliability, therefore, emerges from the dynamic interaction between material properties, sweat chemistry, and wear-induced perturbations over time. This complexity has been widely recognized in several recent reviews where they have systematically compared material platforms [72–74] and microfluidic architectures [39,75,76] in wearable sweat sensing, highlighting how trade-offs between electrochemical performance, long-term stability, and skin compatibility govern practical on-body applicability. Therefore, in this review we emphasize the material-dependent interfacial and operational constraints rather than reiterating detailed material-specific comparisons available elsewhere.

More broadly, real-time sweat sensing operates far from the steady-state assumptions that underpin classical electrochemical analysis. Variations in sweat rate modulate analyte transport and dilution, evaporation alters local concentration gradients and conductivity, and body motion perturbs electrode geometry and contact. These dynamic factors shift analytical performance from being sensitivity-limited to being interface- and transport-limited. Electrode fouling, enzymatic deactivation, membrane instability, and calibration drift, therefore, emerge as dominant constraints across sensing modalities. Importantly, many observed signal changes during on-body operation reflect interfacial evolution rather than true physiological variation unless explicitly accounted. Collectively, these principles highlight that reliable real-time on-body sweat sensing depends less on nominal figures of merit and more on a mechanistic understanding of interfacial chemistry, mass transport, and signal evolution under physiological perturbation. As illustrated in subsequent sections, recurring limitations across stress markers, metabolic analytes, and electroactive small molecules can be traced to shared electrochemical and transport phenomena intrinsic to sweat as a dynamic, non-equilibrium analytical matrix.

4. Analytical constraints in real-time on-body sweat sensing

Electrochemical sweat sensing efforts have primarily focused on low-molecular-weight species that are amenable to direct electrochemical transduction or indirect detection through enzymatic or ion-selective mechanisms [77]. These include metabolites, hormones, electrolytes, and redox-active small molecules that can be accessed at the skin surface under wearable formats. Within real-time on-body studies, commonly targeted analytes include metabolic markers such as glucose and lactate, small molecules such as urea, ascorbic acid (AA) and uric acid, stress-related hormones including cortisol, estradiol and adrenaline, and neurochemicals including levodopa and tyrosine. Integrated wearable platforms have also demonstrated the simultaneous monitoring of multiple metabolites and nutrients directly from sweat, highlighting the expanding scope of analytes accessible through on-body electrochemical sensing [78]. The selection of these targets reflects both physiological relevance and their chemical compatibility with electrochemical transduction under wearable, on-body conditions. Despite this apparent analytical accessibility, reliable quantification of these analytes in human sweat remains inherently challenging [79]. Sweat secretion is intermittent and spatially heterogeneous. As a result, measured concentrations vary significantly across time and location. These values are strongly influenced by sweat rate, ductal transport, and local reabsorption processes occurring prior to analyte arrival at the sensing interface. For low-abundance metabolites and hormones, signal fidelity is further limited by overlapping electrochemical responses from coexisting species. In addition, transient artifacts arise during sweat onset, cessation, and variable flow conditions. These effects complicate real-time interpretation [80]. Enzymatic targets such as glucose and lactate introduce additional constraints, including dependence on local oxygen availability, sensitivity to pH fluctuations, and progressive enzyme degradation during continuous on-body exposure [81].

At the same time, real-time on-body investigations have

demonstrated that electrochemical sensors can resolve dynamic changes in sweat composition during exercise, stress induction, and controlled physiological perturbations [82]. Across diverse analyte classes, these studies consistently show that relative temporal trends are more reproducible than absolute concentration values. This observation highlights the importance of time-resolved analysis in sweat-based monitoring. On-body experiments further reveal analyte-dependent transport delays, transient baseline shifts, and motion-induced artifacts that are largely absent in off-body or ex situ measurements. Together, these findings indicate that sweat sensor output reflects the combined effects of secretion dynamics, transport phenomena, and electrochemical transduction rather than analyte concentration alone [83]. Importantly, these real-time investigations expose shared analytical limitations across analytes, rather than analyte-specific shortcomings unique to individual targets. For example, non-enzymatic detection strategies often face selectivity challenges and electrode fouling in redox-rich sweat matrices. In contrast, potentiometric and ion-selective measurements are limited by reference electrode instability and ionic flux-induced drift [84]. The absence of standardized sweat-rate normalization strategies further restricts quantitative interpretation. In addition, the relationship between sweat and blood analyte levels remains insufficiently understood. As a result, analytical performance established under controlled laboratory conditions frequently overestimates reliability during real-time on-body use [85].

Importantly, the selection and interpretation of sensor performance parameters must be guided by the specific target analyte and its physiological context. For analytes present at low concentrations, such as hormones, sensitivity and limit of detection are critical for resolving biologically relevant fluctuations. In contrast, for metabolites such as lactate, which are present at higher concentrations and exhibit rapid temporal variation, response time and dynamic range become more important performance metrics. For electrolyte sensing, where analyte levels are relatively high and stable, long-term stability, calibration robustness, and resistance to drift dominate analytical requirements. Accordingly, performance metrics should not be evaluated in isolation; instead, they should be interpreted in relation to the intended application, physiological concentration range, and temporal dynamics of the target analyte. Overall, current real-time on-body research indicates that progress in sweat sensing depends less on expanding the range of detectable analytes and more on developing analyte-aware analytical frameworks that account for sweat dynamics, matrix variability, and inter-individual differences. Approaches such as trend-based analysis, personalized baselines, and the incorporation of contextual parameters, including pH and sweat rate, are increasingly recognized as essential components for meaningful physiological interpretation. This perspective provides the analytical foundation for the analyte-specific discussions that follow. In this context, individual biomarkers are considered not just as isolated sensing targets but as case studies that together demonstrate the strengths and limitations of real-time on-body electrochemical sweat sensing.

5. Electrochemical sensing of sweat biomarkers

The analytes discussed in this review vary in their level of established physiological relevance. Biomarkers such as glucose, lactate, urea, UA, and cortisol have documented associations with metabolic status, renal function, oxidative stress, or endocrine regulation and are actively investigated for translational sweat-based diagnostics. In contrast, certain electroactive compounds, including tyrosine and levodopa, are frequently employed in wearable electrochemical studies primarily to demonstrate analytical selectivity, interference suppression, and real-time sensing capability within complex sweat matrices. Although these molecules are found in sweat and can indicate metabolic or pharmacokinetic factors, their presence in many studies mainly acts as proof-of-concept validation rather than directly leading to clinical application. Distinguishing physiological significance from analytical

demonstration is therefore essential when interpreting wearable sweat sensing reports. In light of these considerations, the following discussions are organized in an analyte-wise manner to enable a clearer comparison of sensing strategies, analytical challenges, and physiological relevance across different biomarker classes.

5.1. Stress and neurochemical markers in sweat

Stress-related hormones and neurochemical intermediates represent compelling targets for real-time on-body sweat sensing, as they are directly linked to psychological stress, autonomic nervous system activation, and neuroendocrine regulation. Analytes such as cortisol and adrenaline serve as established biomarkers of physiological and psychological stress, while neurochemical precursors, including levodopa and tyrosine, are associated with neurotransmitter biosynthesis and neurological functions. Monitoring these species in sweat enables non-invasive assessment of acute stress responses, mental workload, and neurophysiological state. These parameters are difficult to capture continuously using conventional biofluids. Importantly, the relevance of these biomarkers lies less in their absolute concentration and more in their dynamic fluctuations, making them particularly suited to real-time analytical strategies.

Despite their significance, the electrochemical detection of stress and neurochemical markers in sweat is exceptionally challenging. These analytes are typically present at ultralow concentrations and exhibit transient, event-driven secretion profiles. Their levels are strongly influenced by individual physiology, sweat gland transport mechanisms, and temporal delays between systemic circulation and sweat appearance [86]. Additional complexity arises from the chemically homogeneous sweat matrix, where pH variation, ionic strength, and coexisting electroactive species can distort sensor response and compromise selectivity. For neurochemical intermediates, structural similarity to common interferents and overlapping redox behavior further complicate reliable detection. Under on-body conditions, these challenges are amplified by motion-induced artifacts and variable sweat secretion rates. In addition, continuous operation without frequent recalibration places stringent demands on sensor sensitivity, temporal resolution, and analytical robustness.

From a sensing perspective, two primary electrochemical strategies have been explored for neurochemical detection in sweat: direct electrochemical oxidation of inherently redox-active species and affinity-based recognition approaches. Neurochemicals such as dopamine, adrenaline, and levodopa possess catechol moieties that enable direct voltammetric or amperometric detection at carbon or nanostructured electrodes. While this approach offers rapid response and simple device architectures, its practical application in sweat is constrained by ultralow analyte concentrations, overlapping oxidation potentials with common interferents such as UA and AA, and progressive electrode fouling resulting from oxidative polymerization of catecholamines. These factors often compromise selectivity and signal stability during continuous on-body monitoring. To address these limitations, many wearable platforms employ affinity-based recognition elements, including MIPs, aptamers, and antibody-derived interfaces, which provide molecular selectivity through target-specific binding interactions. Although such strategies improve discrimination against structurally similar species, they introduce additional challenges related to receptor stability, regeneration, and signal drift during prolonged wear. Consequently, the choice between direct electrochemical detection and affinity-based sensing reflects a trade-off between rapid electrochemical responsiveness and molecular selectivity. Recognition layers are therefore designed to balance these competing analytical requirements under real-time physiological conditions.

5.1.1. Electrochemical transduction strategies for adrenaline in sweat

From an electrochemical perspective, adrenaline is a chemically favorable yet analytically demanding target for sweat-based sensing due

to its intrinsic redox activity associated with the catechol moiety. This functionality enables direct, non-enzymatic electrochemical transduction at carbon-based and nanostructured electrodes, making adrenaline conceptually compatible with wearable sensing formats that require rapid response and operational stability [87]. However, despite this favorable electrochemical signature, real-time on-body adrenaline sensing in sweat remains largely unexplored. This limitation arises primarily from selectivity challenges to structurally similar catecholamines and coexisting redox-active species within the sweat matrix [88]. As a result, reported strategies emphasize surface-level molecular discrimination rather than sensitivity enhancement using selective interfacial architectures such as MIPs, nanocarbon composites, or adsorption-controlled recognition layers. In the context of wearable operation, these approaches aim to balance selective molecular access with efficient electron transfer under dynamically changing sweat conditions. Accordingly, adrenaline sensing in sweat is best viewed as a test case for managing selectivity, matrix interference, and temporal fidelity in neurochemical monitoring, rather than as a mature quantitative sensing modality.

From a broader analytical perspective, these studies collectively suggest that the principal challenge in wearable catecholamine sensing is not signal generation but molecular discrimination within a chemically crowded sweat matrix. Unlike many metabolite sensors that are limited by detection sensitivity, catecholamine sensing requires strategies that selectively regulate molecular access to the electrode interface while maintaining rapid electron-transfer kinetics. This distinction shifts the design priority from maximizing catalytic activity toward engineering interfacial selectivity and fouling-resistant recognition layers capable of operating under fluctuating ionic strength and pH conditions typical of on-body sweat environments.

Building on these transduction strategies, recent real-time on-body investigations have begun to demonstrate the feasibility of monitoring adrenaline dynamics in human sweat under physiologically relevant conditions. In a representative study, a wearable electrochemical platform integrating a selective recognition interface, MIP with continuous sweat sampling (Fig. 2A), enabled simultaneous tracking of adrenaline alongside pH during on-body use [89]. The real-time measurements captured exercise- and stress-induced signal fluctuations, highlighting the importance of temporal resolution for catecholamine sensing, where transient changes carry greater physiological significance than static concentration values. Notably, the inclusion of pH monitoring underscored the strong coupling between matrix conditions and adrenaline electrochemistry, as variations in sweat acidity influenced redox response and signal stability (Fig. 2C). While such demonstrations validate the conceptual viability of adrenaline sensing in real sweat, they also reveal that quantitative interpretation remains highly sensitive to matrix effects, transport delays, and individual variability. These observations highlight an important analytical feature of neurochemical sweat sensing: the physiological relevance of catecholamines lies primarily in their temporal dynamics rather than their absolute concentration. Consequently, wearable platforms designed for catecholamine monitoring may benefit more from high temporal resolution and signal stability than from extremely low limits of detection. This perspective suggests that sensor architectures capable of rapid sampling and minimal signal drift may ultimately provide greater physiological insight than those optimized solely for sensitivity under static laboratory conditions.

Complementing these efforts, recent work has further advanced the concept of wearable adrenaline monitoring through fully integrated electrochemical sensing platforms capable of capturing stress-related biochemical dynamics in real-time. In a notable example, a wearable sweat sensor combining nanostructured electrochemical electrodes with a skin-conformal microfluidic interface was used to track catecholamine dynamics alongside endocrine stress markers, enabling simultaneous monitoring of adrenaline, nor-epinephrine and cortisol in human sweat under real-world conditions [5]. The device integrates nanostructured

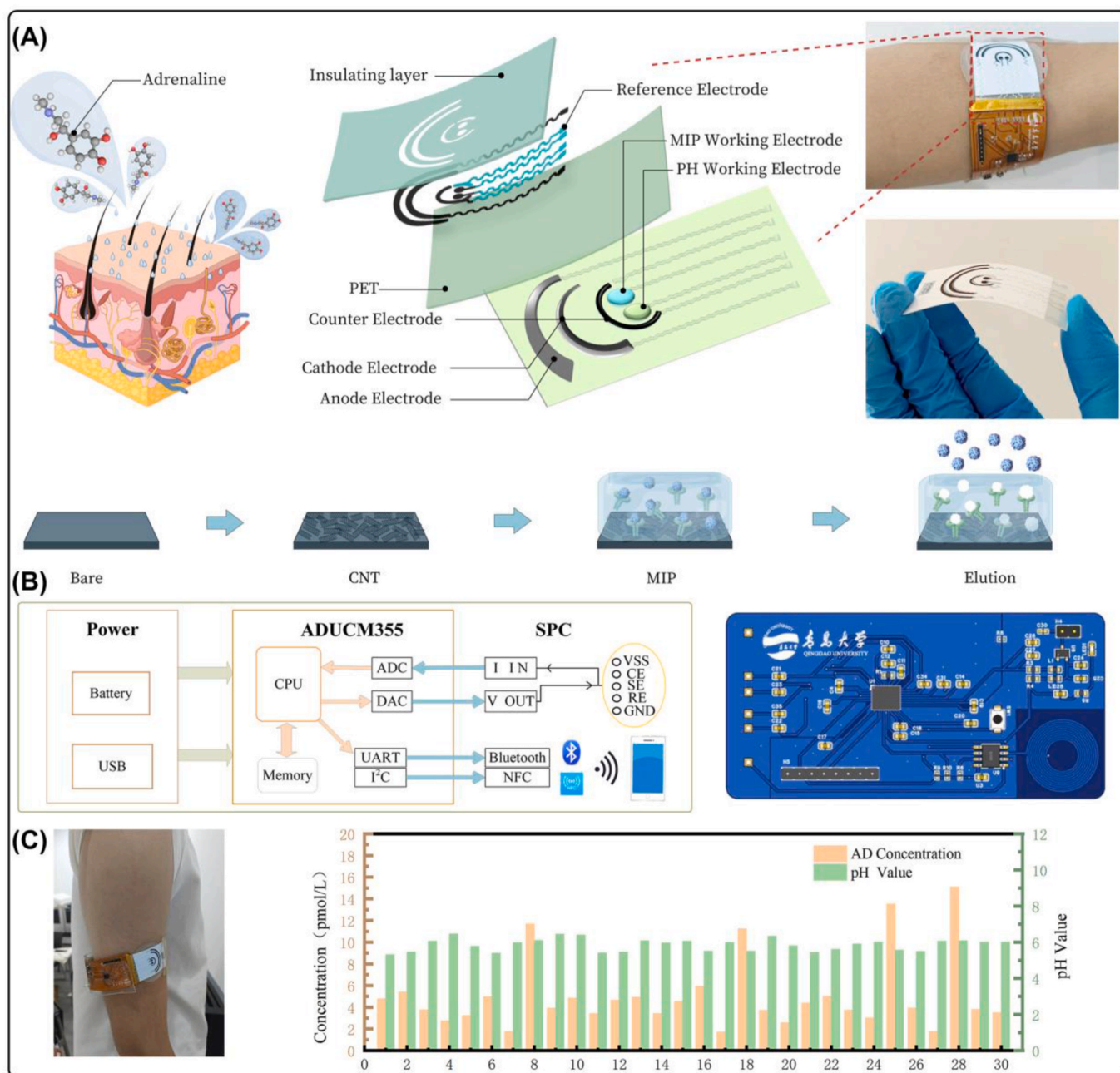


Fig. 2. (A) Overview of the fabrication of the wearable electrochemical sweat sensing system for adrenaline. (B) Printed circuit board design and inspection. (C) On-body deployment of the wearable sensing device and representative analytical results. Reproduced with permission from Ref. [89].

electrochemical sensing interfaces with a skin-conformal microfluidic collection module, allowing continuous sampling and real-time biochemical analysis during ambulatory activity. Human trials demonstrated that adrenaline and norepinephrine exhibited rapid transient fluctuations during acute physical or psychological stress, whereas cortisol displayed comparatively slower temporal variations associated with endocrine stress regulation. These findings highlight the complementary physiological information provided by fast-acting catecholamines and slower hormonal responses. Importantly, the study also showed that measured signals were strongly influenced by sweat secretion dynamics and local matrix conditions, emphasizing that accurate interpretation of neurochemical fluctuations requires contextual physiological measurements. While such multiplexed wearable platforms significantly advance the ability to capture dynamic stress physiology in real-time, quantitative analysis of individual biomarkers

remains challenged by interference from coexisting electroactive species and variability in sweat transport dynamics. Importantly, multiplex detection of catecholamines together with slower endocrine markers provides an emerging framework for interpreting stress physiology through multi-timescale biochemical signatures. Rapid catecholamine fluctuations reflect acute sympathetic nervous system activation, whereas slower hormonal responses provide a delayed endocrine perspective of the same physiological stimulus. Integrating these complementary signals within a single wearable platform may therefore enable more robust interpretation of stress responses than monitoring any single biomarker alone.

Collectively, current investigations indicate that while adrenaline is electrochemically accessible due to its intrinsic catechol redox chemistry, reliable sweat-based sensing remains analytically challenging because of strong interference from structurally related catecholamines

and other redox-active species present in the sweat matrix. Consequently, recent sensor designs increasingly emphasize selective interfacial architectures and contextual sensing strategies rather than purely sensitivity-driven electrode optimization. Despite promising demonstrations of real-time on-body monitoring, adrenaline signals in sweat remain highly sensitive to matrix composition, pH variations, and sweat secretion dynamics, which complicates absolute quantification during prolonged wear. As a result, wearable adrenaline sensors are presently best suited for trend-based monitoring of sympathetic nervous system activity, where transient signal fluctuations associated with stress or physical exertion provide more physiologically meaningful insight than static concentration measurements. More broadly, these findings illustrate a recurring theme across wearable neurochemical sensing: analytical performance must be evaluated in relation to physiological dynamics rather than conventional laboratory metrics alone. For stress biomarkers such as adrenaline, the ability to resolve rapid transient changes, maintain selectivity in a complex matrix, and operate reliably during variable sweat secretion conditions may ultimately be more critical than achieving the lowest possible detection limits.

5.1.2. Electrochemical transduction strategies for serotonin and dopamine in sweat

Serotonin (5-hydroxytryptamine) is a key neurochemical involved in mood regulation, stress response, and peripheral signaling, and its dysregulation is associated with neurological disorders and altered stress physiology [90]. Although serotonin is classically studied in central and circulating compartments, recent evidence suggests that trace levels can be detected in eccrine sweat, reflecting a combination of systemic availability, peripheral metabolism, and local skin-related transport processes. From an analytical standpoint, serotonin presents a challenging target for real-time sweat sensing due to its low concentration, susceptibility to oxidative degradation, and overlapping electrochemical signatures with other indole- and catechol-containing species. These factors complicate selective detection under on-body conditions, where sweat rate variability, pH fluctuations, and matrix interference further modulate electrochemical response. Consequently, sweat-based serotonin sensing serves as a stringent test case for evaluating selectivity, stability, and interpretability of wearable electrochemical platforms designed for neurochemical monitoring. From a broader analytical perspective, neurotransmitter sensing in sweat differs fundamentally from metabolite monitoring because the physiological signals are expected to be transient and extremely low in abundance. Consequently, wearable platforms targeting serotonin must prioritize signal stability, interference suppression, and temporal fidelity rather than solely pursuing lower detection limits. This requirement shifts the design emphasis toward controlled interfacial chemistry and antifouling architectures capable of maintaining reproducible electrochemical responses during prolonged skin contact.

Building on these strategies, a wearable electrochemical platform was developed for real-time on-body serotonin detection, using a palladium, cerium oxide decorated graphitic carbon nitride composite embedded in a calcium alginate conductive hydrogel [91]. Analytically, this study is significant because it addresses two recurrent limitations in sweat electrochemistry: electrode fouling and signal instability under continuous hydration. The hydrogel matrix maintains a stable electrolyte environment at the electrode interface, reducing dehydration-induced drift during on-body operation, while also acting as a diffusion-regulating layer that suppresses abrupt concentration spikes. The interface enhances electron-transfer kinetics, enabling low nanomolar sensitivity; however, the reported performance relies on controlled interfacial chemistry rather than intrinsic serotonin abundance in sweat. On-body measurements demonstrate the feasibility of detecting temporal variations, but absolute quantification remains sensitive to sweat rate and local accumulation effects. Importantly, the study illustrates how hydrogel-mediated interfaces can improve signal stability and mitigate fouling, reinforcing that analytical reliability in

real-time sweat sensing depends as much on interfacial regulation as on catalytic activity. These findings highlight an emerging design strategy in wearable electrochemical sensing, where hydrogel-based interfaces serve not only as mechanical support but also as chemical regulators that stabilize hydration, moderate analyte diffusion, and reduce surface fouling. Such multifunctional interfacial layers are increasingly recognized as essential components for maintaining signal continuity during long-term on-body monitoring, particularly for low-abundance neurochemical targets.

Dopamine is a central catecholamine neurotransmitter that plays a critical role in reward processing, motor control, and stress-related physiological responses. Beyond its neurological functions, dopamine is also involved in peripheral signaling pathways and oxidative stress regulation, motivating interest in its detection with non-invasive biofluids such as sweat [92]. From an electrochemical perspective, dopamine is intrinsically redox-active, enabling direct voltammetric or amperometric detection; however, its practical measurement in real-time human sweat remains analytically challenging. Dopamine occurs at trace levels and exhibits oxidation potentials that overlap with other catecholamines and electroactive sweat constituents, leading to selectivity constraints under on-body conditions. Additionally, dopamine electrochemistry is strongly influenced by pH, electrode fouling, and oxidative polymerization at the electrode surface, which can degrade signal stability during continuous monitoring [93]. As such, sweat-based dopamine sensing provides a stringent benchmark for assessing the limits of selectivity, fouling resistance, and temporal fidelity in wearable electrochemical neurochemical sensors. Importantly, the electrochemical similarities among catecholamine neurotransmitters imply that selective detection cannot rely solely on redox potential separation. Instead, effective discrimination increasingly depends on MIP layers, spatial confinement strategies, or microfluidic sampling architectures that regulate analyte access to the sensing interface.

Considering these challenges, a wearable electrochemical aptasensor based on MOF-on-MOF architecture was fabricated for simultaneous, multiplexed monitoring of neurotransmitters, including dopamine, serotonin, and adrenaline, in sweat [94]. The platform integrates a flexible electrode array within a multilayered microfluidic sampling module that passively directs naturally secreted sweat to the sensing interface, addressing a common analytical hurdle of inconsistent analyte transport in on-body conditions. Calibrated responses obtained via square-wave voltammetry show nanomolar sensitivity and good selectivity across target neurotransmitters, with interference studies confirming minimal cross-reactivity. Critically, on-body validation during exercise with a group of 10 volunteers demonstrates that the platform can resolve temporal variations in multiple neurochemical markers under real physiological sweat dynamics. However, as with other multi-analyte systems, the reliance on calibration curves derived from artificial sweat for quantification highlights ongoing challenges in translating on-body signals to absolute concentrations, given sweat-rate variability and matrix effects. Moreover, motion and transport artifacts remain potential contributors to baseline instability. Nonetheless, this work exemplifies how microfluidic design and flexible aptamer functionalization can advance real-time neurotransmitter monitoring in human sweat, reinforcing that analytical reliability in on-body sweat sensing depends on integrated strategies to manage transport, selectivity, and context variability rather than sensitivity alone. The integration of multiplex neurotransmitter detection within microfluidic wearable platforms also highlights the potential of cross-analyte correlation as a strategy for improving physiological interpretation. Simultaneous monitoring of multiple neurochemicals may provide a more reliable representation of stress-related biochemical responses than single-analyte measurements, particularly when individual signals are susceptible to transport delays or matrix-induced distortion.

Collectively, these studies indicate that although serotonin and dopamine possess intrinsic electrochemical activity that enables direct redox-based detection, their reliable monitoring in sweat remains

analytically demanding due to extremely low concentrations, overlapping oxidation potentials, and susceptibility to electrode fouling and matrix interference. Consequently, recent wearable sensing strategies increasingly emphasize interfacial stabilization, selective molecular recognition, and controlled sweat transport, rather than purely enhancing electrode sensitivity. Hydrogel-regulated interfaces and microfluidic aptamer-based platforms demonstrate that integrated architectures can partially mitigate signal drift, fouling, and transport variability during continuous on-body operation. Nevertheless, quantitative interpretation of serotonin and dopamine signals in sweat remains strongly influenced by sweat rate, pH fluctuations, and localized accumulation effects. More broadly, these observations emphasize that wearable neurochemical sensing should be evaluated in the context of physiological signal dynamics rather than traditional analytical benchmarks alone. For neurotransmitters such as serotonin and dopamine, the ability to reliably capture transient fluctuations during real-world activity may ultimately provide greater physiological relevance than achieving extremely low detection limits under static laboratory conditions. As a result, current wearable electrochemical platforms are best positioned to capture relative neurochemical dynamics and temporal trends, providing insights into stress and neurophysiological responses rather than delivering precise absolute quantification under real-world conditions.

5.1.3. Electrochemical transduction strategies for tyrosine in sweat

Tyrosine, an aromatic amino acid serving as a precursor for catecholamine and thyroid hormone biosynthesis, has been explored as a neurochemical marker in sweat primarily as a proof-of-concept target rather than a clinically established biomarker [95]. From an electrochemical standpoint, tyrosine is moderately electroactive, undergoing oxidation at relatively high potentials, which poses challenges for selective detection in complex biological matrices. Consequently, reported electrochemical strategies typically rely on nanostructured carbon or metal-based interfaces designed to enhance electron transfer kinetics while suppressing interference from coexisting amino acids and redox-active species. In wearable formats, tyrosine sensing remains analytically constrained by low sweat concentrations, overlapping oxidation signals, and strong dependence on local pH and ionic environment, limiting its current application to exploratory on-body demonstrations rather than robust physiological monitoring [96]. From a broader analytical perspective, tyrosine sensing illustrates an important limitation of oxidation-based electrochemical detection in wearable formats. As tyrosine oxidation occurs at relatively high potentials, its signals are particularly vulnerable to interference from other electroactive biomolecules present in sweat, including UA, AA, and catecholamines. As a result, improving selectivity for tyrosine often requires careful interfacial engineering and potential-window optimization rather than simply increasing electrode sensitivity.

Building on the fundamental electrochemical accessibility of tyrosine, early demonstrations of wearable biochemical sensing platforms have included tyrosine as a part of multiplexed sweat analysis systems. In a landmark study, Yang et al. developed a laser-engraved wearable electrochemical sensing platform capable of simultaneously monitoring tyrosine and UA in human sweat while integrating physiological sensing modalities such as temperature and respiration rate [97]. The device was fabricated using laser-induced graphene (LIG) electrodes directly patterned on flexible substrates, enabling scalable production, high surface area, and rapid electron transfer for sensitive electrochemical detection. A microfluidic sweat collection module ensured efficient sweat transport to the sensing interface, allowing continuous monitoring during exercise and dietary interventions. On-body validation demonstrated the platform's ability to track metabolite dynamics in real-time, and UA measurements in sweat correlated with serum levels in gout patients. This work highlights how laser-patterned graphene architectures combined with integrated microfluidics and multimodal sensing can enable scalable, multiplex wearable systems for metabolic

monitoring. Beyond the specific analytes measured, this work also demonstrated an important architectural principle for wearable electrochemical sensing: the integration of scalable electrode fabrication methods with microfluidic sweat handling and multimodal physiological monitoring. Such system-level integration enables contextual interpretation of biochemical signals, which is particularly important for analytes like tyrosine whose electrochemical responses are sensitive to sweat transport dynamics and environmental conditions.

A recent on-body study has explored the feasibility of tyrosine detection in human sweat as a representative neurochemical precursor [98]. The reported wearable platform demonstrated real-time signal acquisition during sweat generation, confirming that tyrosine can be electrochemically resolved under on-body conditions despite its relatively weak electroactivity and low sweat abundance. Importantly, the study emphasized time-dependent signal evolution rather than absolute concentration determination, reinforcing the notion that neurochemical markers in sweat are best interpreted through relative trends. At the same time, the on-body evaluation revealed pronounced sensitivity to matrix conditions, including pH fluctuations and the presence of electroactive interferents, which strongly influenced signal stability and reproducibility. Similarly, a flexible electrochemical sensing platform was developed with extensive optimization performed in artificial sweat, followed by short-duration on-body testing to verify signal responsiveness under physiological conditions [99]. While the device demonstrated discernible tyrosine-associated electrochemical responses during exercise, milk consumption and rest (Fig. 3B), the on-body data primarily served to confirm translational feasibility rather than to establish quantitative reliability, with signal behavior strongly influenced by sweat onset and local matrix variations. These observations reinforce a broader trend in wearable sweat sensing, where laboratory calibration under artificial sweat conditions often overestimates analytical performance compared with real on-body operation. Variations in sweat secretion rate, evaporation, and local accumulation at the skin-sensor interface can significantly distort electrochemical signals, emphasizing that real-time wearable sensing must be evaluated under physiologically dynamic conditions rather than static calibration environments.

A similar trend is observed in the subsequent report employing advanced electrode architectures and signal amplification strategies to enhance tyrosine sensitivity [100]. In this study, artificial sweat was used extensively to refine electrochemical performance, whereas real-time on-body measurements were confined to brief validation experiments. Notably, the on-body results revealed increased baseline drift and reduced reproducibility compared to controlled conditions (Fig. 3C), underscoring the susceptibility of tyrosine electrochemistry to dynamic sweat composition, pH fluctuations, and interfacial instability. Importantly, these discrepancies between laboratory and on-body performance highlight a recurring challenge in wearable electrochemical sensing: improvements in electrode sensitivity do not necessarily translate to improved physiological interpretability. For analytes such as tyrosine, maintaining stable electrochemical interfaces and managing matrix variability may be more critical than maximizing catalytic activity or signal amplification. These observations highlight that, despite promising laboratory performance metrics, the translation of tyrosine sensing to continuous on-body operation remains analytically fragile.

Collectively, these studies indicate that while tyrosine possesses inherent electrochemical activity that enables oxidation-based detection, its reliable monitoring in sweat remains analytically challenging due to low physiological concentrations, high oxidation potentials, and overlapping electrochemical responses from coexisting amino acids and redox-active species. Consequently, most wearable sensing strategies have relied on nanostructured electrode interfaces and signal amplification approaches to improve sensitivity and electron-transfer efficiency. However, on-body investigations consistently demonstrate that the signal stability is strongly influenced by sweat composition, pH fluctuations, and dynamic transport processes during secretion. As a

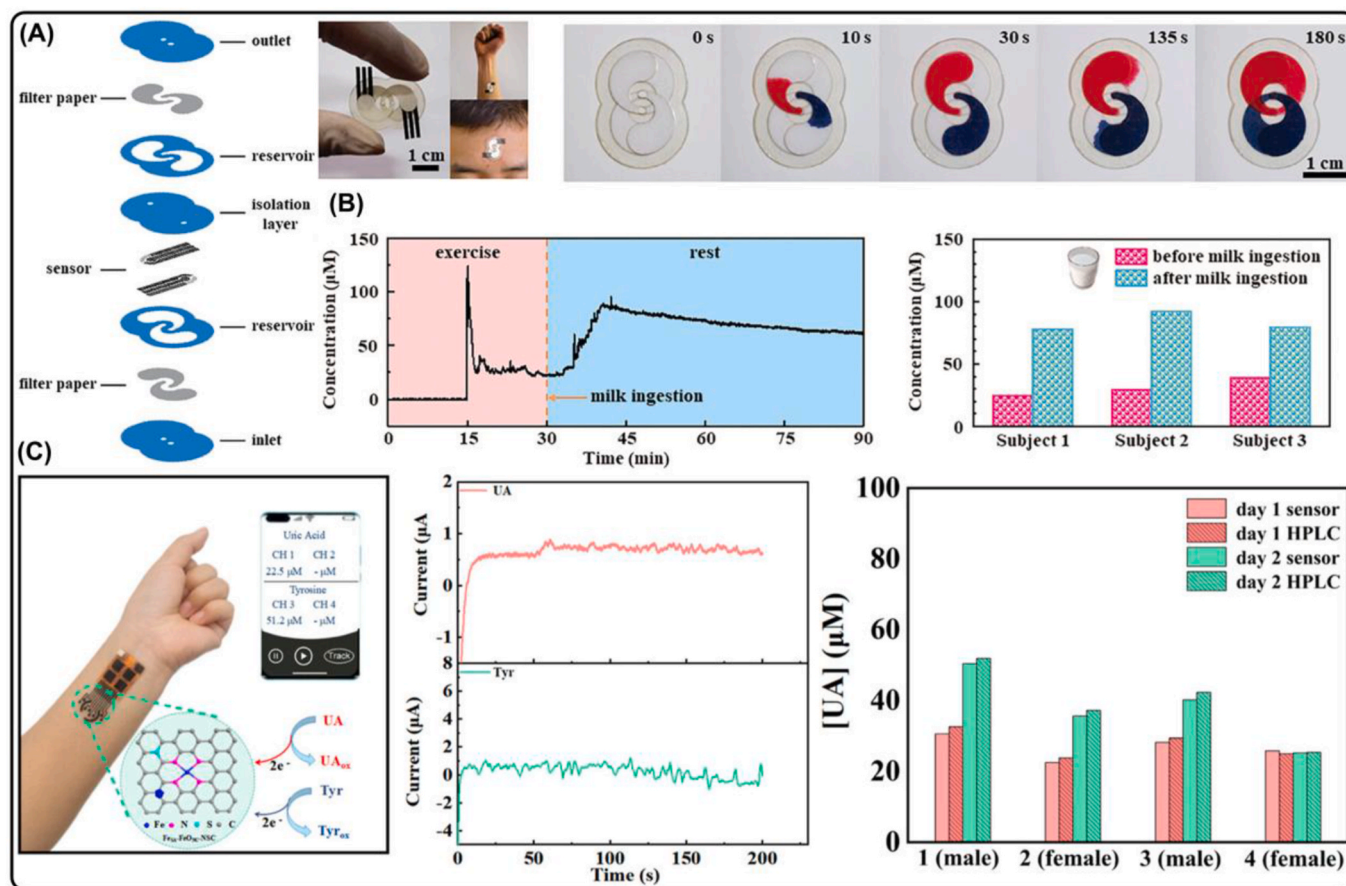


Fig. 3. (A) Exploded illustration and photographs of the flexible dual-channel wearable sweat patch. (B) Real-time and continuous on-body electrochemical monitoring of sweat tyrosine. Reproduced with permission from Ref. [99]. (C) Photograph of the mounted wearable sweat analysis patch and its respective on-body responses. Reproduced with permission from Ref. [100].

result, current tyrosine sensors primarily function as exploratory analytical platforms, validating the feasibility of detecting neurochemical precursors in sweat rather than enabling robust quantitative monitoring. More broadly, tyrosine sensing highlights the distinction between detecting electrochemically accessible molecules and establishing physiologically meaningful biomarkers in sweat. While electrochemical oxidation enables analytical detection, the biological relevance of tyrosine fluctuations in sweat remains incompletely understood, indicating that future studies must address both analytical reliability and physiological validation. Future progress will likely depend on integrating matrix-aware calibration strategies, contextual sensing, and improved interfacial stability to better interpret time-resolved tyrosine dynamics under real physiological conditions.

5.1.4. Electrochemical transduction strategies for cortisol in sweat

Cortisol is a key glucocorticoid hormone governing the physiological response to stress, metabolic regulation, immune modulation, and circadian rhythm. Its secretion profile is characterized by both gradual diurnal variation and rapid elevation in response to acute physical or psychological stress, making it particularly informative when monitored continuously rather than through discrete sampling [101]. Conventional cortisol assessment via blood or saliva provides limited temporal resolution and often fails to capture transient stress events. The detection of cortisol in eccrine sweat has therefore emerged as an attractive route for non-invasive, real-time stress monitoring. From an analytical perspective, sweat-based cortisol sensing offers the potential to track time-dependent hormonal fluctuations directly on the body. However, cortisol is present in sweat at low concentrations and exhibits delayed and highly variable transport from systemic circulation to the skin

surface. These factors, combined with pronounced inter-individual variability, impose stringent requirements on sensor sensitivity, temporal stability, and data interpretation strategies, reinforcing the need for trend-based rather than absolute concentration analysis [102]. From an analytical standpoint, cortisol sensing highlights a key distinction between endocrine and metabolic sweat biomarkers. Whereas metabolites such as glucose or lactate often reflect rapid physiological turnover, steroid hormones like cortisol exhibit slower secretion dynamics and delayed transport to the skin surface. Consequently, wearable cortisol sensors must prioritize long-term signal stability and reliable trend resolution rather than rapid response times or extremely low detection limits.

Unlike catecholamines and other redox-active neurochemicals, cortisol is electrochemically inactive within accessible potential windows, necessitating the use of affinity-based recognition strategies for its detection in sweat. Consequently, reported electrochemical cortisol sensors predominantly rely on immunosensing or aptamer-based approaches, where cortisol binding events are transduced into measurable electrical signals through changes in charge transfer resistance, interfacial capacitance, or redox probe accessibility. These strategies are well-suited to wearable platforms, as they enable selective hormone recognition without requiring enzymatic conversion or high operating potentials. However, these implementations under real-time on-body conditions introduce distinct analytical trade-offs. Antibody- and aptamer-functionalized interfaces are inherently susceptible to signal drift arising from gradual receptor degradation, nonspecific adsorption, and changes in sweat composition over time.

Furthermore, the irreversible or slowly reversible nature of many binding interactions limits sensor regeneration and constrains

continuous monitoring duration. To mitigate these effects, recent wearable designs emphasize nanostructured electrode surfaces, flexible substrates, and indirect signal amplification schemes that enhance sensitivity while attempting to preserve temporal responsiveness. Collectively, these transduction strategies highlight that cortisol sensing in sweat prioritizes molecular selectivity and signal stability over rapid response kinetics, underscoring the fundamental challenges of translating affinity-based electrochemical methods into robust real-time on-body applications. More broadly, these considerations illustrate a fundamental trade-off in wearable hormone sensing: while affinity-based recognition enables high molecular selectivity for

electrochemically inactive targets such as cortisol, the stability and reversibility of the recognition interface ultimately determine the duration and reliability of continuous monitoring.

Tang et al. describe a stress-free, touch-based electrochemical biosensor for sweat cortisol using a MIP-polypyrrole framework embedded with Prussian blue redox probes [103]. By leveraging a high-permeability hydrogel for fingertip sweat collection, the platform achieves rapid label-free detection, enabling the tracking of both circadian rhythms and acute stress responses with accuracy comparable to laboratory gold standards. By integrating an affinity-based cortisol recognition interface with a flexible, skin-conformal electrode platform,



Fig. 4. (A) Redox-active MIP sensing strategy and wearable implementation. Reproduced with permission from Ref. [105]. (B) Schematic design, wearable integration, and on-body evaluation of a flexible cortisol sensor. Reproduced with permission from Ref. [106].

this work establishes that dynamic cortisol fluctuations can be tracked continuously in eccrine sweat during physical activity. A key analytical contribution of this study lies in its explicit shift away from static or endpoint measurements toward time-resolved signal monitoring, revealing cortisol profiles that vary continuously rather than exhibiting steady-state behavior. The wearable stress patch described by Singh et al. represents a pivotal demonstration of real-time cortisol monitoring in human sweat using a conformation-switching aptamer integrated with a flexible microfluidic collection system [104]. In this design, a pseudoknot-assisted aptamer serves as the selective recognition element, minimizing background noise through a two-state conformational restriction that enhances specificity toward cortisol over closely related interferents. Coupled with a skin-worn microfluidic sampler that differentiates fresh from aged sweat, this arrangement enabled continuous tracking of dynamic cortisol changes induced by an acute stress protocol, revealing temporal fluctuations on the order of tens of minutes, which is a key analytical advantage over discrete or off-body sampling. The inclusion of an electrochemical pH sensor for in situ correction further underscores how integrated interface considerations improve signal reliability in the variable chemical environment of real sweat. Notably, the platform demonstrated signal regeneration and sustained responsiveness for up to 90 min of continuous measurement, highlighting both the potential and the analytical constraint of affinity-based on-body cortisol sensing: while high specificity and trend resolution are achievable, the interplay between receptor stability, sweat composition variability, and sweat rate remains a central challenge for quantitative interpretation and long-term continuous monitoring. These studies collectively emphasize that the analytical value of wearable cortisol sensing lies primarily in resolving temporal hormone dynamics rather than establishing single-point concentration values. Continuous monitoring enables identification of circadian patterns and transient stress responses that are difficult to capture using conventional sampling approaches.

A related strategy for wearable hormone monitoring was reported by Yeasmin et al. who developed a hybrid functional polymer-enabled multiplexed chemosensor patch capable of simultaneously detecting cortisol and dehydroepiandrosterone (DHEA) directly in human sweat [105]. In this design, redox-active MIPs were synthesized using a poly(pyrrole-co-(dimethylamino)pyrrole) framework incorporating interpenetrating polyvinyl ferrocene redox centers, allowing target binding events to modulate the intrinsic electrochemical signal without the need for external redox mediators (Fig. 4A). The multiplexed sensor detected cortisol and DHEA within minutes and achieved physiologically relevant detection limits while being integrated into a wireless wearable system for ambulatory measurements. Importantly, the ability to monitor the cortisol-to-DHEA ratio enables assessment of the hypothalamic-pituitary-adrenal axis response, providing a more comprehensive representation of stress physiology than single-analyte detection alone. From an analytical perspective, this work highlights how redox-integrated imprint polymers can improve operational robustness and enable multiplexed steroid hormone monitoring in wearable platforms, although accurate physiological interpretation still depends on controlling sweat sampling variability and matrix-induced signal perturbations during on-body operation. Importantly, multiplex hormone monitoring introduces a systems-level advantage by enabling ratio-based biochemical indicators, such as the cortisol-to-DHEA balance, which can provide more robust insights into stress physiology than single-analyte measurements alone.

In a related wearable implementation, Mei et al. advanced real-time cortisol monitoring by integrating a nanofiber-based microfluidic sweat sampling module with a MIP-functionalized electrode interface [106]. The use of MIP recognition layers tailored for cortisol enhanced selectivity against structurally similar interferents, and when coupled with active microfluidic extraction, promoted more efficient delivery of freshly secreted sweat to the sensing surface. This configuration yielded on-body cortisol signals that tracked temporal variations under dynamic

conditions, illustrating that the combination of tailored recognition sites and microscale fluid handling can improve response continuity and reduce lag associated with passive sweat accumulation (Fig. 4B). Importantly, the study reinforces that analytical performance in human sweat is not solely a function of intrinsic receptor affinity but critically depends on how the electrode interface interacts with the continuously changing chemical milieu prepared by the microfluidic layer. While the MIP system demonstrated robust trend capture during prolonged wear, residual sensitivity to sweat composition and mechanical perturbations highlights ongoing challenges in achieving stable absolute quantification in wearable hormone sensing. In addition, a MIP-based wearable sensor with integrated paper microfluidics was demonstrated by Garg et al. for highly sensitive, label-free electrochemical impedance detection of cortisol in human sweat [107]. By combining tailored MIP recognition cavities with a paper microfluidic sampling interface, the platform achieved cortisol detection down to sub-picomolar levels while simultaneously quantifying sweat volume and secretion rate, thereby providing contextual parameters that enhance the interpretation of dynamic hormonal profiles. These advances illustrate an emerging design paradigm in wearable electrochemical sensing, where microfluidic sweat handling is treated as an integral analytical component rather than a passive sampling layer. By controlling sweat transport, renewal, and dilution, microfluidic interfaces can significantly improve signal interpretability during continuous hormone monitoring. The paper microfluidic layer not only facilitated continuous sweat collection without user intervention but also mitigated transport delays that typically confound real-time trend analysis. By integrating analyte detection with simultaneous sweat-rate monitoring, this design represents an important step toward addressing dilution and transport artifacts that complicate quantitative hormone analysis in sweat.

The wearable MIP-based electrochemical sensor developed by Chen et al. further illustrates how tailored electrode/interface design can enhance cortisol monitoring performance under real sweat conditions [108]. In this work, a flexible gold electrode with an interfacial hydrophilic activation was combined with a silk fibroin-polyvinylidene fluoride composite membrane to facilitate directional sweat transport toward a cortisol-specific MIP sensing layer, improving both analyte delivery and stability of the biointerface. The resulting platform exhibited an ultrawide detection range spanning sub-picomolar to micromolar concentrations and high selectivity against common interferents such as glucose and lactate, while mitigating mechanical deformation effects through a gradient modulus design that preserved signal integrity during wear. Such interface engineering highlights the growing importance of coupling material design with controlled sweat transport to maintain signal stability during continuous on-body operation. A complementary system-level perspective on wearable cortisol monitoring was demonstrated by Torrente-Rodríguez et al., who developed a graphene-based wireless sensing platform capable of real-time cortisol tracking in human sweat under ambulatory conditions [109]. In this work, LIG electrodes functionalized with cortisol-selective recognition layers were integrated with a flexible microfluidic interface, on-board signal processing, and wireless communication to create a fully wearable biochemical monitoring system. The platform enabled continuous measurement of cortisol fluctuations directly from eccrine sweat and successfully captured physiologically relevant variations associated with circadian rhythms and acute stress responses during human trials. Importantly, this study emphasized that accurate interpretation of hormone dynamics requires not only selective recognition chemistry but also stable electrode-sweat interfaces, controlled sweat sampling, and real-time data transmission. Compared with standalone affinity-based sensors, the integrated architecture highlights how wearable electrochemical platforms can transform localized biochemical measurements into longitudinal physiological data streams. At the same time, the results reinforce a broader analytical challenge for on-body hormone sensing: while sensitive detection of cortisol is achievable, quantitative interpretation remains strongly influenced by sweat secretion dynamics,

sampling variability, and the complex physicochemical environment of native sweat. These findings highlight that the reliability of wearable hormone monitoring depends not only on recognition chemistry but also on system-level integration, including stable electrode-skin interfaces, real-time data processing, and controlled sweat sampling.

A related wearable cortisol sensing strategy was reported by Li et al. who developed a flexible electrochemical platform integrating MIP recognition with a microfluidic sweat sampling interface for real-time cortisol detection in human sweat [110]. In this design, a cortisol-selective imprint layer was formed on a conductive electrode surface, enabling label-free electrochemical signal modulation upon target binding. The sensor was integrated within a skin-conformal wearable configuration capable of collecting freshly secreted sweat and delivering it directly to the sensing interface, thereby minimizing delays associated with passive sweat accumulation. On-body measurements demonstrated the ability to resolve temporal variations in cortisol levels under physiological conditions, confirming the suitability of imprint-based recognition layers for wearable hormone monitoring. Importantly, the study further illustrates that while MIP architectures can provide improved chemical stability compared with biological receptors, quantitative signal interpretation remains sensitive to sweat transport dynamics, evaporation effects, and local chemical variability. These observations reinforce the broader analytical challenge in wearable hormone sensing: reliable trend monitoring is achievable, but absolute quantification requires careful control of the sweat sampling microenvironment and long-term interface stability.

Collectively, these studies demonstrate that multiple recognition strategies, including aptamers, antibodies, and MIPs, can enable real-time electrochemical detection of cortisol in human sweat. Affinity-based sensors such as aptamers provide high molecular specificity, whereas MIP-based systems offer improved chemical robustness and operational stability for wearable applications. Meanwhile, advances in microfluidic sampling, multiplexed hormone detection, and fully integrated wireless platforms illustrate how wearable electrochemical technologies are evolving from isolated sensing elements toward complete physiological monitoring systems. Despite these advances, a common analytical limitation persists across all approaches: measured cortisol signals reflect not only hormone concentration but also sweat secretion dynamics, sampling artifacts, and interface stability. More broadly, wearable cortisol sensing illustrates the broader challenge of translating endocrine biomarker monitoring into continuous, non-invasive formats. While affinity-based electrochemical platforms can achieve high sensitivity and specificity, accurate physiological interpretation ultimately requires integrating biochemical detection with contextual parameters such as sweat rate, pH, and environmental conditions. Consequently, future progress in wearable hormone sensing will depend on strategies that integrate selective recognition measurements to enable reliable interpretation of dynamic endocrine signals.

5.1.5. Electrochemical transduction strategies for levodopa in sweat

Levodopa (L-3,4-dihydroxyphenylalanine) represents a distinct class of neurochemical biomarkers in sweat, functioning as a direct biosynthetic precursor to dopamine and other catecholamines rather than as a hormone or terminal neurotransmitter [111]. From an analytical chemistry perspective, levodopa is inherently electroactive due to its catechol structure, enabling direct electrochemical transduction without enzymatic mediation. This theoretical accessibility has motivated its inclusion in wearable sensing research as a potential indicator of neurochemical metabolism and neurological status. However, in contrast to cortisol or adrenaline, levodopa is present in sweat at low and highly variable concentrations, with transport governed by a complex interplay of systemic availability, local skin metabolism, and sweat gland secretion dynamics [112]. In real-time on-body contexts, levodopa sensing poses additional challenges arising from its susceptibility to oxidative degradation, overlaps with structurally related catecholamines, and strong dependence on local pH and ionic strength. These

factors are amplified under dynamic sweat secretion, where fluctuations in sweat rate and evaporation can rapidly alter the electrochemical environment at the sensing interface. Consequently, while levodopa is electrochemically favorable in principle, its reliable detection in human sweat remains analytically demanding. Existing wearable studies, therefore, emphasize feasibility and temporal trend observation rather than absolute quantification, positioning levodopa sensing as an emerging but still exploratory component of real-time neurochemical sweat analysis. From an analytical standpoint, levodopa sensing also illustrates an important distinction between endogenous neurochemical monitoring and pharmacokinetic tracking in sweat. Because levodopa levels may reflect both physiological metabolism and exogenous intake (e.g., medication or diet), wearable sensing platforms must interpret electrochemical signals within a broader pharmacological context rather than assuming a direct correlation with endogenous neurotransmitter activity.

Electrochemical levodopa sensing in sweat occupies a unique niche at the intersection of neurochemical monitoring and drug pharmacokinetics, owing to its role as a biosynthetic precursor to dopamine and its relevance to Parkinson's disease therapy. The catechol structure of levodopa imparts inherent electroactivity, enabling both enzymatic and non-enzymatic detection strategies with potential real-time applicability. Nonetheless, low and variable sweat concentrations, coupled with overlapping responses from structurally related species, impose significant analytical constraints on reliable on-body quantification. One of the first systematic on-body demonstrations of levodopa monitoring employed a wearable patch instrumented for continuous sweat analysis under routine activities (Fig. 5A), integrating microfluidic sampling with electrochemical detection to capture levodopa dynamics following dietary intake of levodopa-containing foods [113]. In this study, levodopa was detected in sweat ~20 min after ingestion, peaking ~35 min later, and exhibited dose-dependent trends that potentially correlate with systemic availability. However, interpretation of absolute levels was complicated by sweat flux variations and individual physiology, highlighting the need to contextualize electrochemical signals within dynamic secretion profiles. These observations emphasize that sweat-based levodopa monitoring is particularly sensitive to sweat flux and sampling dynamics, as changes in secretion rate can influence analyte dilution and transport to the sensing interface. Consequently, interpreting levodopa trends requires concurrent consideration of sweat production and transport kinetics during on-body measurements.

Flexible wearable sensors based on Au nanorods integrated with conductive polymers have demonstrated simultaneous real-time detection of levodopa alongside UA during on-body use. These platforms, combining high surface area nanostructures and microfluidic sampling, achieved continuous levodopa signal generation in human sweat, confirming the feasibility of dynamic monitoring [114]. Real-time on-body measurements were conducted on three healthy adults to evaluate the capability of the fabricated sensor in induced sweat during indoor cycling, along with controlled dietary intake of broad beans, pork and mung bean sprouts. The obtained data showed negligible levodopa and low UA levels prior to food intake, followed by a pronounced increase in both analytes after consumption (Fig. 5C). Their non-enzymatic mechanism avoids the stability limitations of biocatalysts yet still encounters matrix-related variability and baseline drift under long-term wear, underscoring selectivity and stability as persistent analytical challenges. More broadly, these findings highlight a recurring challenge in catechol-based electrochemical sensing: structurally related compounds such as dopamine, norepinephrine, and UA exhibit overlapping redox behavior, making selective discrimination difficult without carefully engineered recognition interfaces or signal-processing strategies.

A wearable levodopa sensor is built on a flexible substrate incorporating a MOF/graphene oxide composite via in-situ growth, creating a high surface area scaffold that promotes enzyme loading and electron transfer [115]. The enzyme tyrosinase is immobilized onto the composite, forming a biorecognition surface that enzymatically converts

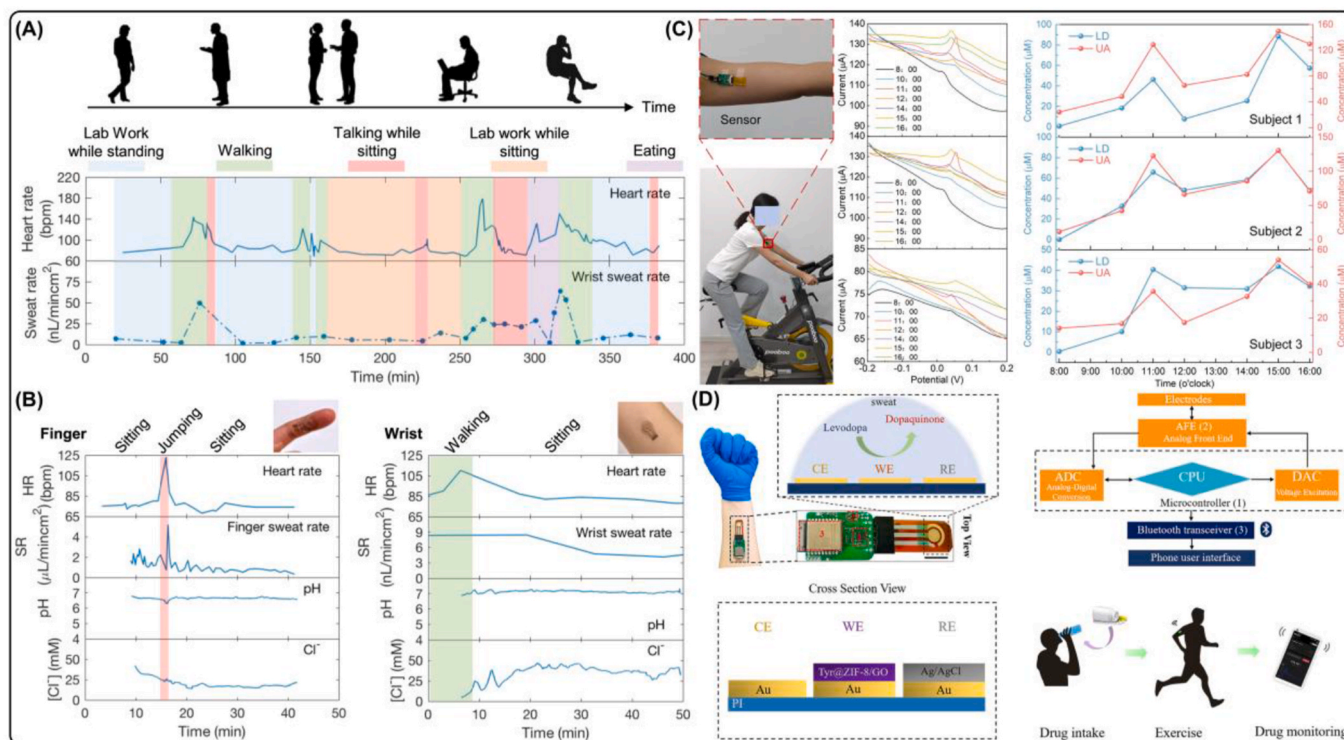


Fig. 5. (A) Continuous on-body monitoring of sweat and cardiovascular dynamics during daily activities. (B) Simultaneous multimodal sweat and physiological monitoring at different body sites. Reproduced with permission from Ref. [113]. (C) On-body dual analyte sweat sensing demonstration. Reproduced with permission from Ref. [114]. (D) Design and implementation of a wearable levodopa sweat sensor. Reproduced with permission from Ref. [115].

levodopa to dopaquinone. The sensor is then combined with a compact wireless electronic module, enabling continuous, real-time sweat levodopa monitoring on the skin (Fig. 5D). Such enzyme-based wearable systems have shown wide linear detection ranges and low limits of detection for levodopa in sweat, with real-time analysis during short on-body trials confirming signal responsiveness. While enzyme-assisted sensing can significantly enhance selectivity for levodopa through substrate-specific catalytic reactions, it also introduces additional dependencies on local environmental conditions, including pH, oxygen availability, and enzyme stability, which can influence long-term signal reliability during continuous wearable operation.

While these studies provide proof-of-concept for continuous levodopa profiling, their reliance on enzyme activity introduces additional dependencies on local pH and oxygen conditions, complicating raw signal interpretation without contextual correction. A recent report on LDHzyme-assisted wearable sensors indicates continued innovation in enhancing levodopa selectivity and sensitivity for real-time Parkinson's management, although full peer-reviewed documentation of on-body performance in sweat remains less explored [116]. These ongoing developments indicate that improving levodopa sensing performance increasingly depends on combining molecular recognition strategies with system-level control of sweat sampling and interfacial stability rather than relying solely on enhanced electrode sensitivity. Together, these works illustrate that real-time levodopa sensing in human sweat is analytically accessible but currently at an emerging, exploratory stage: dynamic trends can be resolved, yet robust quantification is constrained by matrix effects, sweat rate dependence, and variable physiological context. Accordingly, levodopa in sweat may be most immediately useful for trend-based monitoring in pharmacokinetic applications rather than for standalone absolute concentration interpretation. Collectively, these studies indicate that although levodopa possesses intrinsically favorable electrochemical properties arising from its catechol structure, its reliable monitoring in human sweat remains analytically challenging. The low and highly variable concentrations

encountered in eccrine sweat, combined with susceptibility to oxidative degradation and electrochemical overlap with structurally related catecholamines, impose significant constraints on selectivity and signal stability under real on-body conditions. Current wearable platforms, therefore, emphasize trend-based monitoring and pharmacokinetic profiling rather than absolute concentration determination. Microfluidic sampling, nanostructured electrode interfaces, and enzyme-assisted recognition strategies have demonstrated the feasibility of resolving temporal levodopa dynamics following ingestion or physiological perturbation, yet signal interpretation remains strongly influenced by sweat rate, pH variability, and matrix evolution during continuous wear. More broadly, levodopa sensing demonstrates how wearable electrochemical platforms can bridge neurochemical monitoring and personalized pharmacotherapy. By capturing time-dependent variations following ingestion or medication administration, sweat-based levodopa sensors may ultimately support individualized treatment monitoring for neurological disorders such as Parkinson's disease. As a result, levodopa sensing in sweat is best viewed as an emerging analytical capability for tracking relative neurochemical dynamics, with future progress likely depending on improved interfacial stability, contextual sensing integration, and matrix-aware calibration approaches to enable more reliable pharmacokinetic interpretation in wearable applications.

5.1.6. Electrochemical transduction strategies for estradiol in sweat

Estradiol (E2) is the most potent naturally occurring estrogen and plays a central role in regulating female reproductive physiology, including follicular development, ovulation, and menstrual cycle progression. Fluctuations in estradiol levels are closely associated with endocrine health, fertility, pregnancy, and menopause, making it a clinically important biomarker for monitoring reproductive status and hormonal disorders [117]. Conventional estradiol quantification relies primarily on laboratory-based immunoassays performed on blood or urine samples, which require invasive collection and provide only discrete measurements rather than continuous hormonal profiles. The

ability to monitor estradiol non-invasively and in real-time could therefore enable improved understanding of endocrine dynamics and support personalized reproductive health management. However, detecting estradiol in sweat presents substantial analytical challenges because the hormone is typically present at extremely low concentrations and coexists with numerous interfering metabolites and proteins within the complex sweat matrix. From an analytical perspective, estradiol sensing represents one of the most demanding targets in wearable sweat electrochemistry because steroid hormones are electrochemically inactive and occur at extremely low concentrations. Unlike redox-active metabolites, their detection depends entirely on affinity-based molecular recognition, placing strong emphasis on receptor selectivity, signal amplification strategies, and background noise suppression under dynamic sweat conditions.

To address these challenges, Ye et al. developed a wearable aptamer-based nanobiosensor for non-invasive monitoring of estradiol directly from human sweat [118]. The sensing interface integrates a target-induced strand-displacement aptamer with a nanoengineered AuNP-MXene electrode, enabling reagentless electrochemical detection with sub-picomolar sensitivity. This strategy highlights the importance of combining molecular recognition with nanoscale signal amplification when targeting low-abundance endocrine biomarkers in sweat, where direct electrochemical detection is not feasible. Importantly, the sensor is incorporated within a fully integrated wearable platform combining iontophoretic sweat stimulation, microfluidic sweat collection, and wireless signal transmission, allowing autonomous operation even under resting conditions without requiring exercise-induced sweating. To mitigate the influence of sweat composition variability, the system

simultaneously measures auxiliary physiological parameters, including pH, ionic strength, and skin temperature, enabling real-time signal calibration within the wearable device. Such multivariate correction approaches represent an important advancement for hormone sensing in sweat, as fluctuations in sweat rate, pH, and ionic composition can significantly distort affinity-based electrochemical signals if not accounted during real-time measurements. Human studies demonstrated cyclic variations in sweat estradiol levels corresponding to menstrual phases and showed a strong correlation with serum hormone concentrations, highlighting the potential of sweat-based hormone monitoring for reproductive health applications. Importantly, the ability to resolve cyclical estradiol variations demonstrates that wearable sweat sensors may capture endocrine dynamics that are difficult to observe using traditional intermittent sampling methods. More broadly, estradiol sensing illustrates how wearable electrochemical platforms are beginning to expand beyond metabolite and stress biomarkers toward continuous monitoring of reproductive endocrine function. The electrochemical performances of the above-discussed sensors in this section are given in Table 1.

5.2. Energy metabolic markers in sweat

Glucose and lactate are among the most extensively studied metabolic markers in sweat, as they are directly linked to energy metabolism and respond rapidly to changes in physical activity, workload, and physiological stress. Their comparatively higher concentrations in sweat, relative to hormonal or neurochemical targets, have made them primary candidates for real-time on-body electrochemical monitoring

Table 1

Electrochemical sensor performances toward stress and neurochemical markers in native sweat.

Sensors	Analytes	Linear range (μM)	LOD (μM)	Sensitivity ($\mu\text{A mM}^{-1}\text{cm}^{-2}$)	In vivo duration (min.)	Validation Method	Ref.
CNT/MIP	Adrenaline	$1.71 \times 10^{-6} - 1.508 \times 10^{-5}$	7.24×10^{-8}	-	-	ELISA	[89]
LEG/GND	Adrenaline	$0 - 0.1^{\dagger}$	$2.73 \times 10^{-3\ddagger}$	-	-	ELISA	[5]
	Norepinephrine		$9.14 \times 10^{-3\ddagger}$				
	Cortisol	$0 - 100^{\ddagger}$	$2.70^{\ddagger}$				
Pd@CeO ₂ /g-C ₃ N ₄ /CA hydrogel	Serotonin	$1 \times 10^{-3} - 1.2$	6.4×10^{-4}	2.04×10^5	-	ELISA	[91]
CuMOF@InMOF/GnPs-Apt	Serotonin	$1 \times 10^{-3} - 10$	3.3×10^{-4}	-	-	-	[94]
	Dopamine	$1 \times 10^{-3} - 10$	1.8×10^{-4}	-			
	Adrenaline	$1 \times 10^{-3} - 10$	2.7×10^{-4}	-			
LEG-CS	Tyrosine	$0 - 200$	3.6	610	-	HPLC, Commercial colorimetric kit	[97]
	UA	$0 - 100$	0.74	3500			
CoWO ₄ @CNT	Tyrosine	$5 - 1000$	4.2	-	-	-	[98]
TiO ₂ -CC	Tyrosine	$5 - 40$	-	84.1	90	-	[99]
Fe ₃ A-FeO _{NC} -NSC	Tyrosine	$50 - 250$	0.03	510	3.34	HPLC	[100]
PPy-PB-MIP	Cortisol	$1 \times 10^{-3} - 10$	9×10^{-4}	38.8*	1	Immunoassay	[103]
Gold/Apt/Actin/2 ME	Cortisol	$1 \times 10^{-6} - 10$	-	-	90	Blood Glucose	[104]
poly(Py-co-DMAPy)	Cortisol	$1 \times 10^{-4} - 1$	1.15×10^{-4}	-	1	LC-MS/MS	[105]
PBNPs@MIP/GnPs@CnFM/FCE	Cortisol	$1 \times 10^{-3} - 1$	3.5×10^{-4}	-	2	ELISA	[106]
MIP/LIG	Cortisol	$1 \times 10^{-7} - 1$	-	-	-	-	[107]
MIP/PI	Cortisol	$1 \times 10^{-7} - 5$	-	-	2	-	[108]
Graphene/HQ/PPA/HRP	Cortisol	$0 - 10^{\ddagger}$	$0.08^{\ddagger}$	-	0.5	ELISA	[109]
CNTs/PU/PVA/Ni-CoMOF	Cortisol	$0.1 - 100^{\ddagger}$	$0.032^{\ddagger}$	-	-	-	[110]
AG-GLY hydrogel/tyrosinase	Levodopa	$0 - 50$	-	$0.2^{\#}$	1440	-	[113]
GNRs/PEDOT:PSS	Levodopa	$0 - 500$	0.29	1264	-	HPLC	[114]
ZIF-8/GO/tyrosinase	Levodopa	$1 - 95$	0.45	-	40	Electrochemical workstation	[115]
CuCoFe-LDHzyme	Levodopa	$2 - 16$	0.028	$83.08^{\#}$	-	Blood sample	[116]
MXene/GnPs/SH-ssDNA	Estradiol	$1 \times 10^{-7} - 1 \times 10^{-4}$	1.4×10^{-7}	-	1	ELISA	[118]

AG-GLY – agarose glycerol film; Apt – aptamer; CA – calcium alginate; CC – carbon cloth; CnFM – carbon nanofiber membrane; CNT – carbon nanotube; CS – chitosan; DMAPy – 1-(dimethylamino)pyrrole; ELISA – enzyme-linked immunosorbent assay; FCE – flexible carbon electrodes; GND – gold nanodiamond; GnPs – gold nanoparticles; GNRs – gold nanorods; GO – graphene oxide; HPLC – high-performance liquid chromatography; HRP – horseradish peroxidase; HQ – hydroquinone; LDH – layered double hydroxides; LIG – laser induced graphene; LC-MS/MS – liquid chromatography-tandem mass spectrometry; ME – mercaptoethanol; MIP – molecularly imprinted polymer; NSC – N, S co-doped; PU – polyurethane; PVA – polyvinyl alcohol; PPA – 1H-pyrrole propionic acid; PB – Prussian blue; PBNPs – Prussian blue nanoparticles; PI – polyimide; PPy – polypyrrole; Py – pyrrole; SH-ssDNA – thiolated single-stranded DNA; ZIF – zeolitic imidazolate framework. * – $n\text{A log [nM]}^{-1}$; # – $\mu\text{A mM}^{-1}$; † – ng mL^{-1} .

[119]. Consequently, enzyme-based electrochemical sensing strategies have been widely adopted to track their temporal evolution during continuous wear. Despite this analytical accessibility, the interpretation of glucose and lactate signals in sweat remains challenging. Measured concentrations are strongly modulated by sweat rate, dilution effects, and transport delays between systemic circulation and sweat secretion, limiting direct quantitative correlation with blood levels. In enzyme-mediated sensors, signal output is additionally governed by local pH, oxygen availability, and enzyme stability, all of which fluctuate under on-body conditions. On the other hand, continuous exposure to sweat can further lead to gradual enzyme degradation and baseline drift, particularly during prolonged or high-intensity activity. Real-time on-body studies consistently demonstrate that relative temporal trends in glucose and lactate are more reproducible and physiologically informative than absolute concentration values. These observations emphasize the need for analytical frameworks that prioritize dynamic trend analysis and contextual parameters, rather than static calibration, when leveraging sweat-based glucose and lactate sensing for wearable metabolic monitoring.

5.2.1. Electrochemical transduction strategies for glucose in sweat

Electrochemical glucose sensing in sweat has attracted sustained attention despite the intrinsically low analyte concentrations, owing to glucose's central role in systemic metabolism and its clinical relevance. Glucose detection typically requires highly sensitive enzyme-mediated transduction schemes to generate measurable signals under wearable conditions. The electrochemical response is therefore strongly influenced by enzyme activity, oxygen diffusion, and local pH at the electrode-sweat interface, making signal stability a primary analytical concern during continuous operation [120]. In addition, glucose transport into sweat is governed by complex glandular and diffusion processes rather than direct equilibrium with blood, necessitating sensor designs that prioritize temporal resolution and robustness over absolute quantification. These constraints have shaped the development of wearable glucose sensors focused on long-term operational stability, drift mitigation, and reliable trend monitoring during real-time on-body deployment. More fundamentally, sweat glucose sensing highlights a key limitation of non-invasive metabolic monitoring: unlike interstitial fluid, sweat does not maintain a direct or instantaneous equilibrium with blood glucose levels. As a result, electrochemical signals obtained from sweat inherently reflect a convolution of systemic glucose dynamics and local transport processes rather than a direct physiological concentration.

A seminal contribution to real-time on-body sweat sensing was demonstrated using a 3D-printed electrochemical ring (e-ring) for nonenzymatic sweat glucose sensing, representing an early demonstration of finger-worn electrochemical analytics [121]. The sensing electrode is fabricated from a conductive carbon filament and subsequently modified with an electrodeposited gold layer, enabling direct amperometric glucose oxidation without enzymatic mediation. This nonenzymatic strategy eliminates oxygen dependence and enzyme instability, offering improved operational robustness for wearable use. The ring geometry facilitates continuous skin contact at a sweat-rich finger location and is interfaced with a smartphone-controlled wireless potentiostat, enabling real-time signal acquisition. Electrochemical measurements showed a linear glucose response within the physiologically relevant sweat range and acceptable selectivity against common electroactive interferents. However, glucose detection relies on alkaline electrochemical conditions, and signal fidelity remains influenced by sweat rate, local mass transport, and surface fouling. From an analytical perspective, the work primarily establishes a form-factor-driven sensing paradigm, highlighting the trade-off between fabrication simplicity and quantitative reliability in real-time sweat glucose monitoring. This early demonstration also illustrates a broader design trade-off in wearable electrochemical sensing, where simplified, robust device architectures often sacrifice precise control over the electrochemical environment,

thereby limiting quantitative accuracy under variable on-body conditions.

Subsequent real-time on-body sweat glucose studies have moved beyond form-factor feasibility toward explicitly addressing the physiological and transport-driven constraints that govern glucose appearance in sweat. In contrast to early proof-of-concept demonstrations, these works recognize sweat glucose as a non-equilibrium analyte, whose temporal behavior is dominated by sweat secretion dynamics, diffusion delays and dilution effects rather than instantaneous systemic glucose levels. As a result, analytical emphasis has shifted from static calibration toward time-resolved trend analysis under realistic on-body conditions. Recent investigations employing continuous amperometric sensing during exercise and controlled physiological perturbations consistently report delayed and attenuated glucose responses relative to blood glucose, alongside strong dependence on sweat rate and individual variability [122,123]. These studies demonstrate that absolute glucose concentrations in sweat are unstable across subjects and sessions, whereas intra-session temporal trends remain comparatively reproducible. Importantly, baseline drift at sweat onset and transient signal artifacts associated with gland activation were identified as intrinsic analytical features rather than sensor failures. These findings establish that temporal lag and signal attenuation are not artifacts of sensor design but inherent characteristics of sweat-based glucose measurement, arising from diffusion delays and glandular transport mechanisms.

Parallel efforts further corroborate these findings under extended on-body operation, showing that improvements in electrode sensitivity or wearable integration alone do not resolve variability arising from sweat transport and matrix effects [124,125]. Even under optimized enzymatic transduction and flexible device architectures, glucose signals remain strongly modulated by local hydration, evaporation, and sweat flux, underscoring the limited utility of single-point calibration approaches. Complementary studies have reinforced this analytical framework by systematically comparing off-body calibration with real-time on-body data, revealing that laboratory-derived figures of merit consistently overestimate quantitative reliability during wear [126]. This discrepancy underscores a critical gap in wearable electrochemical sensor validation, where performance metrics derived under controlled laboratory conditions fail to capture the dynamic and heterogeneous nature of real sweat environments.

Building on the recognition that sweat glucose signals are inherently governed by physiological transport and secretion dynamics, the following studies have focused on system-level strategies to manage analytical variability rather than eliminate it. These works extend beyond electrode optimization to incorporate integrated electronics, multiplexed sensing, modeling, and data-driven calibration, reflecting a maturation of sweat glucose research toward holistic analytical frameworks. Several platforms integrate continuous glucose sensing with auxiliary contextual parameters, such as sweat rate, temperature, pH, or motion, to enable post-processing correction and trend stabilization. A fully printed multiplexed epidermal sweat sensing system was fabricated [127], comprising glucose, alcohol, pH and temperature sensors designed to conform to the skin while enabling controlled sweat transport and localized sensing (Fig. 6A). Real-time on-body sensing was carried out during controlled intake protocols and daily activities with male and female test subjects (Fig. 6D), demonstrating the platform's capability for continuous, multi-analyte sweat analysis under realistic physiological conditions. In addition to a patch electrode, a fully integrated self-powered smartwatch was developed for continuous non-invasive monitoring of sweat glucose [128]. The strap incorporates flexible photovoltaics that harvest ambient light to power the system, while batteries address safety concerns for long-term wear (Fig. 7A–C). The electrochemical glucose sensor module operates in real-time, with signal processing and user feedback fully supported by the harvested energy. Demonstrated performance includes glucose level detection during indoor and outdoor activities (Fig. 7D and E), establishing one of

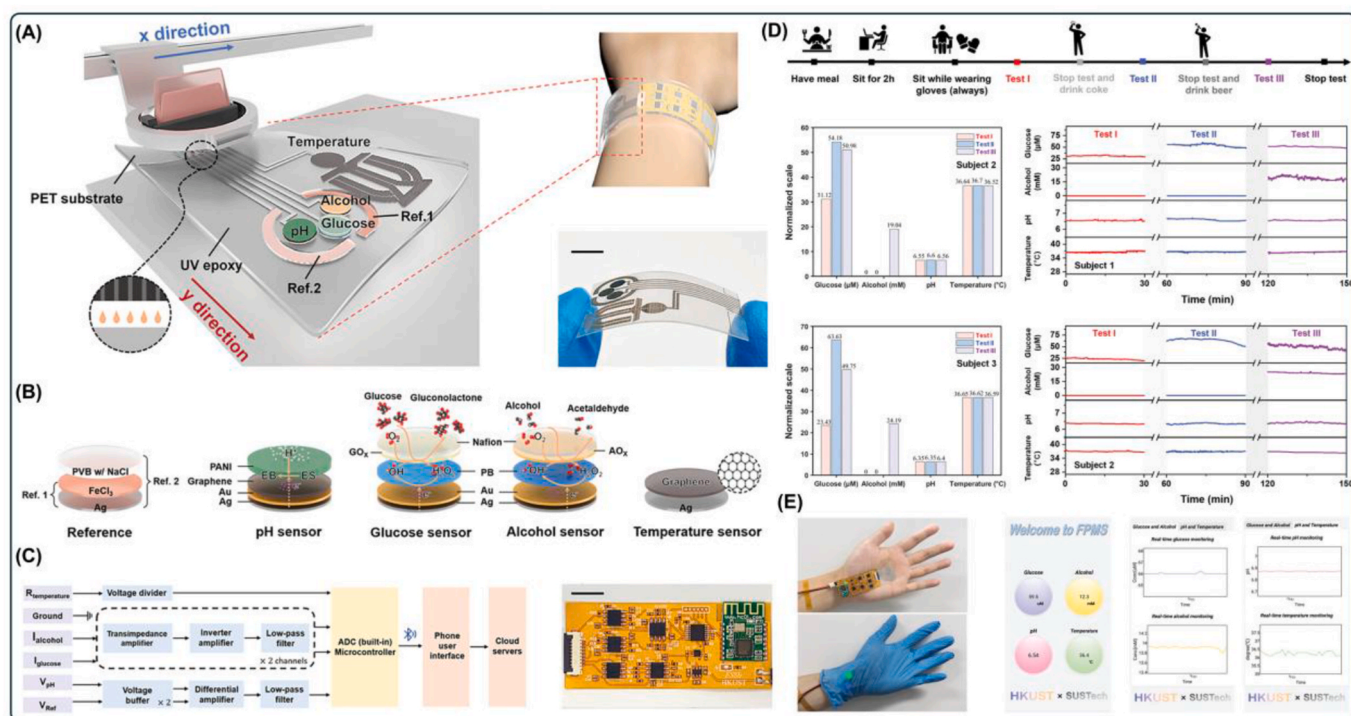


Fig. 6. (A) Schematic diagrams and photographs of a printed flexible sensor. (B) Fabrication of multiple sensor electrodes. (C) System-level block diagram and its corresponding photograph of the flexible patch electrode circuit. (D) Schematic representation of the experimental protocols and corresponding real-time analysis. (E) Photographs of the wearable sensor patch and corresponding user interface. Reproduced with permission from Ref. [127].

the first examples of a self-powered, continuous sweat glucose monitoring platform integrated into a consumer-oriented device and highlighting the potential for correlated metabolic tracking in wearable healthcare systems. Rather than treating variability as sensor noise, these studies explicitly model it as a physiological input, demonstrating that incorporating contextual signals improves the interpretability of glucose trends during prolonged on-body monitoring. However, these approaches also reveal that correction strategies remain highly individualized, limiting generalizable calibration. Consequently, wearable glucose sensing is increasingly shifting from a calibration-centric paradigm toward a context-aware analytical framework, where physiological variability is incorporated into data interpretation rather than treated as noise to be eliminated.

Within this system-level perspective, several studies have further interrogated how sweat glucose signals should be interpreted once physiological variability is acknowledged as unavoidable. An advanced modeling-assisted framework in which sweat glucose data are analyzed using subject-specific transport and response models, demonstrating improved intra-individual trend consistency but reaffirming the absence of a universal sweat-blood glucose relationship [129]. Complementing this computational approach, experimental validation under real-time on-body conditions showed that analytical figures of merit derived from off-body calibration deteriorate markedly during wear due to sweat-rate coupling, baseline drift, and temporal instability [130]. Positioned together, these studies reinforce that sweat glucose sensing reliability is governed less by electrode performance and more by how physiological dynamics are incorporated into data interpretation, underscoring the necessity of integrated analytical frameworks rather than further sensitivity-driven sensor optimization. This shift highlights that future progress in sweat glucose sensing is likely to depend more on advances in data analytics and physiological modeling than on incremental improvements in electrode materials or catalytic performance.

In another work, a flexible, silk fibroin-based microcolumn array sensor was designed for real-time on-body sweat glucose analysis [131]. Building on a biocompatible silk fibroin substrate structured into an

array of microcolumns, the platform facilitates efficient sweat sampling and enhanced analyte transport to the sensing interface. The microcolumn architecture improves contact with the epidermis and supports stable electrochemical interrogation of glucose during continuous wear. On-body demonstrations confirm their potential for non-invasive metabolic monitoring with improved mechanical flexibility and user comfort compared to conventional planar sensors. In addition, a fully integrated wearable biosensing system for dynamic monitoring of sweat glucose was developed with real-time pH adjustment that enhances electron transfer and stabilizes enzyme immobilization for continuous monitoring [132]. The sensor incorporates an adaptive calibration mechanism that dynamically compensates for pH fluctuations in sweat, ensuring more accurate physiological data during user activity. By combining this interface with on-board signal processing and a microfluidic sweat collection module (Fig. 8A and B), the platform delivers continuous, real-time sweat glucose profiles under varying conditions, supporting personalized health monitoring with improved analytical reliability compared to static calibration approaches.

Furthermore, a rhizome bioinspired wearable electrochemical sensor platform was fabricated [133] for continuous, real-time sweat glucose monitoring that integrates a hierarchically porous nanostructured electrode interface with a microfluidic sweat sampling layer to enhance mass transport and analyte accessibility (Fig. 8C). This bio-inspired approach not only enhances sensitivity and response speed but also improves operational stability during continuous wear, where sweat rate and composition fluctuate. Importantly, the design philosophy emphasizes function-driven structure, using nature-inspired transport and interface principles to address core analytical challenges in real-time on-body sweat sensing rather than relying solely on material sensitivity enhancements. Such approaches reflect an emerging trend in wearable electrochemical sensing, where bioinspired transport architectures are used to regulate analyte delivery and stabilize interfacial conditions under continuous operation. These recent analytical chemistry investigations further highlight that even with improved electronics, flexible integration, and multiplexed architectures, quantitative

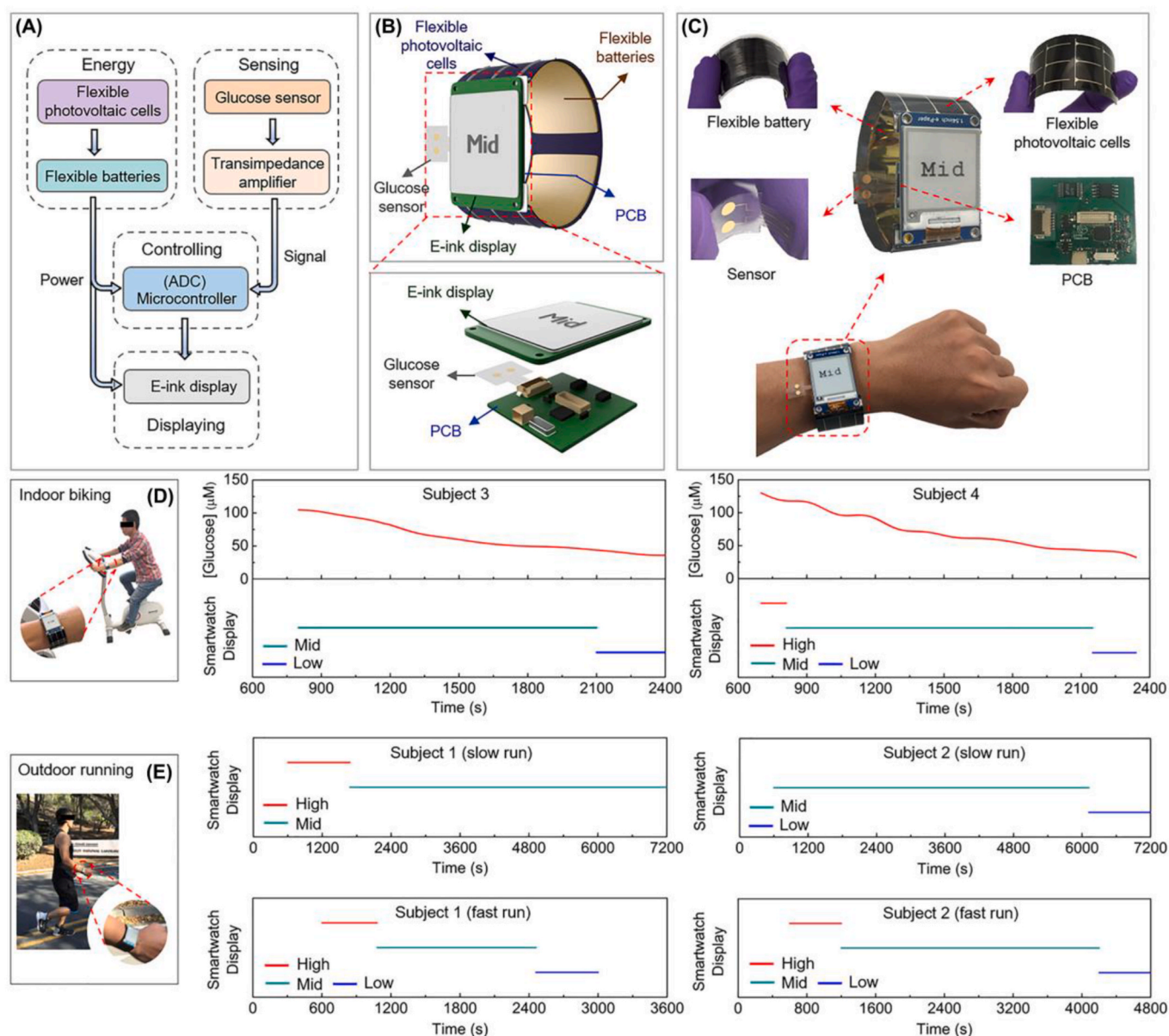


Fig. 7. (A) System-level block diagram, (B) Schematic illustration and (C) Photographs of the developed smartwatch. On-body deployment of the smartwatch sensor during (D) indoor cycling and (E) outdoor running, and their corresponding real-time tracking of glucose fluctuations. Reproduced with permission from Ref. [128].

uncertainty persists due to time-dependent sweat secretion and matrix evolution. Moreover, these works underscore that wearable glucose sensors increasingly function as dynamic analytical systems, where signal interpretation depends on coordinated sensing, computation, and physiological context rather than isolated electrochemical performance.

Recent work further reinforces the transition toward integrated wearable architectures that prioritize system-level signal interpretation over isolated electrode optimization. A wireless epidermal sensing platform reported recently integrates NFC-powered electronics, microfluidic sweat routing, and enzyme-mediated electrochemical sensing within a compact skin-mounted device capable of real-time glucose monitoring under ambulatory conditions [134]. In this configuration, glucose detection relies on a Prussian blue-mediated glucose oxidase interface, enabling low-potential amperometric transduction compatible with physiological sweat environments. Importantly, the system couples glucose sensing with additional electrochemical channels and wireless smartphone-based data acquisition, illustrating how multiplexed architectures can contextualize glucose signals during

continuous wear. However, similar to earlier wearable platforms, on-body measurements reveal that glucose signal dynamics remain strongly influenced by sweat secretion variability, transport delays, and local matrix evolution. Consequently, while the integrated electronics and battery-free wireless operation significantly improve device practicality, the analytical reliability of sweat glucose sensing remains governed primarily by physiological transport processes rather than intrinsic electrode sensitivity. Positioned within the broader trajectory of wearable glucose analytics, this work underscores the continued shift toward holistic sensing systems in which signal interpretation depends on coordinated device integration, physiological context, and data-driven analysis rather than standalone electrochemical performance. Importantly, these integrated platforms demonstrate that device-level innovation alone cannot overcome the intrinsic physiological variability of sweat, reinforcing the need for coordinated sensing and interpretation strategies.

More broadly, sweat glucose sensing serves as a model system for understanding the limitations of non-invasive biochemical monitoring,

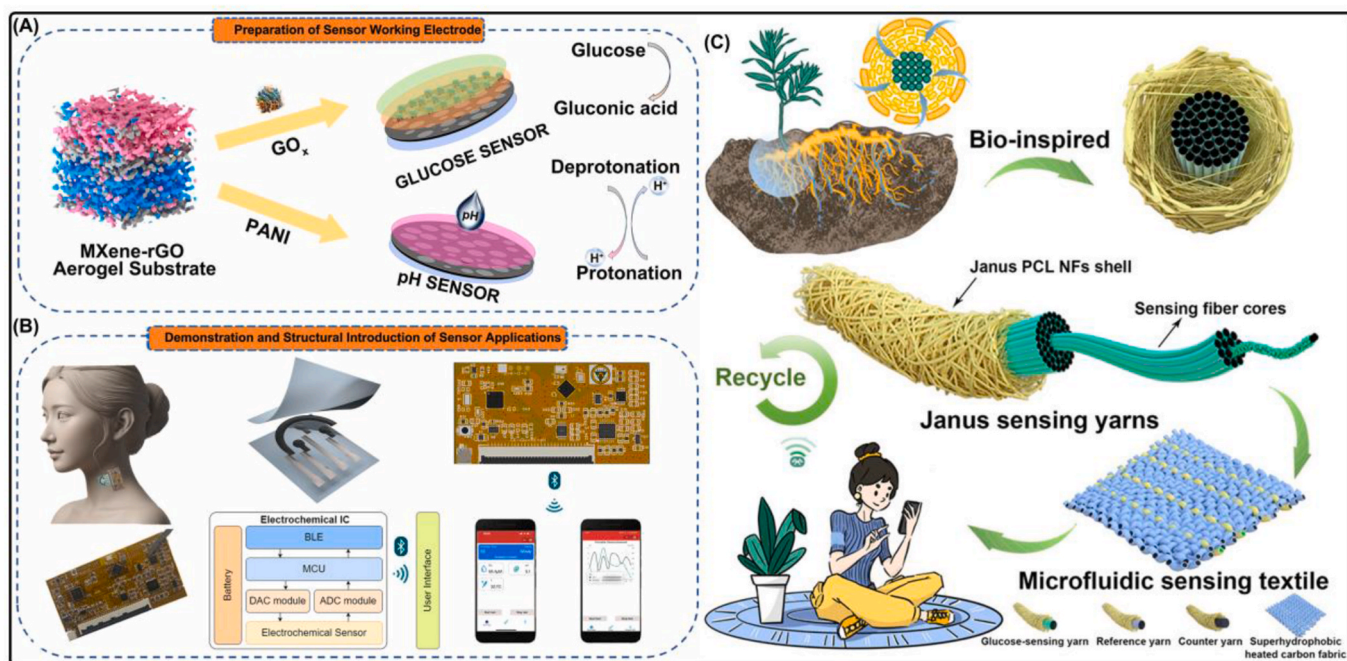


Fig. 8. (A) Fabrication protocol and (B) systematic illustrations of the integrated glucose and pH sensors. Reproduced with permission from Ref. [132]. (C) Schematic illustration of rhizome-inspired Janus sensing yarn-based microfluidic textile for glucose sensing. Reproduced with permission from Ref. [133].

where analytical challenges are dominated by physiological transport phenomena rather than sensor sensitivity. Taken together, the current body of work demonstrates that the primary challenge in wearable sweat glucose sensing lies not in electrochemical transduction itself but in the physiological transport processes that govern glucose appearance in sweat. Across diverse device architectures, including nonenzymatic electrodes, enzymatic amperometric sensors, and fully integrated wireless platforms, similar analytical constraints consistently emerge. Glucose signals measured on the skin are delayed, diluted, and strongly modulated by sweat secretion rate, gland activation dynamics, and local evaporation effects, producing substantial variability between individuals and measurement sessions. As a result, improvements in electrode sensitivity or device miniaturization alone have not translated into reliable quantitative glucose monitoring. Instead, the field is increasingly converging toward context-aware analytical frameworks in which glucose signals are interpreted alongside auxiliary physiological parameters and computational models that account for sweat transport dynamics. Within this perspective, wearable sweat glucose sensors function less as direct proxies for blood glucose and more as dynamic physiological observables, where meaningful interpretation arises from longitudinal trend analysis rather than absolute concentration measurements.

5.2.2. Electrochemical transduction strategies for lactate in sweat

Electrochemical lactate sensing in sweat has been extensively explored because lactate concentrations are sufficiently high to permit robust signal generation without aggressive amplification strategies. The electrochemical detectability of lactate is further facilitated by well-established enzyme-mediated transduction pathways that enable continuous amperometric monitoring under wearable conditions [135]. Importantly, lactate secretion in sweat reflects a combination of glandular metabolism and localized biochemical activity, introducing analyte-specific considerations related to enzyme kinetics, oxygen availability, and pH dependence at the sensing interface. These factors have driven the development of sensor architectures optimized for sustained operation, interference management, and mechanical stability during prolonged on-body use. From an analytical perspective, lactate represents one of the most accessible targets in sweat electrochemistry

because its relatively high concentration reduces the need for aggressive signal amplification and enables more stable continuous monitoring compared to low-abundance biomarkers such as hormones or neurotransmitters.

One of the earliest real-time demonstrations employed a flexible, enzyme-based wearable sensor capable of tracking lactate fluctuations concomitant with exercise intensity, revealing clear time-resolved correlations between sweat lactate and workload that were not evident from static measurements alone [136]. Importantly, this study highlighted the sensitivity of enzymatic transduction to local oxygen availability and pH, variables that influence both catalytic efficiency and signal stability under continuous on-body conditions. These observations highlight a fundamental characteristic of enzyme-based wearable sensors, where signal output reflects not only analyte concentration but also the local biochemical environment governing enzymatic activity. Complementary work using nanostructured electrode surfaces and redox mediators emphasized that enhanced electron transfer can improve signal amplitude, interference from co-secreted electroactive species, and baseline drift remain persistent analytical challenges in prolonged wearable operation [137]. This indicates that enhancements in electron transfer kinetics alone are insufficient to ensure reliable long-term sensing, as interfacial fouling and coexisting electroactive species continue to influence signal stability during continuous wear. Recent advancements extend these observations, demonstrating that optimized electrode architectures and fluidic interfaces can achieve sustained lactate monitoring with minimal signal degradation across a range of sweat rates, but also revealing that mechanical deformation and evaporation effects continue to complicate long-term data fidelity [138]. These findings demonstrate that mechanical and environmental perturbations are intrinsic to wearable sensing conditions, requiring sensor designs that maintain performance under deformation and fluctuating hydration states. Notably, a systemic exploration of lactate sensor performance further established that multi-parameter contextualization, for instance, simultaneous tracking of pH and sweat dynamics, which enhances the interpretability of lactate trends by decoupling enzymatic response variability from true physiological changes [139]. Such multi-parameter approaches represent a critical advancement in wearable electrochemical sensing, as they enable differentiation between

biochemical signals and artifacts arising from variations in the sensing microenvironment. A hybrid electro-colorimetric wearable sweat sensor was introduced that integrates an electrochemical sensing core with a low-power electrophoretic display to enable reversible, multi-use digital colorimetric visualization of sweat biomarkers (Fig. 9A and B). This platform overcomes limitations of traditional single-use colorimetric assays, offering continuous and adjustable range readout with high sensitivity. The human exercise trials for detecting lactate were demonstrated (Fig. 9C and D), highlighting the potential of incorporating reusable digital colorimetric interfaces into wearable sweat sensors to achieve richer, user-interpretable data alongside continuous biochemical monitoring. Beyond analytical performance, these hybrid platforms also address an important translational challenge by improving user interpretability, enabling real-time visualization of biochemical trends without requiring complex external data processing.

Recent analytical chemistry investigations further extend this framework by emphasizing the importance of device integration and signal processing in improving the reliability of wearable lactate sensing. A recently reported wearable electrochemical platform incorporated enzyme-mediated lactate detection within a miniaturized wireless sensing architecture designed for real-time on-body monitoring under dynamic physiological conditions [140]. In this system, lactate oxidase-based amperometric transduction was integrated with flexible electronics and wireless data acquisition, enabling continuous lactate tracking during physical activity while maintaining stable signal transmission. Importantly, the study demonstrated that although improved electronic integration and miniaturized device architectures can enhance operational practicality and signal continuity, lactate measurements during prolonged wear remain sensitive to sweat secretion variability, oxygen availability at the enzyme interface, and local matrix evolution. These findings reinforce the broader analytical observation that reliable interpretation of sweat lactate signals requires contextual understanding of enzymatic kinetics and sweat transport dynamics, rather than reliance on electrode sensitivity alone. This reinforces a broader trend in wearable biosensing, where advances in electronics and data handling complement electrochemical detection but do not eliminate the influence of physiological and environmental variability on signal reliability.

More broadly, lactate sensing serves as a model system for understanding the capabilities and limitations of enzyme-based wearable electrochemical sensors under real-world conditions. Collectively, these

studies demonstrate that while electrochemical lactate detection in sweat is analytically favorable due to relatively high analyte concentrations and well-established enzymatic transduction pathways, reliable interpretation of on-body signals remains strongly coupled to the local physiological environment. Variations in oxygen availability, pH, sweat secretion rate, and mechanical deformation continuously modulate enzymatic activity and mass transport at the sensing interface, introducing variability that cannot be fully mitigated through electrode optimization alone. As a result, current research increasingly emphasizes integrated sensing frameworks, where lactate signals are interpreted alongside contextual parameters such as pH, sweat dynamics, and motion to distinguish true metabolic trends from interface-driven artifacts. Compared with low-concentration biomarkers, lactate sensing more clearly demonstrates how continuous sweat monitoring can yield physiologically meaningful insights despite variability, provided that data are interpreted in a time-resolved and context-aware manner. Within this emerging perspective, wearable lactate sensors function most effectively as dynamic indicators of metabolic activity during exercise, where time-resolved trend analysis provides more meaningful insight than absolute concentration measurements.

5.2.3. Electrochemical transduction strategies for both glucose and lactate in sweat

An emerging class of wearable sensors seeks to improve sweat access and mass transport, crucial for capturing both low-concentration glucose and relatively higher-level lactate signals. The dual-analyte systems integrate enzyme-based recognition with microfluidic or microstructured interfaces to capitalize on established biocatalytic transduction while contending with physiological variability. From an analytical standpoint, multiplexed sensing introduces a fundamentally different challenge compared to single-analyte systems, as each biomarker exhibits distinct concentration ranges, transport kinetics, and enzymatic response characteristics that must be simultaneously resolved within a shared sensing environment. A landmark demonstration of multiplexed sweat analysis was reported using an integrated wearable sweat sensing platform capable of simultaneously monitoring glucose and lactate alongside several additional biochemical and physiological parameters during exercise [141]. In this system, flexible electrochemical sensors incorporating enzyme-functionalized electrodes for glucose and lactate were embedded within a soft microfluidic interface that facilitated continuous sweat collection and transport across the

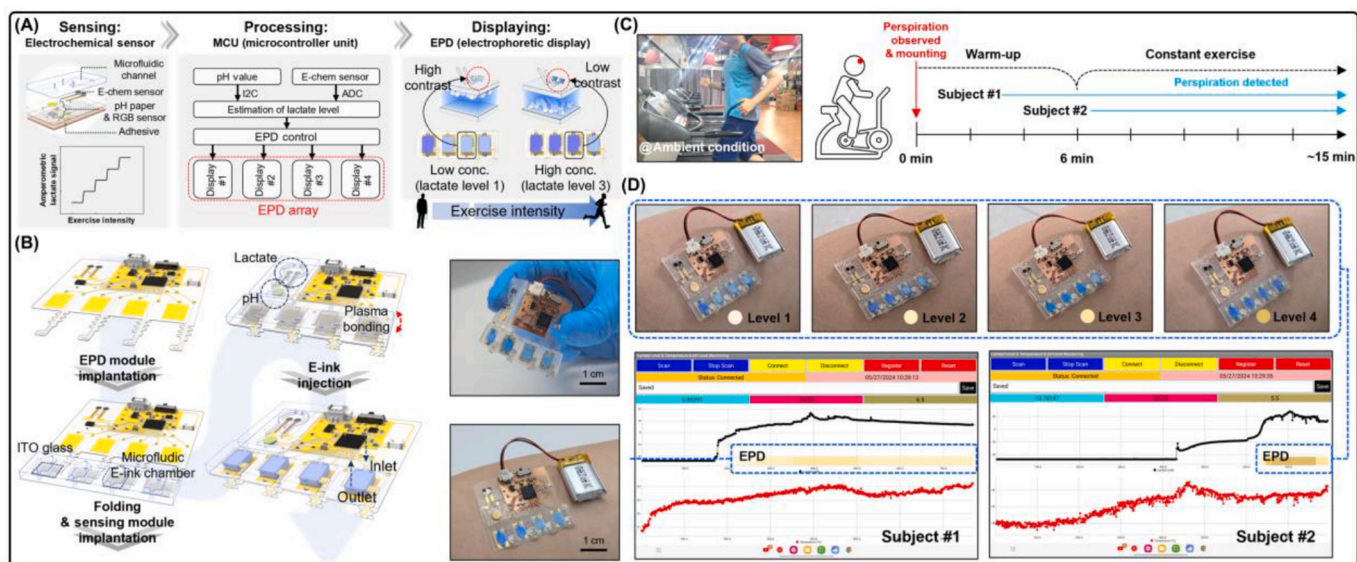


Fig. 9. (A) The operational protocol, (B) Fabrication process and actual images of the lactate sensor platform. (C) The experimental protocol and (D) photographs showing the lactate levels using the developed lactate sensor. Reproduced with permission from Ref. [139].

sensing array. The device further integrated temperature sensing and wireless electronics for real-time data transmission, enabling dynamic monitoring of sweat composition under active physiological conditions. Importantly, the platform demonstrated that simultaneous detection of glucose and lactate is feasible within a single wearable architecture when enzyme-mediated electrochemical transduction is combined with controlled sweat routing and on-body signal processing. From an analytical standpoint, this work highlighted that multiplexed biochemical sensing requires careful management of sweat transport and sensor cross-interactions, as variations in sweat secretion rate and local microenvironment can differentially affect the enzymatic responses of glucose and lactate sensors during prolonged wear. This work also established an important principle for wearable multiplexing, namely that analyte-specific responses cannot be interpreted independently, as shared environmental factors such as sweat rate and temperature simultaneously influence multiple sensing channels.

In another work, an omnidirectionally permeable and deformable wearable sweat analysis system based on gold nanowire sponges demonstrates how electrode architecture influences multi-analyte electrochemistry [142]. The vertically aligned gold nanowires embedded in a porous sponge matrix increase electrochemically active surface area and enable simultaneous amperometric detection of glucose and lactate during exercise by providing improved sweat permeability and reduced diffusion barriers. The platform's design addresses a common analytical constraint, ensuring that both glucose (which is present at lower millimolar levels) and lactate (an order of magnitude higher) reach the transduction interface without significant depletion or lag caused by mass transport limitations. In this system, both glucose oxidation and lactate detection are supported by the high surface area and consistent sweat exposure afforded by the sponge material, highlighting how surface morphology and fluid permeability can modulate dual-analyte sensitivity and temporal fidelity. These findings demonstrate that electrode architecture plays a critical role in balancing analyte accessibility, particularly when targeting biomarkers with significantly different concentrations and diffusion characteristics. Similarly, a highly integrated cellulose-based wearable sensing paper demonstrates that efficient sweat collection pathways and strategic enzyme immobilization can facilitate concurrent glucose and lactate analysis. The folded multi-layer three-dimensional structure enhances both sweat diffusion and enzyme accessibility, enabling dual channel amperometric responses to glucose and lactate with distinct sensitivities [143]. This configuration exemplifies how tailored matrices with dedicated diffusion paths mitigate competing mass transport effects between analytes, which is critical when simultaneously interpreting the low-level glucose oxidation current and the larger lactate signal in dynamic sweat.

A wearable paper-based dual sensor further illustrates how miniaturized electrochemical platforms can achieve simultaneous detection, with reported sensitivities for glucose and lactate distinctly calibrated to their respective physiological ranges [144]. Here, integration of dual enzyme pathways within a low-cost, flexible substrate demonstrates that cost-effective layouts can still support multiplexed biocatalysis, though the analytical potential is bounded by enzyme stability during prolonged sweat exposure and motion. Collectively, these studies highlight that low-cost and paper-based platforms can support multiplex sensing, but their analytical performance is often constrained by limited control over enzyme stability and fluid dynamics compared to more integrated microfluidic systems.

More comprehensive physiological contexts are addressed by studies that combine dual-analyte sensing with contextual correction strategies. For instance, platforms incorporating both microfluidic sweat transport and multi-parameter sensing have shown that simultaneous trends in glucose and lactate can be correlated with exercise intensity more reliably than single-analyte outputs alone [145]. These systems indicate that synchronizing glucose and lactate dynamics, where lactate typically leads due to local secretion and glucose lags due to transport, can provide a richer metabolic context, enabling relative trend interpretation

that is more robust against sweat rate variability. Importantly, the temporal offset between lactate and glucose signals provides complementary physiological information, reflecting the distinction between local metabolic activity and delayed systemic transport. Large-scale analytical evaluations have also explored integrated electrochemical and system logic to improve the interpretability of concurrent glucose and lactate signals. A battery-free, skin-interface microfluidic and electronic platform (Fig. 10A–D) was introduced that enables simultaneous, multi-modal analysis of sweat by integrating electrochemical, colorimetric and volumetric sensing modules in a single wearable platform [146]. The system streams sweat into defined analysis zones where sweat rate, pH, lactate, glucose and chloride are concurrently monitored without an onboard power source. Human trials demonstrate continuous, on-body tracking of multiple analytes (Fig. 10E–G), providing a semi-quantitative profile of sweat biomarkers and suggesting a pathway toward noninvasive, semi-continuous physiological monitoring under realistic conditions. Following this, a standalone, stretchable epidermal sweat sensing platform was reported that integrates electrochemical sensors, a printed battery, and a low-power electrochromic display, enabling direct, on-device visualization of sweat analyte concentrations such as glucose and lactate with wireless connection to external systems [147]. On-skin deployment demonstrates the platform's ability to continuously monitor sweat biomarkers and present results through a reusable display, highlighting an important step toward self-powered, autonomous wearables that combine sensing, power, and feedback in a single epidermal patch. Similarly, a wearable epidermal sweat sensor patch was developed that integrated biomimetic microfluidic channels with an electrochemical sensing array [148]. The microfluidic design mimics ginkgo-vein architecture to enhance unidirectional sweat transport, and electrochemical sensors enable dynamic tracking of glucose and lactate changes with dietary intake and exercise in real-time. Overall, real-time analytical platforms that integrate trend analysis and modeling have demonstrated that, even with dual enzymatic detection, the dynamic interplay between sweat composition and physiological state requires contextual normalization, such as sweat rate, pH, and interfacial effects. These integrated systems illustrate that multiplex wearable sensing is evolving toward holistic analytical platforms, where biochemical signals are interpreted in conjunction with physical and environmental parameters to improve overall reliability.

More broadly, multiplex glucose-lactate sensing highlights the transition from single-analyte detection toward integrated metabolic profiling in wearable electrochemical systems. Collectively, these studies demonstrate that simultaneous electrochemical monitoring of glucose and lactate in sweat is analytically feasible when enzyme-based transduction is coupled with architectures that promote efficient sweat transport and stable enzyme activity. However, dual-analyte sensing introduces additional challenges beyond those encountered in single-analyte systems, particularly because glucose and lactate exist at substantially different physiological concentrations and exhibit distinct enzymatic kinetics. Consequently, sensor architectures must balance mass transport, enzyme loading, and signal dynamic range to prevent cross-interference and disproportionate signal amplification. As a result, recent designs increasingly emphasize microfluidic routing, structured electrode morphologies, and multiplexed data interpretation to ensure that each analyte reaches the sensing interface under comparable conditions. In particular, the large disparity in physiological concentrations between glucose and lactate necessitates careful calibration and signal normalization strategies to avoid dominance of high-abundance analytes in the electrochemical response. Within this framework, multiplex glucose-lactate platforms represent an important step toward comprehensive metabolic monitoring, although reliable interpretation of dual-analyte signals remains strongly influenced by sweat secretion dynamics and enzyme stability during extended on-body operation. Ultimately, multiplex sensing underscores that future wearable electrochemical systems will rely increasingly on coordinated sensor arrays and data-driven interpretation frameworks rather than independent analyte

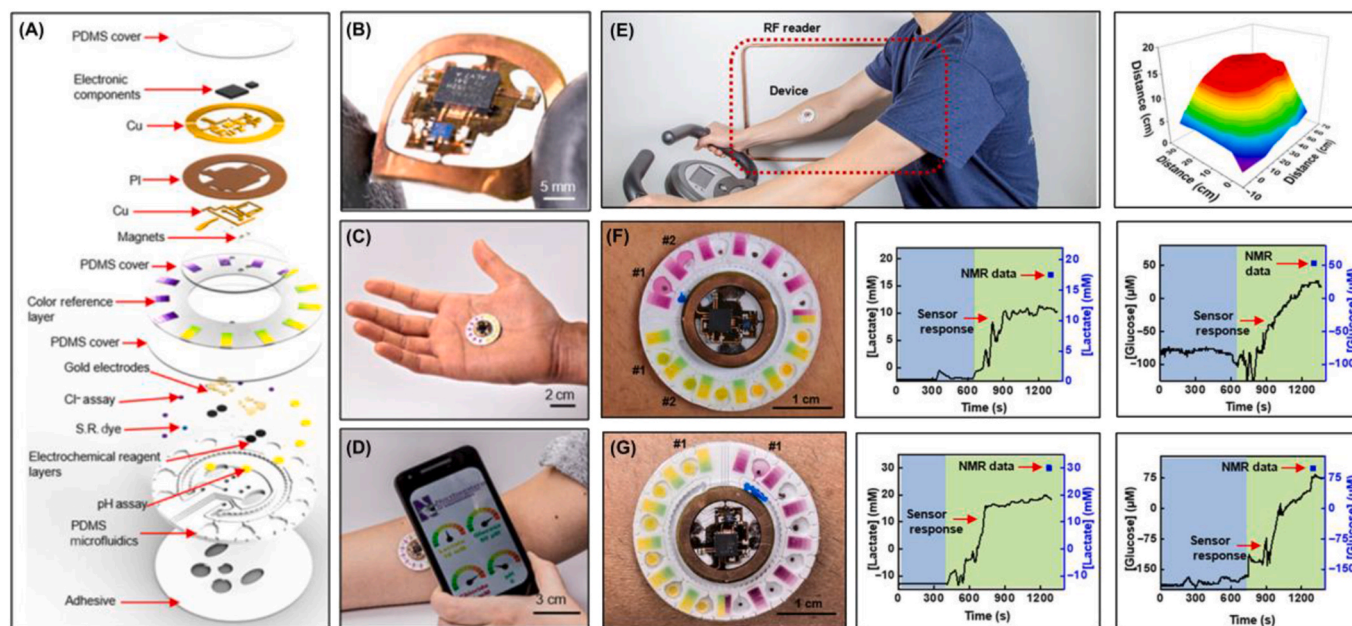


Fig. 10. (A) Exploded illustration and (B) photographs of a battery-free NFC system, (C) complete wearable sensing system and (D) NFC-controlled smartphone integrated user-interface. (E) Photograph of the subject wearing the sensor device and signal reading distance. Photographs of the complete system obtained during cycling by (F) Subject 1 and (G) Subject 2, and their corresponding sensing data for lactate and glucose. Reproduced with permission from Ref. [146].

detection modules. The evolution toward multiplex wearable electrochemical platforms has enabled simultaneous monitoring of glucose and lactate alongside electroactive small molecules such as AA and UA, introducing additional analytical challenges associated with redox interference, signal decoupling, and matrix effects that are examined in the upcoming sections. The electroanalytical performances of the sensors discussed in this section are tabulated in Table 2.

5.3. Small-molecule markers in sweat

5.3.1. Electrochemical transduction strategies for urea in sweat

Urea is the small and principal end-product of nitrogen metabolism and serves as a key biomarker of protein catabolism, renal function, and hydration status. In eccrine sweat, urea is secreted predominantly through passive diffusion and exhibits relatively slow transport kinetics compared to metabolites associated with rapid energy metabolism [149]. As a result, sweat urea concentrations tend to reflect cumulative physiological and hydration states rather than instantaneous metabolic fluctuations. This accumulation-dominated behavior presents both opportunities and challenges for real-time on-body electrochemical sensing, as urea signals are less sensitive to transient activity but are strongly influenced by sweat rate, skin accumulation, and prolonged sensor-skin contact. From an analytical perspective, urea represents a transport-limited biomarker, where measured concentrations are governed more by accumulation and clearance dynamics than by rapid biochemical production, distinguishing it fundamentally from metabolites such as glucose or lactate.

Wearable urea sensors have adopted a range of electrochemical strategies to address the unique analytical challenges posed by accumulation-dominated secretion and the relatively wide physiological concentration range of urea in sweat. Flexible electrochemical platforms utilizing surface MIP-nanotubes illustrate one of the earliest approaches, where hierarchical carbon nanotube and gold nanotube networks imprinted for urea recognition enable selective and mechanically robust detection in human sweat, with minimal interference from co-existing species and clear signal changes following physiological perturbations such as exercise [150]. This approach highlights that enhancing molecular selectivity alone does not fully address the challenges of urea

sensing, as signal interpretation remains coupled to slow diffusion and accumulation processes at the skin interface. Building on this foundation, potentiometric biosensors fabricated on screen-printed carbon electrodes have demonstrated rapid urea detection over a broad concentration range (~5–200 mM) encompassing typical sweat levels by incorporating a co-located pH sensor for in situ pH correction, which mitigates the influence of local pH shifts on the urea signal and enhances reliability under bending and on-body conditions [151]. This demonstrates that urea sensing is particularly sensitive to the local chemical environment, where pH-induced speciation and ionic interactions can significantly alter potentiometric responses. This pH-corrected potentiometric architecture underscores the importance of contextual parameter monitoring in urea analysis, as local pH and ionic strength can markedly skew electrochemical responses. Additionally, multimodal wearable microfluidic systems integrating electrochemical and colorimetric arrays have achieved simultaneous quantification of urea alongside other sweat analytes, revealing how microfluidic sweat capture and routing architectures can support continuous urea measurement while protecting individual sensing units from crosstalk and contamination, thus advancing real-time sweat analytics beyond single-analyte detection [152]. Importantly, controlled sweat routing in such systems helps mitigate surface accumulation effects, enabling more consistent temporal sampling of urea despite its inherently slow transport kinetics. Across these efforts, common analytical themes emerge, urea sensing accuracy depends strongly on sweat collection strategy, matrix correction (especially pH), and flexible sensor design, with physiological interpretation benefiting from concurrent contextual measurements that help distinguish true urea concentration changes from transport or surface accumulation effects. These studies comprehensively indicate that urea sensing reliability is governed less by transduction sensitivity and more by how effectively the sensor system manages sweat residence time and interfacial equilibration.

More broadly, urea sensing exemplifies a class of sweat biomarkers whose analytical behavior is dominated by slow transport and accumulation rather than rapid physiological turnover. Collectively, these studies demonstrate that electrochemical urea sensing in sweat has progressed toward mechanically robust and selective wearable platforms capable of operating across the relatively broad physiological

Table 2

Electrochemical sensor performances toward energy metabolic markers in sweat.

Sensors	Enzymes	Analytes	Linear range (mM)	LOD (μM)	Sensitivity ($\mu\text{A mM}^{-1}\text{cm}^{-2}$)	In vivo duration (min.)	Validation Method	Ref.
Gold film	-	Glucose	0.0125 – 0.4	1.2	-	1.67	Blood Glucose	[121]
PB	GOx	Glucose	0 – 2	14	-	-	Blood Glucose	[122]
Pt1–NiCo-LDH/MXene	-	Glucose	0.01 – 2.5	0.035	506.6	30	HPLC	[123]
GNPs@ZIF-8-C/calcium alginate	-	Glucose	0.01 – 0.2	4.99	-	90	Blood Glucose	[124]
Graphene/HEMA/NF	GOx	Glucose	0 – 0.32	-	-	25	Blood Glucose	[125]
PB/CS/SWCNT	GOx	Glucose	0.035 – 0.135	15.32	3.35*	-	-	[126]
Ag/Gold/PB/NF	GOx	Glucose	0.02 – 0.2	-	313.28	30	-	[127]
Gold/PB/NiHCF	GOx	Glucose	0.050 – 0.2	-	3.29*	120	Electrochemical workstation	[128]
ZnO	GOx	Glucose	0 – 0.4	-	-	30	-	[129]
CNTs/CNFs/PB	GOx	Glucose	0.1 – 1.5	100	-	-	Blood Glucose	[130]
SF/PU/MWCNT/PB/NF	GOx	Glucose	0.1 – 1	4	35.28	13.34	-	[131]
MXene/rGO	GOx	Glucose	0.02 – 0.2	33.69	15.5	-	Blood Glucose	[132]
Janus sensing yarns	-	Glucose	0.003 – 0.25	-	36570	-	-	[133]
PB	GOx	Glucose	0 – 0.45	16.5	0.19*	120	Blood Glucose	[134]
PB/ETH/PVC/DOS	LOx	Lactate	0.015 – 0.4	32.6	0.021*	75	-	[136]
MIP-Ag nanowire	-	Lactate	0.001 – 100	0.22	-	-	-	[137]
CRP/MXene/CoONPs/N-carbon/MXene/CoONPs/N-carbon	-	Lactate	0.01 – 0.36	3.2	-	-	-	[138]
CNT/TTF/GLU/PVC/CS	LOx	Lactate	0 – 20	-	-	13	Commercial sensor	[139]
SI@HLF	LOx	Lactate	5 – 30	218	0.0549*	-	Assay kit	[140]
PB	GOx	Glucose	0 – 0.2	-	2.35*	50	-	[141]
	LOx	Lactate	0 – 30	-	0.22*	-	-	[142]
Gold sponge/PB	GOx	Glucose	0.010 – 1	1.86	31.09	-	-	[142]
	LOx	Lactate	0 – 10	32.16	3.246	-	-	[143]
Gold/Pt black	GOx	Glucose	0.1 – 0.4	-	-	-	-	[143]
	LOx	Lactate	0 – 25	-	-	-	-	[144]
Gold/Graphene	GOx	Glucose	0 – 0.15	-	110 [#]	20	-	[144]
	LOx	Lactate	0 – 15	-	2.48 [#]	-	-	[145]
Carbon fiber fabric/CNT/MXene/PB	GOx	Glucose	0.001 – 1.5	0.33	35.3	-	-	[145]
	LOx	Lactate	0 – 22	0.67	11.4	-	-	[146]
CNT/TTF/NF	GOx	Glucose	0 – 0.4	-	-	20	NMR	[146]
	LOx	Lactate	0 – 15	-	-	-	-	[147]
CNT-COOH/NQ	GOx	Glucose	0 – 10	-	-	-	Blood Glucose	[147]
	LOx	Lactate	0 – 25	-	-	-	Commercial sensor	[148]
GNPs/PB	GOx	Glucose	0.01 – 0.2	0.55	2*	5	Blood Glucose	[148]
	LOx	Lactate	5 – 25	652	0.08*	-	-	[148]

CNF – cellulose nanofibers; CRP – carbonized rice-paper; CS – chitosan; DOS – bis(2-ethylhexyl) sebacate; ETH – quaternary salt tetradecylammoniumtetrakis(4-chlorophenyl)borate; GLU – glutaraldehyde; GNTs – gold nanotubes; GOx – Glucose oxidase; HEMA – 2-hydroxyethyl methacrylate; HPLC – high-performance liquid chromatography; HLF – hook-and-loop fastener; LOx – lactate oxidase; NF – Nafion; NQ – naphthoquinone; NMR – nuclear magnetic resonance; PB – Prussian blue; Pt1 – single atom platinum; PU – polyurethane; PVC – polyvinyl chloride; rGO – reduced graphene oxide; SI – single carbon microyarn; SF – silk fibroin; SWCNT – single walled carbon nanotubes; TTF – Tetrathiafulvalene. * – $\mu\text{A mM}^{-1}$; # – mV mM^{-1} .

concentration range encountered during on-body monitoring. Strategies incorporating MIP recognition layers, potentiometric architectures with integrated pH correction, and multimodal microfluidic systems highlight the importance of interfacial selectivity, contextual sensing, and controlled sweat sampling for reliable urea detection. However, unlike rapidly fluctuating metabolic markers, sweat urea primarily reflects transport-limited accumulation processes, meaning that measured concentrations are strongly modulated by sweat rate, local pH, and prolonged skin-sensor interactions. This contrasts sharply with metabolites such as lactate, where rapid fluctuations can be directly captured, highlighting that different classes of sweat biomarkers require fundamentally different sensing and interpretation strategies. Consequently, current wearable urea sensors are best interpreted as tools for tracking gradual physiological trends related to hydration status and nitrogen balance, rather than for instantaneous metabolic assessment. Ultimately, accurate urea monitoring will depend on integrating temporal sampling control with context-aware calibration, enabling differentiation between true physiological accumulation and artifacts arising from sweat retention and evaporation. Future advances will likely depend on improved microfluidic sweat management, matrix-aware calibration, and integration of contextual parameters, enabling more reliable differentiation between true physiological changes and transport-driven signal variability during continuous on-body operation.

5.3.2. Electrochemical transduction strategies for ascorbic acid in sweat

Ascorbic acid (AA) is an electroactive antioxidant present in human sweat that contributes to redox balance and has been explored both as a target of physiological interest and as a model interferent in multi-analyte electrochemical sensing [153]. Unlike enzyme-mediated metabolites, AA can be detected through direct electrochemical oxidation, but its overlapping oxidation potential with other endogenous species and its susceptibility to surface fouling and kinetic modulation complicate real-time measurements on the body. From an analytical perspective, AA represents a redox-active interferent-prone analyte, where signal reliability is governed primarily by potential overlap and interfacial stability rather than detection sensitivity. In efforts to improve AA specificity and analytical reliability, several wearable platforms have adopted surface modification and signal discrimination strategies. For instance, a flexible sensor incorporating nanostructures with catalytic sites demonstrated enhanced AA oxidation currents with reduced potential separation from coexisting species, emphasizing how electrode surface engineering can tune redox kinetics to improve selectivity in complex sweat matrices [154]. Although primarily validated under flow or semi-controlled conditions, this work underscores the importance of membrane/electrode interface design when discriminating AA against common interferents during continuous operation. This highlights that tuning electron transfer kinetics can partially resolve overlapping

oxidation signals, but does not eliminate interference when multiple electroactive species coexist within a narrow potential window. Parallel approaches have leveraged conductive polymer composites and hierarchical nanomaterials to facilitate AA oxidation with improved electron transfer and reduced fouling. A notable example used carbon nanotube-conductive polymer hybrids to achieve high AA sensitivity in sweat while mitigating signal drift over extended measurement intervals

[155]. It couples localized sweat stimulation with amperometric detection following intake of fruit juice (Fig. 11). By optimizing the balance between electroactive surface area and fouling resistance, this strategy illustrates the trade-off between enhanced reactivity and long-term stability, which is central to real-time electrochemical sensing of AA in the dynamic sweat environment. These results emphasize a central trade-off in AA sensing, where increasing electroactive surface

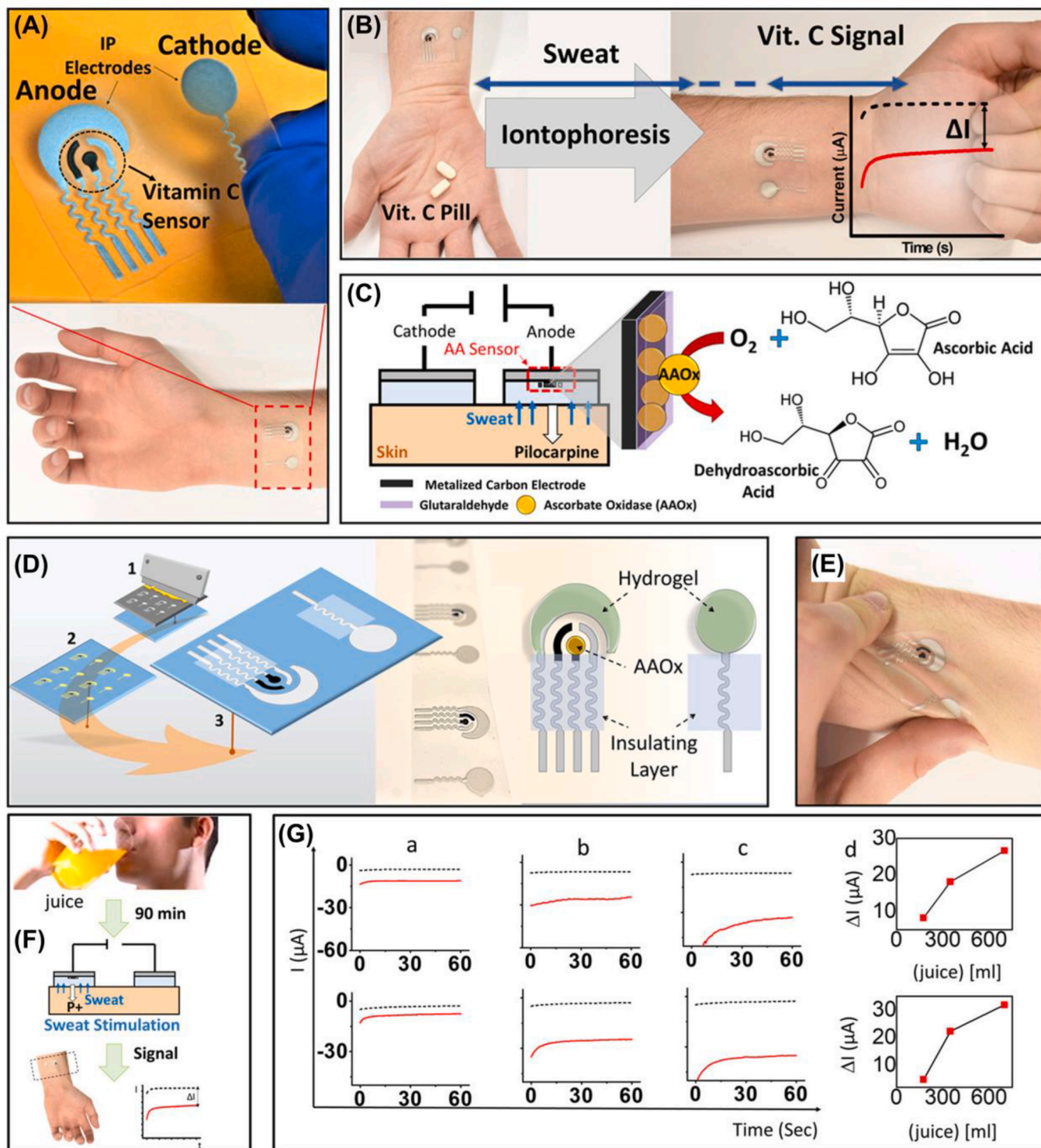


Fig. 11. (A) Wearable sensor architecture and (B) Protocol carried out for electrochemical AA sensing. (C) Schematic representation of sweat stimulation and sensing mechanism. (D) Graphical representation of sensor fabrication. (E) Photograph of the sensor under mechanical deformation. (F) Scheme and (G) electrochemical response of the biosensor after drinking fruit juice. Reproduced with permission from Ref. [155].

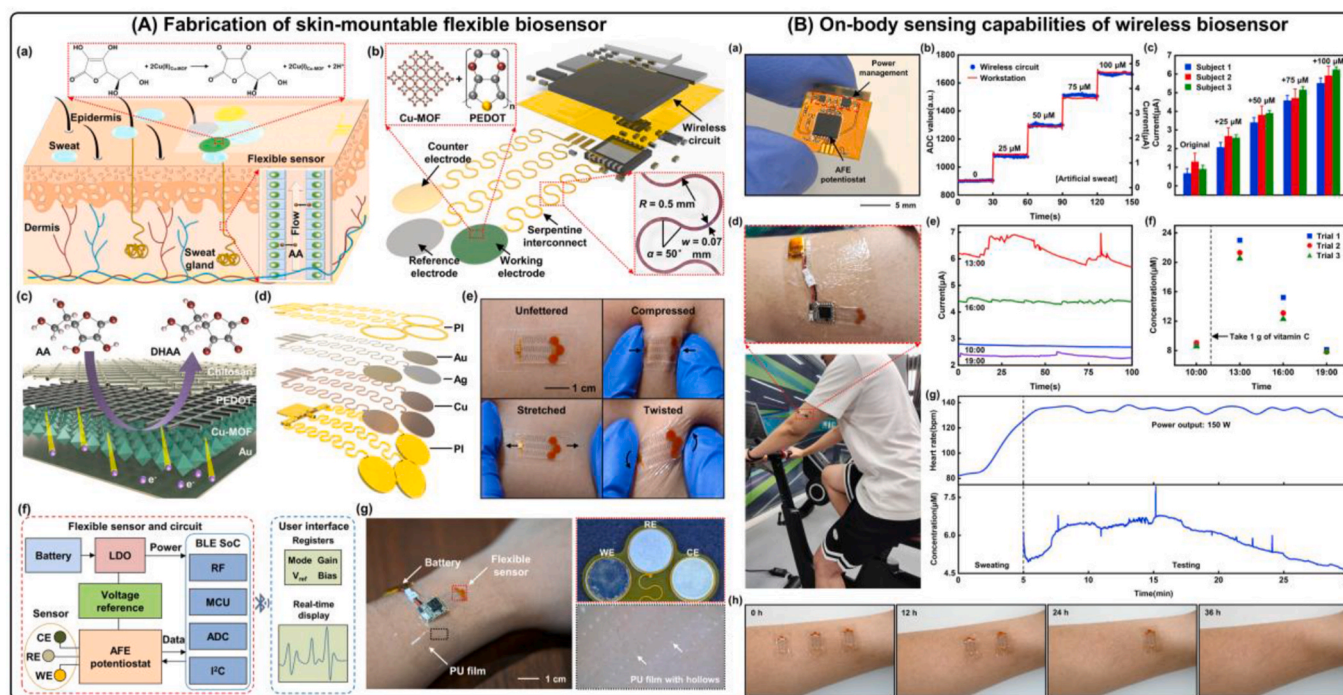


Fig. 12. (A) Fabrication of skin-mountable sensor with (a) schematic illustration of skin layer, (b) sensor components, (c) sensing mechanism, (d) exploded view of the electrode, (e) sensor under mechanical deformation, (f) block diagram and (g) photograph of the fabricated flexible sensor. (B) On-body sensing capability showing (a) miniaturized circuit used along with (b) sensing results, (c) spike tests of the sensor. (d) Photographs of testing an individual wearing a sensor, and (e&f) corresponding sensing results before and after AA intake. (g) correlation of heart rate and sweat AA concentration during exercise, and (h) biocompatibility of the fabricated sensor. Reproduced with permission from Ref. [157].

area enhances sensitivity but also accelerates fouling and signal drift during prolonged exposure to sweat constituents.

Beyond material optimization, integrated interface designs that combine selective binding, local pH buffering, or microfluidic control have been applied to improve AA discrimination without compromising glucose or lactate signals in multiplexed configurations. For instance, platforms employing tailored electrode coatings with pH-tolerant transduction layers demonstrated controlled AA oxidation currents with minimized crosstalk from adjacent analytes [156]. This work emphasizes that effective AA sensing in sweat must address not only intrinsic redox activity but also local chemical environment variability, which can shift oxidation potentials and influence analytical windows. This demonstrates that, unlike enzymatic sensors with defined reaction potentials, AA detection requires continuous control of the local electrochemical environment to maintain signal discrimination. Real-time wearable implementations further highlight the role of electrode fouling and baseline instability in AA measurements. A recent epidermal sensor study showed that although initial AA signals could be resolved clearly from background current, prolonged on-body use led to gradual attenuation attributed to surface adsorption of skin constituents and competitive oxidation processes [157]. Such behavior indicates that electrode fouling is not merely a surface degradation issue but an inherent consequence of continuous exposure to complex biofluids containing multiple adsorptive and redox-active species. Herein, a flexible, enzyme-based wearable biosensor was developed leveraging a nanostructured electrode interface to enhance electron transfer and enzymatic activity (Fig. 12A). Selective amperometric monitoring of AA was achieved under continuous on-body conditions, with integrated microfluidics enabling consistent sweat sampling. On-body tests during physical activity demonstrate dynamic AA profiles correlated with physiological state and sweat rate (Fig. 12B), highlighting the device's capability of real-time tracking of redox-active small molecules in sweat. This finding reinforces that, in addition to selectivity engineering,

dynamic interface maintenance (e.g., anti-fouling layers or periodic regeneration) is critical for sustainable AA monitoring in sweat.

More broadly, AA sensing exemplifies the challenges associated with direct electrochemical detection of small redox-active molecules in complex biofluids. Collectively, these studies demonstrate that while AA is readily detectable through direct electrochemical oxidation due to its intrinsic redox activity, reliable monitoring in sweat is primarily constrained by electrode selectivity and interfacial stability rather than intrinsic detectability. In particular, the narrow potential window shared by many endogenous electroactive species necessitates precise control over electrode surface chemistry and operating conditions to achieve meaningful selectivity. Strategies employing nanostructured catalytic surfaces, conductive polymer composites, and tailored electrode coating illustrate how surface engineering can enhance oxidation kinetics while mitigating interference from coexisting electroactive species. However, real-time on-body measurements consistently reveal that electrode fouling, baseline drift, and local matrix variability, particularly pH fluctuations and competitive oxidation processes, significantly influence signal stability during prolonged wear. This distinguishes AA from metabolites such as glucose or lactate, where enzymatic specificity defines selectivity, whereas AA sensing relies almost entirely on electrochemical discrimination strategies. Consequently, wearable AA sensors are often as valuable for evaluating anti-fouling strategies and electrochemical interface robustness as they are for monitoring physiological antioxidant dynamics. Ultimately, the reliability of AA monitoring will depend on the ability to dynamically maintain a stable and selective electrode interface over time, rather than solely improving initial sensor performance. Future advances will likely rely on improved anti-fouling surface chemistries, controlled sweat-electrode interfaces, and contextual sensing integration, enabling more stable discrimination of AA signals within the dynamically evolving sweat matrix during continuous on-body operation.

5.3.3. Electrochemical transduction strategies for uric acid in sweat

Uric acid (UA) is another intrinsically electroactive small molecule present in human sweat and is commonly associated with purine metabolism, oxidative stress, and systemic metabolic balance [158]. In contrast to AA, UA exhibits oxidation at relatively higher potentials and often coexists with AA in sweat at comparable or lower concentrations, creating challenges for signal discrimination in real-time electrochemical measurements. However, this apparent separation does not fully eliminate interference, as potential shifts induced by pH and matrix composition can bring UA and AA signals into closer overlap under real sweat conditions. Wearable electrochemical platforms capable of in situ UA monitoring in human sweat have demonstrated that selective UA detection is achievable through careful electrode surface design and potential control, yet signal stability remains strongly influenced by sweat composition, pH variability, and competitive oxidation processes during prolonged on-body operation. From an electroanalytical

standpoint, UA represents a resolution-limited analyte, where reliable detection depends on separating closely spaced oxidation signals within a narrow potential window rather than enhancing intrinsic signal magnitude. Consequently, UA sensing in sweat primarily serves as a stringent test of electrochemical selectivity and redox resolution under realistic conditions rather than a straightforward route to absolute quantification, reinforcing the need for interface engineering and contextual interpretation strategies in wearable sweat analytics [159].

UA has been investigated in wearable sweat sensors both as an individual redox-active target and within multiplexed metabolic sensing platforms, reflecting its dual role as a physiologically relevant metabolite and an electrochemical interferent. Owing to its intrinsic oxidizability, UA can be detected through direct electrochemical methods; however, in real sweat, this approach is complicated by low and highly variable concentrations, overlapping oxidation potentials with other endogenous species, and progressive electrode fouling [160]. Early

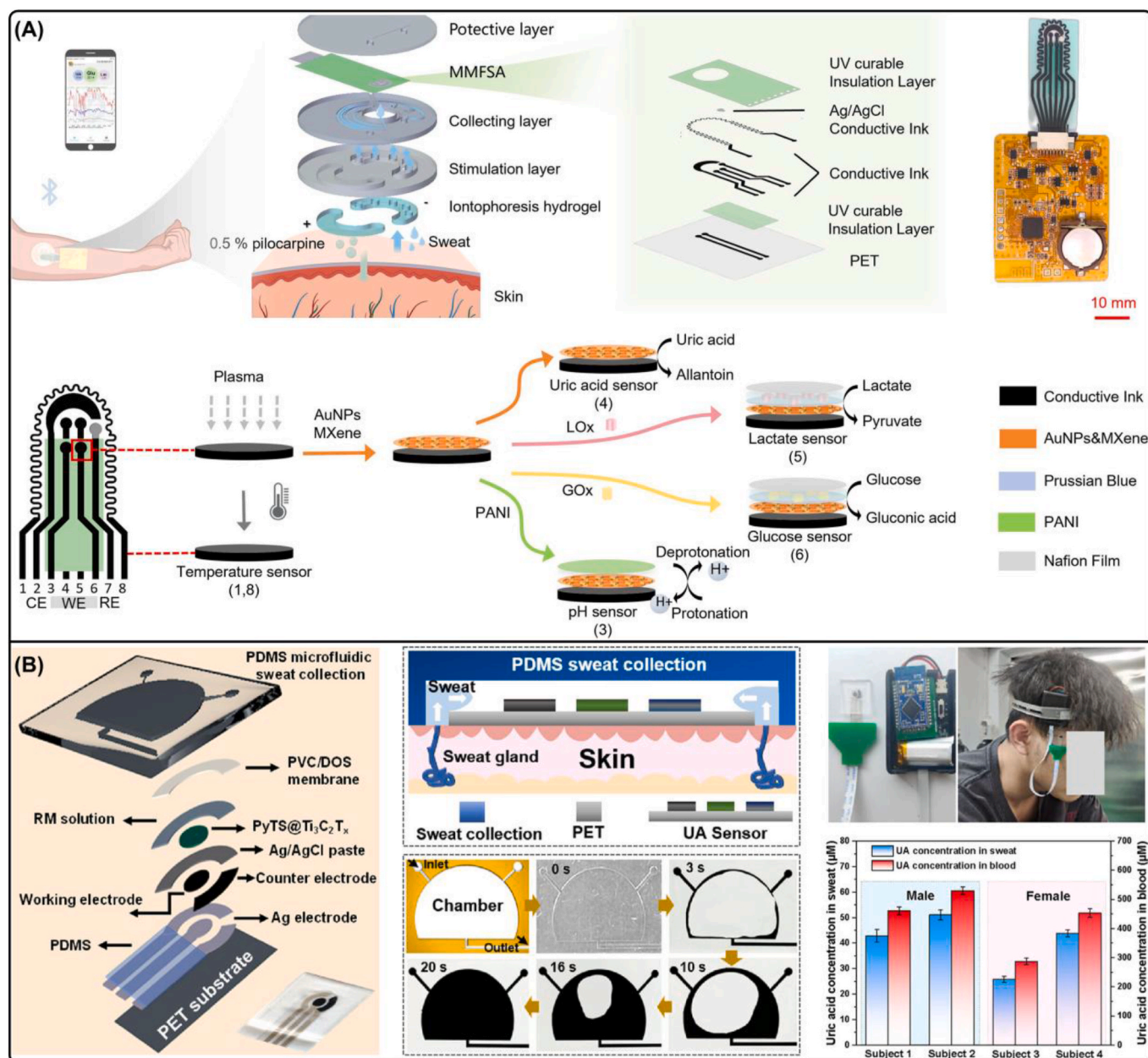


Fig. 13. Schematic illustration of (A) the design and development of the wearable multiplexed sensor. Reproduced with permission from Ref. [162]. (B) Components, cross-sectional view, microfluidic chip of the flexible UA sensor and photograph of the testing individual wearing the device, along with the test results. Reproduced with permission from Ref. [163].

studies in wearable UA analysis integrated UA sensing within multiplexed metabolic platforms that simultaneously monitor glucose and lactate, revealing the interplay of redox signals in complex sweat matrices. For instance, electrochemical arrays that co-deploy enzyme-mediated glucose and lactate detection with direct UA oxidation kinetics required careful tuning of potential windows to prevent overlapping currents and minimize mutual interference during on-body use [161]. In these systems, UA's oxidation peak often resides close to those of other species, necessitating strategic waveform design and electrode surface modification to achieve acceptable discrimination without sacrificing temporal resolution. This highlights that multiplex electrochemical sensing requires dynamic optimization of operating potentials, where improving selectivity for one analyte can compromise resolution or sensitivity for others. Further demonstrating the challenges of multiplex contexts, microfluidic wearable sensors capable of concurrent glucose, lactate and UA monitoring showed that UA signals are disproportionately affected by baseline drift and matrix interferences compared to the more robust metabolic analytes [162]. These findings highlight that, while multiplex architectures can capture broad compositional information from sweat (Fig. 13A), individual analyte fidelity, especially for lower-current UA oxidation signals, must be interpreted with caution, particularly under dynamic sweat rates and variable physiological conditions. In particular, lower-current UA signals are more susceptible to baseline fluctuations, making them inherently less robust than enzyme-amplified signals such as glucose or lactate.

Complementing multiplexed studies, dedicated UA sensing investigations provide deeper insight into selectivity and fouling phenomena unique to UA. A platform employing tailored recognition interfaces and optimized electrochemical windows demonstrated enhanced UA oxidation response with reduced interference from common sweat constituents (Fig. 13B), underscoring the importance of surface chemistry in achieving analytical specificity [163]. These findings emphasize that precise control over interfacial chemistry is essential for UA sensing, as even minor variations in adsorption behavior can significantly alter oxidation kinetics and peak resolution. The UA sensing capability was demonstrated by comparing the results obtained from sweat with those of blood, establishing exceptional sensitivity in UA detection with minimal interference. This work also demonstrated that UA's sorption behavior and oxidation kinetics are sensitive to local pH, necessitating concurrent measurement or compensation strategies to decouple pH-induced shifts from true concentration effects. Parallel work using a flexible enzymatic UA sensor further emphasizes the susceptibility of UA measurements to dynamic interface conditions on skin, where sweat composition, ionic strength and proteinaceous fouling agents can attenuate signal over time [164]. This study highlighted that even with enzyme assistance, long-term real-time monitoring requires protective coatings and anti-fouling architectures to preserve analytical continuity during prolonged wear. This demonstrates that enzymatic assistance can improve selectivity but does not fully eliminate fouling and matrix effects, which continue to limit long-term signal stability.

More broadly, UA sensing exemplifies the challenges of resolving multiple electroactive species within complex biofluids using direct electrochemical methods. Collectively, these studies suggest that UA is inherently electroactive and therefore suitable for direct electrochemical detection. However, reliable real-time monitoring in sweat is largely limited by issues of selectivity, matrix interference, and electrode fouling, rather than by its intrinsic electrochemical properties. In particular, the proximity of UA oxidation potentials to other endogenous species necessitates precise control over both electrode surface properties and applied potential windows to achieve meaningful signal separation. Unlike AA, where fouling dominates signal degradation, UA sensing is equally constrained by peak resolution and signal overlap, placing it at the intersection of selectivity and electrochemical discrimination challenges. Multiplexed wearable platforms highlight the difficulty of isolating UA oxidation signals within complex sweat matrices, where overlapping redox potentials and dynamic sweat

composition can introduce baseline drift and cross-analyte interference. Dedicated sensing approaches employing tailored recognition interfaces and enzymatic strategies demonstrate that surface chemistry optimization, controlled potential windows, and antifouling architectures are essential for improving analytical specificity and signal stability during continuous wear. Nevertheless, UA signals remain strongly influenced by local pH, sweat rate variability, and progressive surface adsorption of skin-derived constituents, which can attenuate responses over time. Ultimately, improving UA sensing reliability will require strategies that combine high-resolution electrochemical techniques with adaptive calibration to account for dynamic shifts in the sweat matrix. Consequently, current wearable UA sensors are best interpreted as tools for tracking relative metabolic or oxidative stress trends, while future progress will depend on improved interfacial robustness, contextual parameter integration, and matrix-aware calibration strategies to enable more reliable long-term sweat analysis.

5.3.4. Electrochemical transduction strategies for simultaneous sensing of AA and UA in sweat

AA and UA are small redox-active molecules that play important roles in oxidative balance and metabolic regulation and are consistently present in human eccrine sweat. Owing to their electrochemical activity, both analytes have been explored using direct, non-enzymatic oxidation at electrode surfaces as well as enzyme-assisted transduction strategies designed to enhance selectivity and mitigate interference [165]. While non-enzymatic approaches exploit the intrinsic redox behavior of AA and UA, enzymatic sensing schemes typically based on oxidase-mediated reactions offer improved molecular specificity at the expense of additional dependencies on oxygen availability, pH stability, and enzyme lifetime. Under real-time on-body conditions, the electrochemical detection of AA and UA remains analytically challenging due to their low and highly variable sweat concentrations, overlapping oxidation potentials, and susceptibility to electrode fouling within complex sweat matrices. Consequently, AA and UA sensing in sweat serves not only as a route to physiological insight but also as a stringent test case for evaluating electrochemical selectivity, interface stability, and signal fidelity in wearable sensing platforms [166]. From a broader electroanalytical perspective, AA and UA together define a class of coexisting redox-active interferents, where analytical performance is governed by the ability to resolve overlapping electrochemical signals within a dynamically evolving biofluid matrix.

Simultaneous electrochemical sensing of AA and UA in sweat has emerged as a stringent test of selectivity in wearable platforms, given their overlapping oxidation potential and shared susceptibility to surface fouling. In a representative fully multiplexed wearable system, AA and UA were monitored alongside glucose and lactate under real-time on-body conditions, revealing that while enzyme-mediated glucose and lactate signals remained comparatively stable, AA and UA responses were more sensitive to redox crosstalk, baseline drift, and matrix-induced variability [167]. This study highlighted that AA and UA sensing performance is governed less by sensitivity and more by the ability to decouple concurrent redox processes within densely populated electrochemical microenvironments. This underscores that, in multiplex wearable systems, electrochemical selectivity is not an intrinsic property of individual sensors but an emergent property of the entire sensing environment. Dual-analyte (AA-UA) systems without enzymatic targets provided additional insight into intrinsic electrochemical constraints, showing that even in simplified configurations, oxidation peak overlap and pH-dependent kinetics limit quantitative reliability under continuous sweat exposure [168]. This demonstrates that even in the absence of enzymatic or multiplex complexity, intrinsic electrochemical overlap and pH-dependent kinetics fundamentally constrain AA-UA quantification. Complementary work integrating UA-selective interfaces within broader sweat-sensing arrays reinforced that effective AA-UA monitoring requires precise control of potential windows and interfacial chemistry to maintain signal fidelity during dynamic sweat secretion. A

wearable, epidermal microfluidic platform was designed for simultaneous multimodal sweat analysis, combining electrochemical sensing with programmable colorimetric assays for continuous and multiplexed detection of metabolites [169]. On-body tests during exercise demonstrate time-resolved sweat biomarker profiles with both colorimetric and electrochemical readouts, illustrating how hybrid detection modalities can enhance real-time interpretability across analyte classes (Fig. 14). Such hybrid approaches suggest that combining orthogonal detection modalities can partially decouple electrochemical interference, offering a pathway to improved robustness in complex sensing environments. Collectively, these studies establish simultaneous AA and UA sensing as an analytical stress scenario that exposes fundamental limits of electrochemical specificity in wearable sweat sensors, emphasizing the need for interface-stabilization and contextual correction strategies over isolated analyte optimization, particularly under conditions where multiple redox-active species compete within overlapping potential windows.

More broadly, AA and UA sensing highlights the fundamental limitations of direct electrochemical detection in complex biofluids. Together, studies on electroactive small molecules such as urea, AA and UA illustrate that real-time on-body sweat sensing is governed less by intrinsic detection sensitivity than by interfacial stability and analytical control under dynamic physiological conditions. For AA and UA, both intrinsically electroactive species, reliable monitoring is limited by redox interference, electrode fouling, and matrix-induced signal distortion arising from coexisting electroactive species in sweat. In contrast, urea is not directly electroactive and is typically detected through indirect electrochemical strategies, presenting complementary challenges related to weak signal transduction, susceptibility to background drift, and strong dependence on local sweat chemistry. Together, these analytes span three distinct electrochemical sensing regimes: non-electroactive species requiring indirect detection (urea), electroactive but fouling-prone species (AA), and electroactive species constrained by signal overlap and resolution (UA). Across all three analytes, sensing performance is therefore dictated by the ability to maintain stable electrode responses, suppress cross-reactivity, and withstand continuous exposure to complex sweat matrices during prolonged wear. Consequently, urea, AA and UA serve as stringent analytical benchmarks for evaluating selectivity, fouling resistance, and signal robustness in wearable electrochemical sweat sensors, underscoring that dependable on-body operation depends more on managing dynamic sweat chemistry

rather than achieving low detection limits alone. In this context, AA and UA illustrate that the primary bottleneck in wearable electrochemical sensing is not the ability to detect an analyte, but the ability to maintain selective and stable signal attribution over time. Future advances will therefore depend on integrated strategies that combine interfacial stabilization, real-time contextual correction, and multimodal sensing to overcome the intrinsic limitations revealed by these model analytes. The electrochemical comparison performances of the sensors discussed in this section are shown in Table 3.

5.4. Electrochemical transduction strategies for electrolytes in sweat

Electrolytes constitute one of the most extensively investigated classes of analytes in wearable sweat sensing because of their relatively high concentrations and direct physiological relevance to systemic fluid balance and thermoregulation [141]. The principal ions present in eccrine sweat include sodium (Na^+), potassium (K^+), and chloride (Cl^-), which originate from plasma filtration into the sweat gland secretory coil followed by partial reabsorption within the sweat duct. This reabsorption process is tightly regulated by epithelial ion transport proteins, resulting in sweat electrolyte concentrations that reflect both glandular function and whole-body electrolyte status. Consequently, sweat electrolyte monitoring has long been used in clinical contexts, most notably for the diagnosis of cystic fibrosis through elevated sweat chloride levels, while variations in sodium and potassium concentrations are also associated with dehydration, electrolyte imbalance during prolonged physical activity, and disorders affecting renal or endocrine regulation of salt balance [46]. Because of these physiological connections, electrolyte monitoring represents a foundational component of wearable sweat analysis systems designed to assess hydration status, electrolyte depletion during exercise, and broader physiological homeostasis [170].

From an electrochemical perspective, electrolyte detection differs fundamentally from the sensing strategies used for redox-active metabolites or enzyme-mediated biomarkers. Rather than relying on oxidation-reduction reactions, most wearable electrolyte sensors operate through potentiometric ion-selective electrode (ISE) architectures, in which polymeric membranes containing selective ionophores generate a potential proportional to the activity of the target ion. This potential response follows the Nernstian relationship, allowing direct quantification of ion concentrations within the millimolar ranges typical of sweat [171]. To enable integration into wearable platforms,

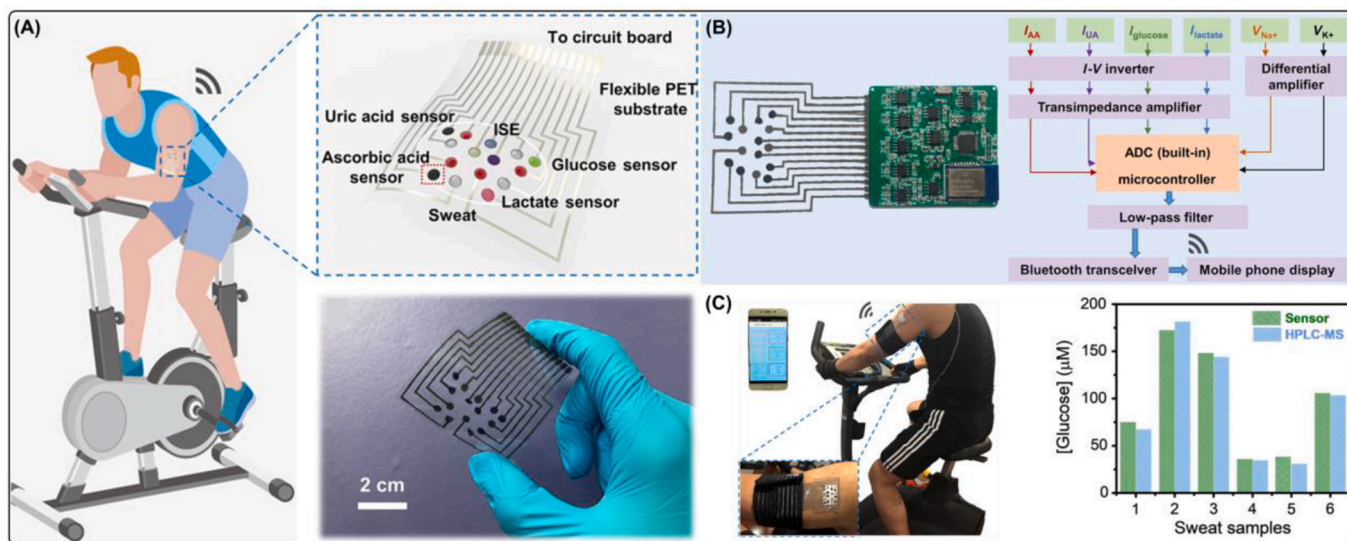


Fig. 14. (A) Schematic illustration, sensor array and photograph of the sweat analysis patch. (B) Photograph and schematic representation of the sweat patch integrated with an electronic circuit and its block diagram. (C) On-body real-time analysis on a volunteer and its obtained data comparison with the conventional technique. Reproduced with permission from Ref. [167].

Table 3

Electrochemical sensor performances toward small-molecule markers in native sweat.

Sensors	Analytes	Linear range (μM)	LOD (μM)	Sensitivity ($\mu\text{A mM}^{-1} \text{cm}^{-2}$)	In vivo Duration (min.)	Validation Method	Ref.
CNT-GNTs/PEDOT-urea	Urea	$1000 - 1 \times 10^5$	100	-	-	-	[150]
Carbon ink	Urea	$5000 - 2 \times 10^5$	-	-	-	-	[151]
CNT/PB	Urea	$6500 - 2 \times 10^5$	1300	31.4 [#]	-	HPLC	[152]
SBMA/PEG/AgNPs-MoS ₂	AA	0.5 – 300	0.12	-	-	ELISA	[154]
RhC/AAOx	AA	0 – 1000	-	-	-	-	[155]
Phytic acid-modified PANI	AA	0.5 – 500	0.17	665.5	-	-	[156]
CuMOF/PEDOT	AA	0 – 100	0.76	725.7	30	HPLC-HRMS	[157]
rGO/N-doped mesoporous carbon/PtNPs/UAO	UA	0 – 500	3.208	103.2	-	Commercial colorimetric kit	[161]
SPE/MXene/GNPs	UA	10 – 70	0.854	0.75 [*]	-	-	[162]
PyTS/MXene	UA	5 – 100	0.48	-	-	Commercial UA kit	[163]
GCE/Cu-MOR/Taurine	UA	0.08 – 1000	0.04	-	-	HPLC	[164]
Silk-N-CT	AA	20 – 300	1	22.7 [*]	-	-	[167]
Silk-N-CT/Pt	UA	2.5 – 115	0.1	196.6 [*]	-	-	[167]
SPE/M-HG/NS-TiO ₂	AA	1 – 2200	0.25	20780	-	-	[168]
	UA	0.25 – 225	0.14	36900	-	-	[168]
Porous Graphene	AA	60 – 1000	11.3	160	-	HPLC	[169]
	UA	3 – 200	0.28	6490	-	-	[169]

AAOx - ascorbate oxidase; AgNPs – silver nanoparticles; Cu-MOR – Cu-Mordenite; ELISA – enzyme-linked immunosorbent assay; HPLC - high-performance liquid chromatography; HRMS – high-resolution mass spectrometry; M-HG - MXene with N, S co-doped holey graphene; N-CT - N-doped carbon textile; NS-TiO₂-N, S co-doped TiO₂; PANI – polyaniline; PEG - polyethylene glycol; PtNPs - platinum nanoparticles; PyTS - 1,3,6,8-pyrene tetra sulfonic acid sodium salt; RhC - rhodium-metalized carbon electrode; SBMA - sulfobetaine methacrylate; SPE - screen printed electrode; UAO - urate oxidase. * - nA μM^{-1} ; # - mV dec^{-1} .

contemporary devices commonly employ solid-contact ion-selective electrodes, where conductive intermediate layers such as conducting polymers, carbon nanomaterials, or metal nanostructures mediate ion-to-electron transduction while eliminating the internal liquid electrolyte reservoirs required in conventional laboratory ISEs. These solid-contact configurations improve mechanical robustness and allow electrolyte sensors to be fabricated on flexible substrates compatible with epidermal wear [24].

Electrolyte sensing modules are frequently incorporated into integrated wearable sweat analysis systems, where arrays of ISEs are combined with electrochemical sensors for metabolites such as glucose, lactate, or UA. Within these multiplex platforms, electrolyte measurements serve both as independent physiological markers and as contextual parameters that help interpret variations in sweat composition [172]. For example, sodium and chloride concentrations provide insight into sweat secretion dynamics and hydration state, which can influence the apparent concentration of co-secreted metabolites during prolonged monitoring [46]. In this way, electrolyte sensing plays an important role not only in assessing ionic balance but also in supporting the broader analytical framework of real-time sweat biosensing.

Given the maturity of this field, numerous dedicated reviews have already examined the materials, device architectures, and wearable implementations of sweat electrolyte sensors in detail [24,46,141,170–172]. Therefore, rather than attempting to exhaustively catalog the extensive body of literature, this section emphasizes the underlying electrochemical transduction principles and the role of electrolyte sensing within integrated wearable systems. Collectively, these studies demonstrate that electrolyte monitoring forms a central and well-established component of wearable sweat sensing technologies, providing physiologically meaningful information that complements the detection of metabolites, hormones, and other biochemical markers in non-invasive continuous monitoring platforms.

6. Passive sweat and low-flux on-body monitoring

While many wearable sweat studies relied on exercise-induced perspiration, recent advances have expanded electrochemical monitoring toward passive or low-rate sweating conditions that occur during sedentary or daily activities. Passive sweat may arise from basal thermoregulation, emotional stimuli, or engineered extraction approaches such as osmotic or iontophoretic stimulation. Compared with exercise-

driven secretion, passive sweating typically generates significantly lower flux, often in the microliter per hour range, imposing stringent constraints on sample volume, evaporation control, and transport kinetics [50]. Recent developments in wearable microfluidic systems and sweat harvesting strategies have begun to address these challenges by enabling efficient collection and transport of extremely small sweat volumes through capillary-driven microchannels, bio-inspired collectors, or discretized droplet sampling architectures capable of handling nanoliter-scale secretions [173,174]. Such approaches aim to maintain continuous analyte delivery to the sensing interface even under minimal sweat flux conditions. Representative studies have demonstrated the feasibility of biomarker monitoring under passive or minimally stimulated sweating conditions using integrated electrochemical sensing platforms. Wearable microfluidic patches and flexible sensing arrays have reported detection of physiologically relevant analytes such as glucose, lactate, and electrolytes through efficient sweat collection interfaces and optimized transport pathways [175–177]. Additional wearable electrochemical systems have further illustrated real-time sweat metabolite detection by combining microfluidic transport with integrated sensing architectures capable of operating with limited sample volumes [159,178,179].

However, low-flux environments introduce distinct analytical challenges. Reduced dilution may increase apparent analyte concentration, yet evaporation-driven enrichment, delayed transport to the sensing interface, and accumulation at the skin surface can distort signal interpretation. Under these conditions, diffusion and transport effects can become comparable to convective flux in microchannels, further complicating accurate quantification of sweat composition. Consequently, passive sweat sensing places heightened demands on ultra-low baseline drift, minimized sample consumption, and stable electrode-sweat interfaces. Importantly, passive sweat sensing does not eliminate the non-equilibrium nature of sweat; rather, it shifts the dominant sources of variability from dilution effects toward transport limitations, diffusion-controlled delivery, and surface interactions at the sensing interface. Accordingly, real-time monitoring and contextual correction remain essential to ensure physiologically meaningful interpretation under both active and passive sweating conditions. The development of passive sweat platforms, therefore, extends wearable electrochemical sensing beyond exercise scenarios while reinforcing the need for rate-aware analytical frameworks that explicitly account for sweat flux, transport dynamics, and evaporation effects during on-body monitoring.

7. Challenges in real-time on-body electrochemical sweat sensing

Despite substantial progress in wearable electrochemical sweat sensors, translating laboratory-scale demonstrations into analytically reliable, real-time on-body measurements remains a central challenge. Unlike artificial or collected sweat systems, human sweat constitutes a dynamic, spatially heterogeneous, and physiologically coupled matrix whose composition evolves continuously during wear. As demonstrated across the diverse analyte classes discussed in this review, the primary limitations of sweat sensing arise not from insufficient sensitivity but from difficulties in interpreting electrochemical signals within this non-equilibrium environment. The following subsections discuss the recurring analytical challenges that constrain data reliability and physiological meaning in real-time sweat electrochemistry.

i) Sweat pH variability and signal interpretation

Sweat pH is a critical contextual parameter that influences the electrochemical response of nearly all wearable sweat sensors. Local pH variations originate from sweat rate, glandular secretion mechanisms, skin buffering capacity, and environmental exposure, and can fluctuate substantially during continuous on-body operation. These variations directly modulate enzyme kinetics, redox potentials, charge-transfer resistance, and baseline stability. Across studies targeting glucose, lactate, urea, AA and UA, uncorrected pH fluctuations frequently manifest as apparent signal drift or peak shifts unrelated to true physiological changes [180,181]. Consequently, sweat pH functions as an independent biomarker and more as a governing contextual variable that determines analytical fidelity. Recent wearable platforms have addressed this challenge through integrated pH sensing and algorithm correction, enabling real-time compensation of enzymatic activity and redox potential shifts, while differential sensing and pH-robust electrocatalysts further enhance signal stability under variable conditions [180, 182,183]. A viable solution, therefore, lies in treating pH as a compulsory co-measured analytical variable, enabling real-time signal normalization through either pH-corrected calibration functions or sensor architectures designed to operate within pH-invariant electrochemical windows.

ii) Sweat rate, transport dynamics, and dilution effects

Unlike blood or interstitial fluid, sweat is secreted intermittently and undergoes surface transport prior to interaction with the sensing interface. Variations in sweat rate introduce complex dilution, accumulation, and evaporation effects that obscure the relationship between measured concentration and underlying physiological state. At low sweat rates, analytes may accumulate locally, while higher secretion rates can dilute concentrations despite increased metabolic flux. This ambiguity is particularly pronounced for metabolic markers such as glucose and lactate, where electrochemical signals often reflect secretion and transport dynamics rather than systemic concentration changes [184, 185]. Quantification of sweat rate in wearable studies is most commonly performed through microfluidic volumetric tracking, in which calibrated channel geometries or collection reservoirs allow estimation of secreted volume over time, thereby enabling calculation of local sweat flux. Representative epidermal microfluidic systems have demonstrated this approach by tracking the progression of sweat within predefined microchannels to determine secretion rates *in situ* [186]. Some platforms further integrate flow-rate sensing modalities, including optical, colorimetric, or impedance-based readouts, to dynamically monitor channel filling and infer real-time secretion rates. In controlled laboratory settings, gravimetric approaches based on mass change over a defined skin area are also used, although these provide average rather than continuous measurements. Importantly, most wearable platforms quantify local sweat rate at a specific anatomical site, which may not

reflect whole-body secretion or systemic metabolic flux [187]. Variations in gland density, skin temperature, motion, and environmental humidity further introduce spatial and temporal heterogeneity [40]. Consequently, analyte concentrations measured at the skin surface often reflect a complex interplay of secretion rate, dilution effects, and transport delays within the microfluidic pathway, highlighting that reliable physiological interpretation of electrochemical sweat sensing requires simultaneous sweat-rate normalization.

To mitigate these effects, recent wearable systems incorporate microfluidic interfaces that actively regulate sweat collection, routing, and delivery to the sensing electrodes [188–190]. The design principles of sweat microfluidics, including channel geometry, capillary-driven flow, hydrophilic surface modification, and controlled reservoir volumes, govern sweat residence time, mixing behavior, evaporation control, and response latency. By isolating freshly secreted sweat, minimizing back-diffusion and contamination from previously accumulated fluid, and enabling sweat-rate estimation or volume tracking, microfluidic architectures improve temporal resolution and reduce transport-induced artifacts. Time-resolved sampling and controlled flow pathways, therefore, enhance measurement reproducibility and enable partial normalization of dilution effects, although spatial heterogeneity and dynamic secretion variability remain influential under real-world conditions. These developments underscore that sweat sensing reflects a convolution of secretion, dynamics, transport phenomena, and electrochemical transduction processes rather than analyte concentration alone, and that microfluidic design constitutes an analytical component governing signal fidelity rather than merely a fluid-handling accessory.

iii) Matrix effects and electrochemical interference

Human sweat contains a complex mixture of electrolytes, metabolites, and redox-active species that collectively impose substantial matrix effects on electrochemical measurements. Small electroactive molecules such as AA and UA exemplify this challenge, as their oxidation potential often overlaps with that of other endogenous species and are sensitive to local chemical conditions [191]. Concurrently, fluctuations in ionic strength and chloride concentration modulate electrode double-layer properties, influencing both amperometric and potentiometric responses. These matrix effects are exacerbated under on-body conditions, where skin contaminants, motion, and prolonged exposure contribute to signal instability. Recent efforts to address matrix interference emphasize selective membranes, electrocatalytic materials, molecularly selective coatings, and multi-modal sensing approaches that improve discrimination and interference tolerance in complex sweat environments [26,192–194]. Nevertheless, maintaining selectivity during prolonged exposure remains an ongoing analytical challenge.

iv) Calibration, inter-individual variability, and physiological context

A persistent limitation in wearable sweat sensing is the absence of universal calibration frameworks that account for inter-individual physiological variability. Sweat composition varies widely across individuals due to differences in hydration status, diet, fitness level, sweat gland density, and thermoregulatory response [195]. As a result, absolute analyte concentrations measured at the skin surface cannot be directly interpreted without contextual information [196]. Many real-time studies consequently emphasize subject-specific trends rather than absolute values, highlighting the need to transition from static, single-point calibration toward adaptive and personalized analytical approaches. Emerging approaches address this limitation through personalized baselines, adaptive calibration models, and data-driven correction strategies, including machine-learning-assisted regression that incorporates contextual variables such as sweat rate, pH, and temperature [78,182,183]. In addition to data-driven correction strategies, several wearable sensing platforms have incorporated contextual calibration approaches designed to compensate for fluctuations in sweat

chemistry during on-body operation [197,198]. These systems measure metabolites alongside physicochemical parameters such as pH and electrolyte composition, enabling signal normalization that accounts for variations in ionic strength and local chemical environment. Integrated wearable platforms capable of simultaneous monitoring of metabolites and electrolytes have demonstrated improved interpretability by correcting electrochemical responses for sweat composition variability. More recently, self-calibrating sensing architectures, including hydro-voltaic or proton-reservoir-based sensing arrays, have been proposed to dynamically stabilize sensor response and mitigate baseline drift during multiplex sweat analysis [199]. Such strategies highlight the increasing recognition that accurate real-time sweat sensing requires not only sensitive transducers but also calibration frameworks capable of compensating for dynamic matrix effects inherent to sweat secretion. While individualized calibration improves physiological relevance, universal cross-user comparability remains constrained by inherent biological variability. Emerging machine learning and neural network-based analytical frameworks are being explored to address drift, nonlinear interference, and inter-individual variability in continuous sweat monitoring [200]. By integrating contextual parameters such as pH, sweat rate, and temperature, these approaches enable adaptive regression and personalized baseline correction. However, their effectiveness remains fundamentally dependent on robust electrochemical signal stability and physiologically grounded validation.

v) Long-term stability and on-body operation

Continuous real-time sweat sensing requires sustained operation under mechanically and chemically demanding conditions. Prolonged skin contact exposes electrodes to biofouling, mechanical deformation, and fluctuating hydration, all of which degrade signal stability [201]. Enzyme-based sensors face additional challenges related to enzyme denaturation and leaching, while non-enzymatic systems must contend with surface passivation and baseline drift [202]. Motion-induced artifacts and variable skin-sensor contact further complicate long-term measurements, reinforcing that durability and stability represent analytical challenges intrinsic to wearable electrochemical operations rather than purely engineering considerations [203]. Material selection further modulates these stability constraints. Advanced electrode platforms, including carbon nanomaterials, metal nanostructures, conductive polymers, and emerging two-dimensional materials, are often introduced to enhance sensitivity and interfacial kinetics; however, their real-world performance during prolonged on-body operation is governed by resistance to oxidation, biofouling, mechanical fatigue, and sweat-induced surface degradation [204–206]. Highly porous or reactive materials may accelerate adsorption of proteins and salts, leading to progressive attenuation of charge-transfer kinetics, whereas mechanically compliant carbon or polymer composites may offer improved durability but different drift characteristics over time [207,208]. Consequently, material platforms should be evaluated not only by intrinsic sensitivity but also by their influence on temporal signal evolution, interfacial robustness, and skin compatibility under dynamic physiological conditions.

Recent efforts have begun to address biofouling through material and interface engineering strategies with demonstrated long-term efficacy. Surface modification approaches, including antifouling polymer coatings (e.g., PEGylation or zwitterionic layers), permselective membranes such as Nafion or polyurethane barriers, and hydrogel-based encapsulation, have been shown to reduce protein adsorption and mitigate salt-induced surface passivation during extended sweat exposure [36,58,141,209]. In enzyme-based systems, crosslinked matrices and protective diffusion layers have been employed to limit enzyme leaching and preserve catalytic activity over several hours of continuous wear. Additionally, microfluidic isolation of fresh sweat from previously

exposed sensing regions has been demonstrated to reduce accumulation-driven fouling effects. Although these approaches have improved operational stability in controlled on-body trials, truly long-term antifouling performance under repeated wear and variable physiological conditions remains an open challenge requiring systematic evaluation and validation.

vi) Effect of strain

Mechanical deformation during wearable operation, including bending, stretching, and twisting, introduces additional analytical variability in electrochemical sweat sensors. Strain can alter electrode geometry, modify skin-sensor contact impedance, induce microcracking in functional layers, and disrupt enzyme immobilization matrices, collectively affecting charge-transfer kinetics and baseline stability. While many studies report bending-cycle durability, few systematically evaluate strain-induced shifts in sensitivity, drift behavior, or impedance evolution under continuous on-body conditions. Recent designs employing serpentine conductors, stretchable composites, and strain-isolating architectures demonstrate improved signal stability under deformation, highlighting the importance of mechanically compliant interface engineering [210–212]. From an analytical perspective, mechanical robustness should be assessed not solely by structural integrity, but by preservation of electrochemical response stability under physiologically relevant deformation. Integrating mechanically compliant materials with strain-tolerant interfacial architecture remains essential to ensure reliable signal interpretation during real-world wear.

vii) Standardization and validation

The translation of wearable sweat electrochemistry from proof-of-concept demonstrations to robust real-world applications will depend not only on sensor performance but also on the establishment of standardized protocols and validation frameworks. Recognizing this need, several groups have begun to emphasize harmonization of experimental conditions, reporting standards, and cross-platform comparability [50, 53,213]. For example, standardized artificial sweat formulations spanning physiologically relevant pH, ionic strength, and metabolite concentrations have been proposed to benchmark sensor performance in a reproducible manner across laboratories [22,48,214]. Efforts to co-register sweat data with reference physiological measures, such as blood analyte levels or established clinical assays, are emerging as important validation metrics [213]. Despite these emerging efforts, rigorous validation of wearable sweat sensors against established gold-standard analytical methods remains limited and inconsistent across the literature. While several studies report promising on-body performance, direct quantitative comparison with conventional techniques, such as blood analysis, is often absent or performed under controlled, off-body conditions that do not fully replicate the dynamic physiological environment encountered during continuous wear. As a result, the analytical accuracy of many reported sensors under real on-body conditions remains difficult to assess in a standardized and comparable manner. Importantly, this limitation is not solely due to experimental constraints but also reflects fundamental differences between sweat and conventional biofluids. Sweat is a non-equilibrium medium in which analyte concentrations are governed by secretion dynamics, diffusion delays, and partial reabsorption within the sweat gland, leading to temporal lag, dilution effects, and inter-individual variability. Consequently, even when comparisons with gold-standard methods are attempted, observed discrepancies may arise from physiological transport processes rather than intrinsic sensor inaccuracy. Therefore, current wearable electrochemical sensors are more reliably suited for capturing intra-individual trends and dynamic physiological changes rather than providing absolute quantitative equivalence with

Multiphysical & Operational Influences on On-Body Sweat Sensing

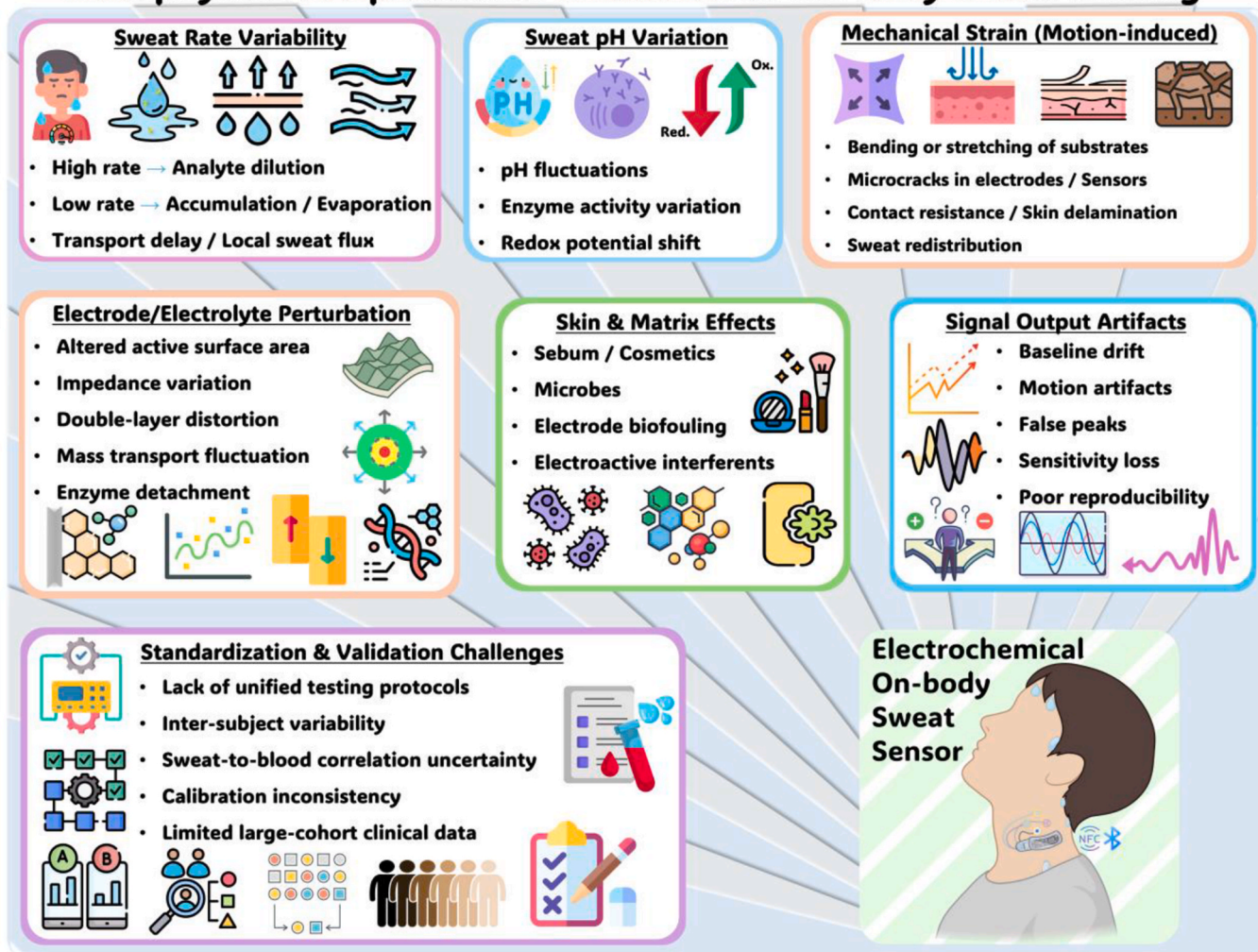


Fig. 15. Schematic illustration of key multi-physical and operational parameters influencing real-time on-body electrochemical sweat sensing. The icons used in this figure were adapted from www.flaticon.com.

traditional clinical assays. Establishing robust validation frameworks that integrate real-time on-body measurements with parallel gold-standard analysis, while incorporating contextual parameters such as sweat rate, pH, and temperature, will be essential for improving the translational reliability of sweat-based sensing technologies.

In addition, multi-device comparisons under controlled exercise protocols have begun to illuminate variability arising from device design, skin contact mechanics, and wear-site selection [215]. These early initiatives reflect a growing recognition that inter-laboratory validation and standardization reporting are essential for meaningful comparison of wearable sweat technologies, enabling researchers to assess analytical reliability, reproducibility, and physiological interpretability across studies. As the field matures, concerted community efforts, including consensus guidelines for testing, data sharing practices, and validation against gold-standard measures, will be necessary to establish wearable sweat sensing as a credible modality in personalized health monitoring.

The analytical behavior of wearable sweat sensors is ultimately governed by fabrication-structure-property-performance relationships that dictate interfacial stability and mass transport under on-body conditions [216]. Fabrication strategies such as printing, electrodeposition, laser patterning, and templated growth define electrode morphology,

porosity, thickness, and mechanical compliance. These structural attributes regulate electroactive surface area, wettability, enzyme immobilization environments, and susceptibility to protein and salt adsorption during continuous sweat exposure [217,218]. Highly porous nanostructures and framework materials enhance analyte accessibility and signal magnitude, yet their large surface area and chemical reactivity accelerate biofouling and charge-transfer attenuation over time [207, 208]. Conversely, dense metal or oxide films offer superior electrochemical stability but may compromise mechanical conformity, increasing motion-induced contact artifacts [219,220]. Similarly, membrane architecture and microfluidic geometry control analyte transport, residence time, and dilution, thereby shaping temporal response and physiological interpretability [221]. Recognizing these interconnected relationships shifts sensor optimization from maximizing sensitivity alone toward balancing transport efficiency, fouling resistance, mechanical compliance, and interfacial stability for reliable real-time operation. Many of the recurring limitations discussed in this section originate from fabrication-dependent structural features that govern interfacial chemistry and mass transport. Electrode porosity, membrane architecture, and microfluidic geometry collectively influence analyte flux, fouling susceptibility, dilution effects, and signal drift. Establishing fabrication-structure-property relationships is therefore

essential for designing wearable sweat sensors capable of maintaining analytical reliability under dynamic physiological conditions. These interconnected multi-physical and operational factors collectively govern the analytical performance of electrochemical sweat sensors during real-time on-body operation and often lead to signal variability and drift, as schematically illustrated in Fig. 15.

8. Future prospects and outlook

The evolution of real-time on-body electrochemical sweat sensing is increasingly shifting from isolated sensor development toward integrated and intelligent physiological monitoring systems. As highlighted throughout this review, the primary barriers to translation are not limited to analyte detectability, but rather arise from contextual ambiguity, signal drift, and inter-individual variability inherent to sweat as a dynamic biofluid. Addressing these challenges will require future wearable platforms to move beyond single-analyte readouts and toward multi-layered analytical architectures combining chemical sensing, contextual monitoring, and adaptive data interpretation. A key future direction lies in the convergence of electrochemical sweat sensors with artificial intelligence (AI) and machine learning (ML) frameworks. Data-driven models offer a powerful means to disentangle analyte-specific signals from confounding influences such as sweat rate, pH fluctuations, motion artifacts, and environmental variation. Rather than relying on static calibration curves, ML-enabled systems can learn subject-specific baselines, recognize physiological patterns, and dynamically adjust signal interpretation in real-time. Importantly, AI-assisted interpretation complements electrochemical sensing by extracting physiologically meaningful information from complex multidimensional signal streams rather than replacing the sensing interface itself.

Emerging studies already demonstrate the potential of such approaches. For example, ML-assisted analysis has improved prediction accuracy in perspiration-driven lactate sensing under fluctuating sweat rates and motion artifacts [222]. Similarly, neural-network-based correction strategies have been applied to separate target signals from environmental and fouling-induced drift during continuous UA monitoring [223], while ML-based interpretation of electrochemical impedance responses has been explored for hormone sensing platforms [224]. As wearable sweat sensing evolves toward multiplexed and longitudinal monitoring, ML-assisted modeling is expected to enable multi-analyte deconvolution, adaptive baseline correction, and individualized physiological profiling, transforming raw electrochemical signals into actionable health insights. Integration of sweat sensing with digital health infrastructure further expands the potential impact of wearable electrochemical systems. Wireless connectivity enables continuous data transmission, longitudinal data aggregation, and remote physiological monitoring. When combined with multimodal physiological inputs such as heart rate, motion, and temperature, these platforms can support predictive modeling, early anomaly detection, and personalized health trajectories rather than isolated concentration measurements. Such integration positions sweat sensing within a broader ecosystem of continuous and personalized healthcare monitoring.

An important extension of these developments is the potential integration of sweat sensing within closed-loop health management systems. In such architectures, continuous biochemical monitoring would not only provide diagnostic insight but also inform automated or semi-automated interventions, including hydration management, electrolyte replenishment, metabolic regulation, or personalized behavioral guidance. While closed-loop control has been successfully demonstrated in glucose monitoring using interstitial fluid, translating this paradigm to sweat-based sensing presents unique analytical challenges. Sweat analyte concentrations are influenced not only by systemic physiology but also by secretion rate, transport dynamics, evaporation, and skin-sensor interactions, creating time lags and nonlinear relationships with

circulating biomarkers. Without appropriate correction, these factors could lead to erroneous feedback decisions. Consequently, reliable closed-loop sweat monitoring will require multi-parameter contextual sensing, individualized calibration frameworks, and predictive analytics capable of distinguishing true physiological changes from secretion-driven artifacts.

While advances in data interpretation and system integration are critical, the long-term success of wearable sweat sensing will ultimately depend on robust analytical performance under real-world physiological conditions. A single universal metric cannot define performance requirements for wearable sweat sensors, as analytical priorities vary with the physiological target and monitoring context. Although sensitivity and limit of detection are frequently emphasized, real-time on-body applications often demand broader evaluation criteria, including response time, operational stability, drift resistance, mechanical durability, and tolerance to matrix interference. For electrolyte monitoring (e.g., Na^+ , K^+ , Cl^-), sensors must maintain long-term potential stability and minimal drift under fluctuating ionic strength and temperature. On the other hand, metabolic biomarkers such as glucose and lactate require rapid response and reliable performance across dynamic sweat rates, where transport and dilution effects dominate signal interpretation. Stress-related and neurochemical markers, often present at low concentrations, necessitate enhanced selectivity and interference suppression rather than extreme sensitivity alone. During prolonged wearable use, resistance to biofouling, mechanical deformation, and hydration variability becomes more critical than nominal detection limits. Accordingly, appropriate performance metrics must align sensor characteristics with physiological dynamics, sweat secretion behavior, and intended monitoring duration. Future device development will therefore increasingly focus on long-term interface stability, antifouling materials, and self-diagnostic sensor architectures capable of autonomous operation during extended wear. Advances in microfluidic control, self-calibrating architectures, fouling-resistant interfaces, and energy-efficient electronics will be essential for sustained operation in real-world environments. Coupling sweat sensing with multimodal physiological monitoring may further improve contextual interpretation and biomarker relevance. Such multimodal integration will support the development of predictive digital health frameworks in which continuous biochemical and physiological data streams are jointly analyzed to identify early physiological deviations and guide personalized interventions.

Although this review primarily emphasizes analytical performance under real-time physiological conditions, future translational success will depend on scalable fabrication, long-term biocompatibility, mechanical durability, and cost-effective manufacturing. Materials and device architecture must therefore be evaluated not only for sensitivity improvements but also for manufacturability and sustained skin compatibility under prolonged wear. As the field matures, the true impact of sweat electrochemistry will be measured not by the number of detectable analytes but by the reliability, interpretability, and clinical relevance of continuous sweat-derived data in real-world healthcare and performance monitoring settings.

CRediT authorship contribution statement

Sairaman Saikrithika: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Laraib Zahra:** Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. **K. Theyagarajan:** Conceptualization, Data curation, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. **Young-Joon Kim:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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