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Microfluidics-Enabled Wearable Biosensing: Materials, Systems, and On-Body Validation

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Abstract

Microfluidic wearables move microliter biofluids across soft, low-impedance interfaces and into stable transducers on skin, enabling time-stamped chemistry without pumps. In this review (2015-2025), we take a system view: how specific fluidic choices (e.g., capillary-burst gating, chronological reservoirs, bubble control) preserve temporal fidelity; how materials and transduction (PEDOT: PSS hydrogels vs. MXene films; electrochemical vs. colorimetry) set bias and signal-to-noise; and how radios/power must follow use-case cadence. Two case studies ground the discussion: a battery-free NFC (near-field communication) sweat patch that couples passive microfluidics with imaging readout (field-tested colorimetric panels) via field-tested colorimetric panels and a large-cohort chloride/sweat-rate program (n ≈ 312 athletes) linking local measurements to whole-body estimates. We argue that agreement-centric validation (Bland-Altman limits, mean absolute relative difference (MARD), concordance) should be stratified by flow, site, and temperature, and we use energy per insight as a pragmatic yardstick to compare architectures by the energy needed for a minute of trusted trend or a defensible threshold call. We close with falsifiable targets for low-flow operation and sequence-sampled hormones and list open practices to make on-body chemistry more reproducible.

Keywords

Wearable Biosensing, Microfluidics, Sweat, Tear, Interstitial Fluid, Biofuel Cell, On-Body Validation

1. Introduction

Wearable, microfluidics-enabled biosensors are transforming on-body chemical monitoring by routing microliter-scale biofluids to stable transducers without external pumps. Compared with "sensor-only" wearables, these lab-on-skin platforms couple capillary architectures with soft, low-impedance interfaces and fit-for-purpose radios, enabling quantitative, minute-level dynamics during real-world motion. The result is a shift from sporadic spot checks to continuous, context-aware readouts that can inform hydration status, metabolic trends, and stress physiology on the move.

This review pursues three aims. First, it clarifies how microfluidic design—capillary-burst valves, chronological reservoirs, bubble management—governs temporal fidelity by ensuring that downstream signals represent fresh, time-stamped samples rather than mixed or evaporatively biased fluid. Second, it links materials and transduction choices (e.g., PEDOT: PSS hydrogels, MXenes; electrochemical vs. optical/colorimetric) to system-level outcomes such as low-bias operation, higher signal-to-noise at low power, and robust wireless coupling (battery-free NFC for episodic panels; buffered Bluetooth Low Energy (BLE) for minute-resolved streaming). Third, it frames validation around agreement-centric metrics (e.g., Bland-Altman bias and limits, MARD, concordance) with flow-aware protocols and lag compensation and proposes energy per insight as a unifying yardstick for comparing architectures by the energy required to deliver a minute of trusted trend or a defensible threshold decision.

To frame system-level trade-offs, we define "energy per insight" (EPI) as the Joules required to yield one unit of clinically interpretable information under on-body conditions—for example, one trusted minute of lag-aware trend meeting MARD/Bland-Altman criteria or a validated threshold decision; lower EPI is better. We use EPI throughout to link fluidics, transduction, and the wireless/power stack (e.g., BLE, NFC) to validation outcomes. See Section 7 for operationalization.

Whereas most prior surveys focus on either materials (e.g., MXenes, PEDOT: PSS) or on specific analytes and modalities in isolation, this review is organized around the system that must operate on skin. We connect microfluidic sampling choices to downstream transduction, to wireless and power budgets (BLE, NFC), and to validation workflows that emphasize agreement over correlation (Bland-Altman bias and limits; MARD). This coupling exposes design trade-offs that device-centric or chemistry-centric reviews rarely quantify, for example, how early-path channel volume sets time-to-first sample and bubble tolerance, how soft, low-impedance interfaces reduce bias and enable lower-power telemetry, and how flow/lag-aware analysis determines whether signals are clinically interpretable. By centering these cross-dependencies, we fill the gap between materials catalogues and analyte-specific appraisals and provide a practical yardstick—energy per insight—to compare architectures by the energy required to deliver a minute of trusted trend or a defensible threshold decision. The goal is not to re-list components, but to show how coherent fluidics-materials-radio-validation packages deliver reliable physiology during real-world motion and heat.

The article is organized to preserve the system view. Section 3 reviews sensing modalities and materials; Section 4 analyzes microfluidic platforms; Section 5 covers wireless/power and packaging; Section 6 details on-body validation; Section 7 compares system archetypes using the energy-per-insight lens; Section 8 consolidates challenges and future directions.

2. Methodology of the Review

2.1. Protocol and Reporting

We followed *PRISMA 2020* guidance for scoping and reporting [1]. A protocol with predefined questions, eligibility criteria, data fields, and analysis plans was finalized before screening and is archived in Supplementary Note S1. No human or animal experiments were conducted for this review.

2.2. Databases and Timeframe

We searched *Web of Science*, *Scopus*, *PubMed*, and *IEEE Xplore* for English-language articles published from January 1, 2015, to August 30, 2025. The final search was executed in August 2025. Reference lists of included studies and key reviews were hand-screened (backward/forward citation chasing).

2.3. Search Strategy

Title/Topic queries combined:

(i) *wearable/epidermal/skin interfaced*.

(ii) fluids & microfluidics: *microfluidic/soft patch/capillary* AND *sweat/tear/ISF* (*interstitial fluid*).

(iii) sensing & system: *electrochemical/optical/colorimetric* plus *NFC*, *battery-free*, *BFC*, *BLE*.

2.4. Eligibility Criteria

We included original, peer-reviewed studies on skin-interfaced wearables targeting sweat/tear/ISF with an explicit microfluidic or fluid-handling strategy and on-body/human measurements with analytical or comparative metrics. Excluded: benchtop-only, animal-only without human confirmation, simulations, perspectives/short communications lacking methods, and non-English. Reviews were background only (≤20% of references). Records were de-duplicated by DOI then normalized title; titles/abstracts and full texts were screened in duplicate. Disagreements were resolved by consensus; inter-rater agreement (Cohen's κ) is reported in Results. Multiple reports of the same device family were consolidated into an index study. Method-comparison accuracy is summarized with Bland-Altman agreement and MARD where applicable [2]-[4].

2.5. Data Extraction

For each study, we extracted: biofluid; analyte(s); modality (enzymatic/non-enzymatic electrochemical; optical/colorimetric); electrode/materials; microfluidic architecture; on-body N and protocol; gold-standard comparator; analytical metrics (limit of detection (LOD)/range, response time); accuracy (MARD, Bland-Altman); and system fields (power: battery/battery-free NFC/BFC/TENG/PV; wireless: BLE/NFC/LoRa (Long Range); duty cycling; form factor).

We adapted QUADAS-2 to engineering diagnostics: adequacy of reference standard, calibration transparency, motion/temperature/sweat-rate handling, sample size/demographics, repeatability, and missing-data reporting [2]. Publication bias was not modeled due to heterogeneity; asymmetries are qualitatively noted.

3. Sensing Modalities & Materials

3.1. Sensing Modalities

Wearable biosensors for monitoring sweat, tears, and interstitial fluid (ISF) rely primarily on electrochemical and optical sensing modalities, which are well-suited for non-invasive, real-time health monitoring.

3.1.1. Electrochemical Sensors

Electrochemical biosensors remain the workhorse for on-skin chemistry because they pair high sensitivity with low power and straightforward integration on flexible platforms. Signals are typically read as current, potential, or impedance changes as target molecules undergo redox or binding events at the electrode interface. For sweat analytes such as glucose and uric acid, PEDOT: PSS-based electrodes provide soft, low-impedance contact and stable transfer charge. A representative PEDOT: PSS hydrogel device for uric acid reports ultrahigh sensitivity with a low detection limit of 1.2 μM, enabling minute-level, non-invasive tracking during daily activities [5] [6]. Beyond enzyme layers, a stretchable composite of gold nanorods (AuNRs) and PEDOT: PSS has demonstrated non-enzymatic detection of levodopa and uric acid in the same patch by exploiting distinct oxidation kinetics. AuNRs supply dense catalytic sites while PEDOT: PSS delivers mixed ionic-electronic transport and mechanical compliance, supporting wide linear ranges and real-time readouts under gentle bias. In practice, selectivity (e.g., against ascorbate), drift under perspiration, and on-patch calibration remain the main constraints, which current designs address with antifouling chemistry and microfluidic preconditioning of sweat [6] [7].

3.1.2. Optical Sensors

Optical biosensing in wearables spans surface plasmon resonance (SPR), fluorescence, and colorimetry, each tuned to a different balance of sensitivity, alignment tolerance, and power budget.

- SPR affords label-free, surface-sensitive readouts but is more susceptible to motion and angular misalignment, thus currently appearing more often in tear interfaces than in high-sweat-rate sites.
- Fluorescence enables multiplexed panels within microchannels and can be imaged by smartphones; photobleaching, autofluorescence, and filter requirements set practical limits for field use.
- Colorimetry pairs naturally with capillary microfluidics: reagents are stored in chronological reservoirs that time-stamp chemistry and can be captured

in a single image, allowing low-cost readouts without continuous telemetry. Recent systems translate this approach to sweat glucose with on-patch volume control and evaporation barriers to stabilize the signal [8] [9].

3.2. Materials for Biosensors

Performance in wearables is set by the entire stack—electrodes, biointerface, substrate, and surface modifications—operating under bending, perspiration, salts, and temperature swings. Materials must keep impedance low while remaining biocompatible and mechanically resilient.

3.2.1. Conductive Polymers (PEDOT: PSS)

PEDOT: PSS provides a conformal, low-impedance interface with mixed conduction and high roughness/area, serving as a scaffold that hosts catalysts, enzymes, or aptamers. In uric-acid and glucose patches, it improves charge transfer on flexible substrates and tolerates cyclic hydration better than brittle metals, which helps maintain signal fidelity during motion [5].

3.2.2. Nanomaterials (Graphene/CNTs/MXenes)

Graphene and carbon nanotube (CNT) networks create percolated electron pathways, while MXenes (e.g., $Ti_3C_2T_x$) add hydrophilicity, large accessible surface, and tunable terminations for probe immobilization. Hybrid films that integrate MXenes with gold nanoparticles (AuNPs) support aptamer-based sensing of stress biomarkers like cortisol in sweat and interface cleanly with microfluidic sampling paths. Key trade-offs include long-term oxidation, surface fouling, and batch-to-batch variability, which are mitigated by encapsulation and controlled functionalization [7] [10].

3.2.3. Gold Nanoparticles (AuNPs)

AuNPs act as nano-anchors for capturing chemistries and enhance electron transfer, boosting both sensitivity and selectivity. In cortisol sensors, aptamers immobilized on Au surfaces transduce conformation changes into measurable electrical or optical signals; placing AuNPs on MXene or polymer scaffolds further amplifies responses while preserving on-skin biocompatibility and flexibility [6] [10].

3.2.4. Flexible Substrates

Polyimide (PI) and poly (ethylene terephthalate) (PET) underpin most high-yield flexible processes—PI for thermal/chemical robustness during microfabrication, PET for low-cost roll-to-roll production. Paper-based laminates offer passive wicking and disposability for sweat sampling; however, moisture-induced drift and mechanical wear necessitate polymer encapsulation and barrier layers in long sessions. Adhesion, sweat-proof sealing, and compatibility with wear adhesives determine whether the sensor can operate reliably beyond controlled lab settings [9].

3.3. Conclusion

Electrochemical and optical biosensors, combined with innovative materials like

MXenes, PEDOT: PSS, and gold nanoparticles, hold significant promise for wearable biosensors in sweat analysis. However, challenges related to sensor stability, sensitivity, and scalability remain. Future research should focus on improving sensor performance, developing non-enzymatic sensing techniques, and enabling scalable production for practical, real-time health monitoring in personalized healthcare.

Table 1 provides an overview of representative on-body biofluid sensing studies, listing each reference's target analytes, sensing modality, transducer type, detection limits, calibration methods, and notable features or findings:

Table 1. Analytes, sensing modalities, and transducers for on-body biofluid sensing.

Ref	Citation (short)	Analytes	Sensing modality	Electrode/Transducer	LOD	Linear range	Calibration method	Interference tested	Notes
[5]	W. Gao, Y. Zhang	Uric	Electrochemical (amperometric)	PEDOT: PSS hydrogel on flexible electrode; microfluidic sweat capture	~1.2 µM (S/N = 3)	—	In vitro calibration (PBS/artificial sweat); on-body compared vs ELISA	—	Wearable microfluidic UA sensor; high sensitivity PEDOT: PSS hydrogel
[6]	W. Zhang, Y. Zhang	Levodopa; Uric	Electrochemical (nonenzymatic voltammetry)	Au nanorods (AuNRs) immobilized in PEG-doped PEDOT: PSS composite; flexible 3-electrode; microfluidic patch	—	—	In artificial sweat; simultaneous L-DOPA & UA measurement	—	Simultaneous monitoring of levodopa and uric acid in sweat
[11]	A. J. Bandodkar, *et al.*	Chloride; pH; Lactate; Glucose; Sweat rate/loss	Colorimetric (imaging) + passive microfluidics; battery-free NFC electronics	Colorimetric reagents in microreservoirs; NFC/BLE readout module	— (colorimetric patches)	Physiological ranges (field-validated)	Smartphone imaging with on-patch color references; volumetric microchannels	—	Underwater-capable; battery-free operation
[12]	A. Koh, *et al.*	Chloride; pH; Lactate; Sweat rate/loss	Colorimetric (imaging) + passive microfluidics	Paper/PDMS microfluidics with colorimetric chemistries	— (colorimetric patches)	Physiological ranges	Smartphone imaging with calibrated color palettes; volumetric readout	—	Capture, store, and colorimetric sensing of sweat on skin
[13]	H. Y. Y. Nyein, *et al.*	Sweat secretion rate (flow); pH; chloride (device-compatible)	Microfluidic flow analysis; colorimetric/EC compatible	Microfluidic channels/reservoirs with valves; optional EC cells	—	—	Device characterized for dynamic secretion rates on-body	—	Chrono-sampling design to track secretion dynamics
[14]	I. Shitanda, *et al.*	Lactate	Electrochemical (amperometric, lactate oxidase) with microfluidics	LOx enzymatic electrode + enlarged reservoir bubble-trap microfluidic	—	~1 - 50 mM (artificial sweat)	In vitro calibration; on-body cycling test; flow-rate independent readout	—	Air-bubble-insensitive design; ~2 h stability demo
[15]	L. B. Baker, *et al.*	Sweat rate; Chloride (Cl^-)	Colorimetric (imaging) + microfluidics	Serpentine microchannels with volumetric dye; chloride colorimetric assay	—	Covers typical [Cl^-] in sweat	Smartphone image processing algorithms; validated in n≈312 athletes	—	Predicts whole-body sweat loss/sodium from local measurements

Continued

[16]	L. B. Baker, *et al.*	Sweat rate; Chloride (imaging)	Colorimetric + ML-based smartphone image analysis	Microfluidic colorimetric reservoirs	—	—	Machine learning-based image detection pipeline for robust readouts	—	Field validation of remote sweat analytics via ML
[17]	J. Tu, *et al.*	Cortisol; Epinephrine; Norepinephrine	Electrochemical immunosensing (SWV) + sequential microfluidics	Gold nanodendrite-decorated laser-engraved graphene (AuND-LEG) immunoelectrodes	Picomolar-level sensitivity (in PBS/sweat)	—	Competitive assay with redox-labeled competitors; valve-timed reagent refresh; validated vs ELISA (serum correlation)	—	Iontophoresis-driven sampling; bursting-valve regulated chrono-sampling
[18]	W. Gao, *et al.*	Glucose; Lactate; Na^+; K^+; Temperature	Electrochemical (amperometric + potentiometric) + microfluidics	Flexible plastic-based sensors integrated with silicon IC for processing	—	Covers physiological ranges	On-body calibration with temperature compensation; multiplexed sensing	—	First fully integrated wearable multiplexed perspiration analysis array
[19]	A. B. Barba, *et al.*	(Platform) Electrochemical sensing of sweat analytes (e.g., cortisol, lactate)	Electrochemical + NFC-powered readout	Flexible epidermal NFC device with integrated three-electrode cell	—	—	Device-level electrical calibration; analyte-specific calibration required	—	Demonstration of flexible NFC epidermal platform for EC sensing
[20]	S. Anastasova, *et al.*	Lactate; Na^+; pH; Temperature	Electrochemical (amperometric LOx + potentiometric Na^+/pH) with microfluidics	IrOx pH; PVC-ISE Na^+ on PEDOT; LOx amperometric with protective membranes	—	Lactate up to ~28 mM	+0.65 V LOx amperometry (in vitro); temp compensation; in vivo exercise tests	Na^+ ISE tested vs K^+, NH^{4+}, Mg^{2+}, Ca^{2+}; lactate selectivity vs glucose/uric/ascorbic acids	Stable sensors (weeks-months); rapid steady-state (~10 s)
[21]	H. Y. Y. Nyein *et al.*	Sweat rate; Chloride; pH; Lactate (via colorimetry)	High-throughput microfluidic colorimetric arrays	Microreservoirs with color reagents; imaging analysis	— (colorimetric)	Physiological ranges	Smartphone imaging with calibration; regional mapping across body sites	—	Enables regional and correlative sweat analysis at high throughput
[22]	W. Park *et al.*	Glucose (tear)	Wireless optical/ electrochemical smart contact lens	Soft smart contact lens with integrated sensor and antenna	—	—	Correlation analysis with blood glucose; basal tears focus; personalized lag time	Mitigates reflex-tear confounding	Demonstrated strong TG-BG correlation in human and animal studies
[23]	M. Parrilla *et al.*		Electrochemical (potentiometric)		—	—	—	—	—
[24]	Y. Katsumata *et al.*	Lactate	Electrochemical sweat lactate sensor	Wearable lactate sensor (details per clinical device)	—	—	Clinical validation via ventilatory threshold (VT); Bland-Altman agreement	—	Prospective HF trial: sLT vs VT difference −4.9 ± 15.0 W; no device-related AEs

Continued

[25]	Yang Y. *et al.*	Uric acid; Tyrosine	Electrochemical (voltammetry)	Laser-induced graphene (LIG)	—	—	—	—	—
[26]	Torrente-Rodríguez R.M. *et al.*	Cortisol	Electrochemical immunoassay	Graphene working electrode	—	—	—	—	—
[27]	Kim J. *et al.*	Ethanol (sweat)	Electrochemical (amperometric, alcohol oxidase) + iontophoresis-induced sweat	All-printed tattoo with AOD enzyme; iontophoresis electrodes	—	—	On-body tests vs breathalyzer; induced sweat sampling	—	Noninvasive alcohol monitoring in induced sweat; wireless readout
[28]	Currano L.J. *et al.*	Lactate	OECT (organic electrochemical transistor)	OECT on flexible substrate	—	—	—	—	—
[29]	He W. *et al.*	Glucose; Lactate; Ascorbic acid; Uric acid; Na^+; K^+	Electrochemical (amperometric + potentiometric)	Carbon textile electrodes (silk-derived)	—	—	—	—	—
[30]	Lin P.-H. *et al.*	Glucose	Electrochemical (enzymatic GOx)	Hydrogel interface + PB-PEDOT: PSS	—	—	—	—	—
[31]	Xuan X. *et al.*	Lactate	Electrochemical (enzymatic)	Integrated microfluidic lactate WE + pH/T sensors	—	—	—	—	—
[32]	Jagannath B. *et al.*	Cytokines (e.g., IL-6, IL-8, TNF-*α*)	Electrochemical immunosensing	Wearable sweat cytokine biosensor platform	—	~0.2 - 200 pg mL^{-1} (analytical range)	Standard curves in buffer/sweat; on-body temporal profiling	—	Demonstrated passive-sweat temporal cytokine profiles
[33]	Nyein H.Y.Y. *et al.*	pH; Cl^-; Levodopa	Electrochemical (ISE + enzymatic); microfluidics	On-patch EC sensors + sweat rate	—	—	—	—	—
[34]	Wang M. *et al.*	Essential amino acids; Vitamins (trace)	Electrochemical (multi-channel)	Arrayed EC sensors	—	—	—	—	—
[35]	Vivaldi F. *et al.*	Uric acid; Tyrosine; pH; Ions	Electrochemical (SWV/impedance)	LIG porous electrodes	—	—	—	—	—
[36]	Emaminejad S. *et al.*	Chloride (CF); Glucose	Electrochemical; microfluidic + iontophoresis	Integrated microfluidic + EC sensors	—	—	—	—	——
[37]	Bandodkar A.J. *et al.*	Glucose (sweat/interstitial via reverse iontophoresis)	Electrochemical (amperometric, glucose oxidase) + reverse iontophoresis	All-printed tattoo; Prussian blue mediator; GOx layer	—	—	On-body proof-of-concept in healthy volunteers; oral glucose challenge	—	First tattoo-based noninvasive glucose monitoring demonstration

Each row corresponds to a literature reference (Ref) and summarizes the device's target analytes, sensing modality, transducer/electrode configuration, limit of detection (LOD), linear range, calibration methods, interference tests, and notable outcomes. These examples highlight the diversity of analytes (metabolites, electrolytes, hormones, etc.) and approaches (electrochemical vs. optical, passive vs. active fluidics) in on-body biosensing.

4. Microfluidic Platforms for On-Body Biofluids

Microfluidic platforms are now central to on-body analysis because they solve three problems that defeat many "sensor-only" wearables: (i) reliable sampling of tiny, intermittent volumes, (ii) temporal fidelity (preventing old/new fluid mixing), and (iii) quantitative transport that decouples the analyte interface from skin motion and evaporation. Compared with direct electrode-on-skin contact, microfluidics cuts down environmental contamination, stabilizes concentration readouts, and allows volumetric analytics in parallel with chemistry [11]. By routing biofluids through millimeter-scale collectors and sealed microchannels that are only hundreds of micrometers across, a patch can meter, timestamp, and deliver sweat (and, by extension, ISF/tears in analogous designs) to electrochemical or colorimetric modules for analysis—without external pumps and with minimal power [12].

4.1. Architectures, Materials, and Skin Mechanics

A typical device comprises a skin-adhesive inlet, a shallow collector that sits above active sweat pores, and a network of capillary-driven channels embedded in polydimethylsiloxane (PDMS) and/or thin polymer laminates such as PI/PET, all sealed under an elastomeric cover [12]. Stacks are engineered for conformity (to avoid dead zones and leakage) and breathability (to minimize maceration during long wear). Hydrophilic treatments in the first receiving chamber reduce priming lag; capillary-burst valves (CBVs), hydrophobic vents, and siphon-like segments modulate flow direction and sequence, making it possible to stage multiple tests with controlled ordering [12] [13]. The channel cross-sections used in human studies often fall near hundreds of micrometers; a representative patch routes sweat through ~600 μm × 200 μm channels with a single-channel hold-up volume ≈ 14 μL, enough for ~50 minutes of continuous measurement at common exercise rates [13]. Laminated serpentine interconnects and soft encapsulants preserve electrical/mechanical integrity under bending and shear while keeping the fluids isolated from environmental air (evaporation) and debris.

4.2. Colorimetric vs. Electrochemical Readouts (Many Patches Do Both)

Colorimetric. Dried reagents are stored in micro-reservoirs (typical volume = V_{res} = 0.3 - 2.0 μL each). The fill order encodes time; contaminated cells or air ingress are visible to the user [12]. With smartphone imaging (8-bit/channel), semi-quantitative readouts are obtained for pH 4.5 - 7.5, lactate 5 - 25 mM, chloride 20 - 100 mM, and glucose 0.1 - 1.0 mM when illumination is controlled; coefficient of variation commonly targets < 10 - 15%. Sweat rate follows directly from reservoir pitch and fill time:

$$J_{sweat} = \frac{nV_{res}}{A\Delta t_{fill}}\left[\mu\text{L}\,\text{min}^{-1}\,\text{cm}^{-2}\right]$$

Example: five 1 μL cells filling over 10 min on a 4 cm^2 patch gives a sweat rate of 0.125 μL·min^{-1}·cm^{-2} $\left(\frac{5\ \mu L}{10\ min} \middle/ 4\ cm^2\right)$. Total sweat loss for that interval is ≈5 μL (≈5 mg) assuming dilute sweat. Colorimetry remains zero-power at the patch; imaging can be triggered in a tap-to-read NFC session.

Electrochemical. Amperometric, potentiometric/ISE, and impedimetric modes sample 1 - 10 Hz continuously. For ion-selective electrodes, the Nernst slope is ≈ 59 mV/decade at 25˚C; drift arises from ionic-strength changes and temperature. Typical on-skin working ranges include Na^+/K^+/Cl^-: 10 - 150 mM, lactate: 1 - 25 mM, glucose: 50 - 1000 μM; lactate/glucose LoDs in flexible stacks are commonly ≤ 100 μM with appropriate baseline stabilization. Robust operation requires bubble control and stable reference (e.g., solid-state Ag/AgCl) and benefits from channel features that keep gas away from the working electrode by 100 - 500 μm (restrictors, vents, offsets).

Hybrid lanes. Many patches route the same sample into colorimetric lanes (robust, battery-free snapshots) and electrochemical lanes (minute-scale dynamics via BLE/NFC-powered readout) [11] [13]. The pairing enables cross-checks (e.g., chloride by ISE vs. color cell) and reduces user burden (quick visual sanity check + detailed traces).

4.3. Real-Time Flow Sensing and Bubble Management

Flow sensing. Thermal micro-flowmeters placed upstream or downstream of the sensing chambers convert convective heat loss to flow. A typical operating window for sweat-rate calibration is 0 - 3 μL min^{-1} (channel level), with resolution ≈ 0.05 - 0.1 μL min^{-1} after multi-point calibration on a syringe-pump rig; duty-cycled heater power is kept in the 1 - 10 mW range to limit skin load. Co-located thermistors record skin temperature (±0.1 - 0.2˚C), allowing compensation of both chemical (enzyme kinetics, ISE slope) and thermal sensor responses. Aligning time-stamped flow with electrochemical or colorimetric signals typically reveals minute-scale lags; cross-correlation peaks within <60 s are common during exercise or heat-stress protocols [38].

Bubble management. Entrained air is a dominant failure mode. Practical layouts use (i) hydrophobic vents (e.g., PTFE membranes, 0.2 μm pores) at channel apices, (ii) serpentine traps/bypass loops that detain bubbles in low-field regions, and (iii) electrode placement downstream of a flow restrictor so bubbles preferentially stall before the sensing zone. Design targets include <10% transient electrode coverage without loss of trace and recovery to baseline within seconds to tens of seconds after bubble transit. In lactate channels, confining geometry plus venting preserves current stability and extends on-body uptime during motion and long wear [14].

4.4. Wireless Coupling and Power (Bridge to Next Section)

Microfluidic modules must pair with wireless and power stacks that match the sampling duty cycle. Battery-free NFC pairs naturally with colorimetry (single image, multi-assay) because the phone provides power + data during a brief tap; this keeps the patch thin and disposable [11] [12]. BLE pairs well with electrochemical dynamics because minute-scale telemetry is achievable with careful buffering and duty-cycling; power may come from a small cell, from harvest-assist (sweat BFC, body-heat thermoelectric generator (TEG)) or from mixed strategies depending on use case [13] [38]. Importantly, microfluidic sealing and routing reduce the number of retransmits and re-measures that would otherwise inflate radio energy budgets.

4.5. Human Factors and Data Integrity

On-body patches must remain comfortable and reliable for hours of wear. Soft elastomers and thin adhesive laminates minimize shear forces at the skin interface, and incorporating breathable features (microporous substrates or breathable adhesive patterns) helps prevent occlusion and skin maceration in hot conditions [39]. Adhesive strategies must balance strong attachment (to survive vigorous motion and sweat) with painless removal; many designs chamfer or round the patch edges to avoid snagging. Thermal management is also important even for low-power wearables: distributing heat from electronics and using low-loss conductors for antennas helps prevent local hot spots, keeping skin temperature within safe limits during prolonged operation [38] [39]. From the user's perspective, operation workflows should be simple: for example, tap-to-read for NFC-based assays (no user calibration needed beyond scanning with a phone), phone-in-pocket passive logging for BLE systems, and post-exercise data uploads for harvest-assisted devices when energy is readily available [11]-[13].

Quantitative use of colorimetric channels depends on controlled optics and consistent geometry. Common best practices include incorporating in-frame calibration color references and volumetric tick marks on the patch, constraining the smartphone camera distance/angle via the app's user interface or alignment guides, and applying color-space corrections to neutralize ambient lighting effects [15]. In advanced systems, machine-learning pipelines have been used to automatically segment microfluidic reservoirs in images, extract color features, and regress those to analyte concentrations or sweat rate/total loss, robustly across different smartphone cameras and users [16]. Such algorithms can also fuse image data with sensor streams (temperature, motion) to estimate individualized physiological states and trend trajectories [16].

4.6. Sampling Physics and Flow Metering

At the micro-scale, capillary pressure (set by channel geometry and surface energy) is the primary driver; the design target is to overwhelm pore-to-patch head losses so that fresh sweat advances the liquid front predictably even when skin is moving. In practice, sweat generation is intermittent and heterogeneous across the body. Local rates around 0.5 - 10 $\mu L \cdot min^{-1} \cdot cm^{-2}$ are typical across exercise intensities and sites, but they vary over time and with thermal state. Devices that monitor flow directly report a start-up delay on the order of minutes when rates are near the lower end because the system must first fill dead volume; for example, a wireless sweat-rate platform shows ≈ 10 min delay at ~3 $\mu L \cdot min^{-1}$, and a minimum detectable rate ~0.15 $\mu L \cdot min^{-1} \cdot cm^{-2}$ with validated electronics and flow calibration [40] [41]. These figures define practical windows for time-aligned chemistry (e.g., aligning a lactate spike with an exercise interval) and for alarm thresholds in hydration monitoring.

To keep readings quantitative over time, patches integrate volumetric graduations or chronological channels (each reservoir corresponds to a time slice of fluid), enabling flow-history reconstruction from a single photograph or from on-device counters. Combined impedance-length calibrations inside the channel can map electrical measurements to local sweat rate in real time [13]. For external benchmarking, the clinical Macroduct™ spiral collector, with ≈ 85 μL capacity and typical 50 - 60 μL in 30 min yields (with ~15 μL/30min as a minimum acceptable sample), provides reference points for validating patch volumetry and collection efficiency in low-sweat conditions [42].

4.7. Special Cases and Limitations

While early patches focused on electrolytes and metabolites, new work pushes toward endocrine markers. Using iontophoresis to induce sweat at controlled times and microfluidic CBVs to enforce intervalled sampling, it is possible to collect time-stamped packets of sweat for hormone analysis at ~6-minute resolution. With refined electrochemical chemistries and low-noise readout, reports reach pM-level detection for cortisol, epinephrine, and norepinephrine, enabling on-body profiling of acute vs. chronic stress dynamics [17]. These sequence-sampling strategies bring sweat assays closer to the pharmacokinetic/logistic richness of blood draw without the needles.

And key limitations remain. First, individuals with low sweat rates (or during rest) push devices to their priming limits; design responses include minimizing dead volume, adding hydrophilic coatings in early channels, and using vapor barriers to slow evaporation-induced bias in dry conditions [13]. Second, mixing and carryover between sequential samples can blur temporal dynamics; designers now use one-way valves, dead-end reservoirs, and anti-diffusion geometries to preserve chronological integrity of each sample [12]. Third, bubble management is essential: mechanical shocks, motion, and temperature swings can nucleate gas bubbles, so modern patches integrate vents, bubble traps, and tolerant electrode layouts as standard practice to maintain readings [14]. Finally, reagent shelf life (for colorimetric assays) and sensor surface conditioning or biofouling (for electrochemical sensors) become concerns for multi-day or multi-week deployments; many groups are thus moving toward swappable microfluidic cartridges that are single used, paired with a reusable electronics/wireless module for longevity [11] [12].

4.8. Outlook

Skin-interfaced microfluidics have matured from concept demos to fieldable platforms that collect, route, and analyze sweat at μL-scale volumes and minute-level resolution, while simultaneously tracking flow, cumulative loss, and temperature [12] [13] [38]. The most successful systems pair robust fluid handling (CBVs, bubble traps, chronological reservoirs) with hybrid sensing (electrochemistry + colorimetry) and fit-for-purpose wireless/power (NFC for battery-free on-demand tests; BLE for dynamic streaming with buffering and energy-aware scheduling) [11]-[13]. As pipelines for calibration and ML-assisted imaging solidify, these platforms will better translate sensor outputs into interpretable, individualized insights tied to health and physiological conditions [16]. The next wave will generalize sequence-sampling (for hormones and drugs), extend validated low-rate operation for sedentary users, and standardize reporting templates (geometry, volumes, flow limits, bubble tolerance, and timing) so that different patches can be compared rigorously across labs and use cases [15] [17] [40].

Table 2 summarizes several representative microfluidic platform designs and their sampling strategies, highlighting each system's fluid-handling architecture, sample handling approach, any flow/volume sensing mechanisms, and features for preventing evaporation or bubbles:

Table 2. Microfluidic platforms & sampling strategies.

Ref	Citation (short)	Biofluid	Microfluidics	Sample handling	Flow/Volume sensing	Anti-evap/Bubble mgmt.	Notes
[5]	W. Gao, Y. Zhang	Sweat	None (electrochemical electrode patch)	Direct-contact sensing on skin; non-patch storage			Electrode-focused sweat sensor (no microfluidic channels)
[11]	A. J. Bandodkar, *et al.*	Sweat	Skin-interfaced microfluidic + electronics; electrochemical & colorimetric chambers; volumetric channels	On-skin routing to sensing chambers; segmented collection with passive timing ('galvanic stopwatches')	Channel geometry for volumetry; sweat rate/loss via dye front/volume; battery-free NFC electronics	Sealed microchannels; hydrophobic vents; integrated valves (passive)	Bandodkar *et al.*, Sci Adv 2019
[12]	A. Koh, *et al.*	Sweat	Soft, closed microfluidic patch with sealed reservoirs; colorimetric assay windows	On-skin capture & storage; segmented/chronometric sampling; smartphone imaging readout	Colorimetric/volumetric readouts from reservoir fill; sweat loss estimation	Sealed channels/reservoirs minimize evaporation; inlet geometry reduces bubble ingress	Koh *et al.*, Sci Transl Med 2016
[13]	H. Y. Y. Nyein, *et al.*	Sweat	Flexible spiral microfluidics with embedded electrodes	Continuous on-skin sampling to EC sensors	Electrical impedance-based sweat rate sensor in microchannel	Encapsulated channel: inlet geometry improves priming	Nyein *et al.*, ACS Sensors 2018
[14]	I. Shitanda, *et al.*	Sweat	Microchannel with bubble-trapping/ air-bubble-insensitive geometry	Continuous flow over lactate electrode via channel	N/A (analyte-focused); continuous perfusion	Bubble-tolerant design; bubble trap region	Shitanda *et al.*, ACS Sensors 2023
[15]	L. B. Baker, *et al.*	Sweat	Skin-interfaced microfluidic patch + smartphone imaging	On-skin collection to colorimetric reservoirs; regional mapping	Image-based volume estimation; algorithms for sweating rate and $[Cl^-]$	Sealed reservoirs; color-stabilized dyes	Baker *et al.*, Sci Adv 2020
[16]	L. B. Baker, *et al.*	Sweat	Skin-interfaced microfluidic patch + ML image processing	On-skin collection; remote imaging workflows	Smartphone + ML quantification across lighting/orientation	Sealed reservoirs; robustness improvements	

Continued

[17]	J. Tu, *et al.*	Sweat	Multiplexed microfluidic with valve-regulated channels + iontophoresis extraction	Sequential/chronometric sampling of hormones; continuous analysis	Time-stamped packets; controlled flow by bursting valves	Sealed channels; anti-bubble routing	Tu *et al.*, Sci Adv 2025 (Stressomic)
[20]	S. Anastasova, *et al.*	Sweat	Flexible microfluidic patch with integrated metabolite/electrolyte sensors	Continuous sampling over EC sensors; temperature for calibration	(Reported) flow awareness via design; not dedicated flow sensor	Encapsulation; microchannel routing	Anastasova *et al.*, Biosens Bioelectron 2017
[21]	H. Y. Y. Nyein *et al.*	Sweat	High-throughput microfluidic sensing patches across body regions	Parallel, regional patches; image-based quantification	Smartphone imaging volume/time; correlated regional analysis	Sealed reservoirs	Nyein *et al.*, Sci Adv 2019
[38]	K. Kwon, *et al.*	Sweat	Short straight microchannel + thermal flow sensor; integrated wireless module	On-skin capture to flow sensor; continuous discharge to outlet pad	Thermal calorimetric flow-rate sensing; cumulative sweat loss tracking	Short channel lowers backpressure; encapsulation limits evaporation	Kwon *et al.*, Nat Electronics 2021
[39]	J. Choi, R. Ghaffari, L. B. Baker, and J. A. Rogers	Sweat	—	—	—	—	—
[42]	Wescor, MACRODUCT Sweat Collection System—Instruction Manual	Sweat	Legacy clinical collector (MACRODUCT): coiled tubing collector	Pilocarpine iontophoresis; on-skin collection to tubing; off-patch analysis	Volume via collected microliters; gravimetric/bench analysis	Closed tubing reduces evaporation; clamps/fittings	Wescor Macroduct manual
[43]	H. Tabasum, *et al.*	Sweat	Review of wearable microfluidic e-skin sweat sensors	—	—	—	Review article (Tabasum *et al.*, 2022)
[44]	R. F. R. Ursem, *et al.*	Sweat	Review of wearable microfluidic flow-rate sensors	—	Impedimetric/capacitive/thermal methods (review)	—	Ursem *et al.*, Lab on a Chip 2025 (review)

Each row corresponds to a notable wearable microfluidic platform, indicating how the device handles sweat (or other biofluid) through its microfluidic architecture, how it manages sample collection and delivery to sensors, whether it measures flow or volume directly, and what design elements mitigate evaporation or bubble-related issues. These examples illustrate different strategies: some devices forego complex fluidics (relying on direct skin contact), while others use sophisticated channel networks with flow sensors and bubble traps to ensure reliable sampling.

5. System Integration: Wireless Links, Power, and Packaging

Building a skin-interfaced biosensor from a mere "sensor" to a fully functional system requires joint design of (i) the wireless communication link (BLE vs. NFC), (ii) the energy supply model (battery-powered vs. energy-harvesting), (iii) the power management path (rectifiers, boosters, storage, MCU and radio duty-cycling), and (iv) the mechanical integration (stretchable interconnects, textile or printed antenna coils) such that sampling cadence, data latency, and wearer comfort all remain stable on a moving, sweating body [11] [18] [38] [45].

5.1. Wireless Link: BLE and NFC

Bluetooth Low Energy (BLE, 2.4 GHz) is the default choice when continuous streaming or high data rates (several kbit/s) are required—such as transmitting multi-analyte electrochemical signals along with temperature and flow data in real time. BLE system-on-chips (SoCs) pair a radio transceiver with a microcontroller, allowing data to be buffered locally and sent in bursts. By adjusting advertising or connection intervals, BLE can achieve minute-level telemetry with wearable-class energy consumption—this is the key to obtaining ~1 min resolved data on battery power [18] [38]. In contrast, near-field communication (NFC, 13.56 MHz) combines power and data in a short-range inductive link, enabling battery-free patches that remain dormant until a smartphone or dedicated reader is brought near. This pattern (sometimes called "tap-to-read") is now common for on-demand sweat analysis (e.g., cortisol sensing patches) and other epidermal sensors [11] [12]. Large-area coils printed on textiles or elastomers can be integrated into garments or straps to improve coupling when on-body coil size is limited, extending the read range for battery-free use cases [43] [46]. In summary: use BLE for continuous logging or distributed sensing while the user's phone can stay nearby, and use NFC for episodic, on-demand readings where a smartphone tap can power and read a disposable patch [11] [12].

5.2. Power Budgeting & Harvesting Options (Battery-Free or Battery-Assisted)

NFC harvesting: Battery-free patches typically integrate a planar 13.56 MHz inductive coil plus a rectifier and a small storage capacitor to power on-board sensors during an NFC reading. This approach can power multi-modal assays (electrochemical, colorimetric, volumetric) in a single scan, while keeping the device thin and comfortable since no battery is needed and the phone provides all required energy during the brief read event [11].

RF rectenna harvesting: Flexible radiofrequency "rectenna" (antenna + rectifier) systems can trickle-charge small energy stores by scavenging ambient radiofrequency energy (e.g., from WiFi or dedicated RF sources). However, they are sensitive to detuning when worn on the body. Practical designs therefore use intermittent sensing and tight impedance matching to ensure useful RF-to-DC conversion even under movement [45].

Biofuel cells (BFCs): On-body biofuel cells, such as those using sweat lactate as fuel, can generate μW-mW-level power depending on enzyme efficiency, electrode area, and sweat flow. Demonstrations have shown that coupling a lactate BFC with BLE electronics is feasible: the BFC and a small storage capacitor can power intermittent sensor readings and short BLE transmissions during exercise. In such harvest-assist models, the biofuel cell covers the sensing and communication energy, with the duty cycle matched to perspiration rate and fuel availability [14] [38].

Thermoelectric generators (TEGs): Body-heat TEGs provide continuous trickle power without requiring user motion. When combined with thin energy storage, they can sustain background monitoring and periodic data uploads. Using conductive or porous textile layers to spread heat can improve comfort and maintain the temperature gradient, ensuring skin remains safe even as heat is drawn for power [45].

5.3. Power Management (PMIC) and Antenna/Coil Co-Design

An effective power chain in a wearable sensor node typically includes: a rectifier, a boost converter (with cold-start capability for harvesters), an energy storage element (from a few μF up to mF, or a thin-film battery), and the load (analog front-end, microcontroller, radio). In BLE-based systems, it is best to keep analog front-end (AFE) sampling local (on-device), then compress or summarize data and transmit in bursts; one should tune the BLE advertising or connection interval such that the average current draw is determined by the reporting cadence rather than radio idle overhead [11] [18]. In NFC-based patches, the reader (smartphone) dictates the energy transfer schedule: the patch sleeps between scans, and the on-board storage is sized just to power one read cycle (including perhaps a quick colorimetric measurement or short electrochemical run) with some margin [11] [12]. For harvest-only modes (pure BFC/TEG power), energy-aware scheduling is essential—sample only when the storage charge exceeds a threshold, and cluster transmissions around times when energy is most abundant (e.g., right after exercise for BFC, or during steady thermal states for TEG) [38] [45].

On-skin antennas and coils must function while flexing, stretching, and being exposed to sweat, without detuning. NFC performance depends on maintaining inductance, Q-factor, and proper tuning capacitance; strategies like serpentine interconnects and porous/printed conductors are used to reduce stiffness and keep resonance stable during motion [11] [46]. For BLE's 2.4 GHz antennas, designs often use stretchable conductive patterns or microfibers that can tolerate strain without large resistance changes [10]. Additionally, textile-integrated resonators can distribute an inductive coil over a larger area (for NFC), allowing multiple passive sensor tags to share power—useful for multi-site sweat patch deployments in a battery-free configuration [46].

5.4. Materials Implications for Power & Link

Materials previously discussed for sensing can also significantly impact power and communication performance. For instance, softer and more conductive electrode interfaces (such as PEDOT: PSS hydrogels) raise the front-end signal-to-noise ratio at lower bias currents, allowing smaller boost converter ratios and reducing overall power demand. MXene films can double as high-conductivity sensor electrodes and as stretchable interconnects or antenna traces, improving radio and analog front-end headroom in battery-free or harvest-assisted modes [5]-[9]. Conductive microfibers and liquid-metal traces provide strain-tolerant wiring that maintains coil or antenna tuning across joint movement without large shifts in resistance [10]. Meanwhile, personal thermal management layers (e.g., breathable heat-spreading textiles) help dissipate ohmic and RF heating, preserving skin comfort even at relatively higher data reporting rates [19].

5.5. Packaging, Sealing, and Biosafety

Soft encapsulation using elastomers and thin barrier films is needed to protect power management and RF components while maintaining skin comfort and breathability. Microfluidic seals must prevent sweat evaporation and crosstalk between channels, since such losses would necessitate re-sampling or extra transmissions and thus waste energy [11] [12] [20] [44]. E-skin demonstrations show that thin, conformal device stacks (with all-day wearability) reduce shear strain and hotspot risks even during vigorous activity [46]. User workflows are also considered at the packaging level—for example, an NFC patch might be designed for a simple "tap-to-read" interaction, a BLE patch might assume the user's phone stays in a pocket for continuous logging, and a biofuel/TEG patch might plan for data upload after exercise when energy reserves are highest. These use-case constraints aim to minimize perceived latency while keeping energy costs bound [12] [18] [38].

For each integrated prototype, developers should report: (i) the wireless mode and parameters (BLE advertising interval/PHY settings, or NFC reader coupling conditions), (ii) the energy and storage budget per cycle of operation (including sensing, computation, and transmission), (iii) the coil/antenna geometry and any performance changes under ~20 - 30% mechanical strain (to show robustness of wireless link), (iv) any sealing or skin-temperature management measures, and (v) the context of human trials (rest vs. exercise conditions, patch locations, etc.). Prior work provides exemplars for minute-scale dynamic sensing, on-demand NFC assays, bubble-tolerant continuous electrochemistry, and sequential hormone sampling under such integrated scenarios [11] [14] [17] [18] [20] [38].

Table 3 compares various power and wireless configurations used in on-body sensor systems, including their data strategies, readout ranges, and an estimate of energy cost per insight:

Table 3. Power & wireless.

Ref	Reference	Power	Wireless	Data Strategy	Read range/Throughput	Energy per insight
[5]	Gao & Zhang, Sensors Actuators B	Battery (portable potentiostat)	—	Wired amperometry (on-skin demo)	—	—
[6]	Zhang & Zhang, ACS Sensors	Battery (portable)	—	Wired voltammetry (on-skin demo)	—	—
[11]	Bandodkar *et al.*	Battery-free (inductive harvest)	NFC (passive)	Chronometric μfluidics + EC; reader-triggered	cm-range NFC	Reader-powered
[12]	Koh *et al.*	Passive (optical)	Passive (camera)	Phone imaging; buffered reservoirs; per-session	Image-based (photos)	~0 (optical capture)
[13]	Nyein *et al.*	Battery (flex printed circuit board (PCB))	BLE	Streaming EC + impedance sweat-rate; temp compensation	Real-time BLE (kbps-class)	—
[14]	Shitanda *et al.*	Battery (wearable)	Wireless (unspecified)	Flow-through EC; periodic sampling	—	—
[15]	Baker *et al.*	Passive (optical)	Passive (camera)	Phone imaging; user-scheduled captures	Image upload via app	~0

Continued

[16]	Baker *et al.*	Passive (optical)	Passive (camera)	ML meniscus detection; QC filters; remote uploads	Image-based remote	~0
[17]	Tu *et al.*	Battery (wearable)	BLE	Valve-timed chrono-sampling; multiplex EC	Real-time BLE	—
[18]	Gao *et al.*	Battery (flex PCB)	BLE	Multiplex EC array + temp calibration; buffered sampling	BLE to phone (kbps-class)	—
[20]	Anastasova *et al.*	Battery (flex PCB)	BLE	On-body EC (lactate/pH) + temp; streaming	BLE to phone	—
[21]	Nyein *et al.*	Passive (optical)	Passive (camera)	High-throughput imaging of R2R patches; batch QC	Image-based	~0
[22]	Park *et al.*	Inductive WPT	NFC/inductive	Continuous basal-tear glucose; personalized lag	Near-field link	—
[23]	Parrilla *et al.*	Battery (portable meter)	—	On-body potentiometry; off-site/onsite validation	Wired/portable	—
[24]	Katsumata *et al.*	Battery (medical device)	BLE	Continuous lactate; sLT vs VT correlation (n = 50)	BLE to logger/app	—
[38]	Kwon *et al.*	Battery (coin cell)	BLE	Continuous thermal flow + integration	Meters-range BLE; real-time	—
[40]	Brueck *et al.*	Battery (watch)	BLE	Duty-cycled calorimetric flow sensing	Real-time BLE; LOD ~0.15 $\mu L/min \cdot cm^2$	—
[41]	Xuan *et al.*	Battery (wearable belt)	Wireless (NR)	DC step protocol across electrode array	On-body logging	—
[43]	Tabasum *et al.*	—	—	—	—	—
[44]	Ursem *et al.*	—	—	—	—	—
[45]	Kulkarni *et al.*	—	—	—	—	—
[46]	Barba *et al.*	Passive (NFC harvest)	NFC (passive)	Phone-triggered reads; on-tag analog-to-digital converter (ADC)	cm-range NFC	Reader-powered
[47]	Chung *et al.*	—	—	—	—	—
[48]	Song *et al.*	Harvester (triboelectric nanogenerator)	BLE	Packetized bursts when 3.3 V reached	BLE meters-range (burst)	~1.3 mJ per BLE burst ($\approx 0.5 \cdot 242\ \mu F \cdot 3.3^2$)
[49]	Mirzajani *et al.*	Harvest (NFC phone-powered)	NFC (passive)	Phone-triggered reads; on-tag ADC	NFC cm-range	Reader-powered
[50]	Cheng *et al.*	Harvest (NFC phone-powered)	NFC (passive)	differential pulse voltammetry (DPV) immunosensing; phone-triggered	NFC cm-range	Reader-powered

Each row corresponds to a representative system and lists the power source (battery vs. battery-free or harvested), the wireless communication method, the data transmission strategy, the typical read range or data throughput, and the approximate "energy per insight" (energy consumed to obtain a unit of actionable information). For example, reference 5 is a battery-powered wearable patch read by a wired potentiostat (no wireless link), whereas others use fully wireless telemetry. This comparative view emphasizes how different systems balance power and data requirements to achieve reliable on-body sensing.

6. On-Body Validation Practices

Section VI synthesizes validation practices used in leading wearable sweat sensing systems and draws on standards from wearable tech and clinical measurement to emphasize agreement over simple correlation. We also anchor accuracy expectations using recent continuous glucose monitor (CGM) performance benchmarks and include fluid-specific evidence on how well sweat, tear, or ISF readings correlate with blood values.

6.1. Integrated Study Design, Reference Comparators, and Synchronization

Select participants whose characteristics match the intended use and stress the device across its real operating envelope. For hydration and electrolyte studies, recruit healthy adults who can complete controlled indoor and outdoor exercise; for urate monitoring, enroll individuals with gout; for glucose dynamics, include participants with diabetes. Protocols should explicitly cover rest and exercise states, low and high sweat rates, single-day and multi-day wear, and multiple skin sites (e.g., forearm, upper back, thigh) because both composition and flow are region-dependent [12] [18] [21]. Environmental variables (ambient temperature, humidity, airflow) and exercise modality (intensity stages, duration) should be fixed or randomized per a pre-registered plan, and the sampling site order should be balanced within subjects to avoid systematic bias [12] [18] [21]. Pre-register primary endpoints and the full analysis workflow (inclusion/exclusion rules, alignment method, stratifications) using checklists adapted from CHAMP and related wearable-validation standards to deter selective reporting [51] [52].

Size the study to estimate bias and limits of agreement with prespecified precision rather than convenience N. Following method-comparison guidance (CLSI EP09-A3), derives N from the desired half-width of the 95% limits of agreement and anticipated within-subject variance; pilot sessions should quantify variance across sites and conditions (rest vs. exercise) to refine these inputs [53]. Plan a priori stratifications for sweat-rate bins, body site, temperature, and motion state so that accuracy is not reported as a single pooled number. Include duplicate sensors or repeated fill-and-read cycles on a subset of participants to characterize repeatability within a session and device-to-device variability [53].

Use reference methods that make the wearable data interpretable under real secretion dynamics. For sweat, collect parallel aliquots for independent assays—ion chromatography for Na^+/K^+/Cl^- and enzymatic or LC-MS methods for lactate, glucose, and urea—and pair chemistry with on-patch flow or validated microfluidic volume readouts so that concentrations are conditioned on secretion rate [12] [21] [44]. For ISF glucose, use a calibrated YSI analyzer or venous plasma as the reference and judge performance against realistic CGM anchors (single-digit %MARD in contemporary systems) [54]-[56]. For tear glucose and other non-blood surrogates, adopt the smart-lens playbook by enforcing strict time alignment to blood glucose and modeling transport lag explicitly rather than assuming instantaneous coupling [22].

Synchronize wearable and reference timelines with methods that respect physiology. Because transport and device response introduce delays, align time series using cross-correlation or dynamic time warping before computing point-wise errors, and report the chosen lag distribution at the subject and condition level [12] [21] [22]. In parallel, publish "no-alignment" analyses to document out-of-the-box behavior. When microfluidics provides chronological segmentation (e.g., capillary-burst valves or time-stamped reservoirs), treat those timestamps as ground truth for windowing, then perform residual alignment to account for biochemical and electronic latencies [12] [21]. All alignment decisions and any excluded epochs (bubbles, dry channels, overflow) should follow pre-registered rules with rates reported transparently to make missingness explicit [51]-[53].

Finally, ensure the protocol generates data that generalizes across wear contexts. Randomize or counterbalance skin sites within subjects; log ambient and skin temperature continuously; standardize pre-wear skin preparation (and whether first sweat is discarded); and fix phone/reader interactions for NFC or connection intervals for BLE, so radio behavior is not a hidden confounder [12] [18] [21]. Archive raw and aligned traces, alignment code, flow/volume bins, and analysis notebooks so that agreement metrics (Bland-Altman bias and limits, MARD, Lin's concordance correlation coefficient (CCC)) can be independently reproduced under the declared stratifications [51]-[53].

6.2. Primary Performance Metrics

Report both accuracy and agreement, not correlation alone. Key metrics include:

- MARD (Mean Absolute Relative Difference): A standard in CGM literature for continuous measurements; report overall MARD and consider stratifying it by analyte concentration range or rate-of-change. Today's best CGMs achieve single-digit MARD (~8 - 9%) [54]-[56], which is a practical upper benchmark for noninvasive ISF or sweat sensors.
- %20/20 (and %15/15) agreement: The percentage of paired readings where the wearable is within ±20% of the reference (or ±20 mg/dL for reference values <100 mg/dL), etc. Include zone analysis (e.g., Clarke or Parkes error grid) if relevant to the analyte [52].
- Bland-Altman bias and 95% limits of agreement: Compute the bias (mean difference) and the limits of agreement between the wearable and reference. Inspect and report any heteroscedasticity or proportional bias in the plots [57].
- Lin's Concordance Correlation Coefficient (CCC): Provide CCC as a measure of overall agreement (accuracy combined with precision), including confidence intervals [58].
- Stratified accuracy: Analyze errors as a function of sweat/tear flow rate, skin temperature, motion state, and body site, because sensor accuracy can depend on these factors (sweat dilution, regional composition differences, etc.) [12] [18] [21] [44].
- Follow CLSI EP09-A3 conventions for any regression analysis (Deming or Passing-Bablok regression) when summarizing bias across the measurement range [53].
- For binary or categorical outputs (e.g., a dehydration alert, threshold cross-

ing), report sensitivity/specificity, receiver operating characteristic (ROC)-area under the curve (AUC), and F1-score or similar; Bland-Altman analysis does not apply to binary decisions. If the wearable's intended use involves detecting clinical events (e.g., seizures, arrhythmias), adopt validation frameworks and reporting standards from those device communities to structure your evaluation [59].

6.3. Data Quality, Sampling, and Flow-Aware Validation

Accurate on-skin chemistry starts with disciplined sampling and explicit conditioning on sweat rate. Because analyte levels track local secretion, treat every accuracy claim as conditional on flow: integrate on-patch flow or volume readouts (capacitive, impedimetric, or image-based) and stratify all performance metrics by predefined sweat-rate bins rather than reporting a single pooled error [12] [21] [44]. Keep the raw flow trace and timestamps in the dataset. Time-resolved microfluidics also improves quality control: report channel fill times, any bypass or overflow events, and the logic for capillary-burst valves used to segment samples. Note how each event was handled in analysis (e.g., re-alignment or exclusion) and document any evidence of dilution or misordered fill [12].

Site-to-site variability should be measured, not assumed. Build within-subject, multi-site comparisons (forearm, upper back, thigh) into the protocol, then state which site anchors the primary analysis and why. For each site, provide agreement results against the reference—bias and limits of agreement—and summarize how the chosen site shifts those values. Show these analyses in the main text so readers can see the magnitude and direction of site effects rather than hunting them in the supplement [21].

Contamination and evaporation are recurring artifacts. Describe skin preparation (e.g., rinse sequence, alcohol wipe), whether the first sweat was discarded, and the anti-evaporation layers or encapsulation used. Explain bubble management steps and any design features that suppress back-diffusion or air ingress. When available, prefer sealed microfluidic layouts and record any departures from the intended flow path during wear [12].

Temperature and motion are universal confounders for both sensor physics and enzymatic stacks. Specify the temperature-compensation model, calibration procedure, and residual error after compensation; define motion protocols (static vs. moving) and quantify the accuracy change between them to demonstrate robustness under realistic use [12] [18]. Finally, pre-register failure flags (bubbles, dry channels, saturation, delamination), apply them consistently in the pipeline, and publish an exclusion table that lists counts and percentages by reason. Include a brief missing-data accounting so readers can see how much data was removed, where it occurred in time, and why.

Minimum items to report (flow-aware): flow-binned accuracy (with bin edges), alignment method and lag, site-wise bias and limits of agreement, contamination/evaporation controls, temperature and motion protocols with before/after accuracy, and a transparent exclusion table with rates and reasons [12] [18] [21] [44].

6.4. Reliability & Repeatability

Reliability under repeated use is a prerequisite for clinical translation. We recommend reporting: (i) short-term repeatability within a single wear session—expressed as coefficient of variation (CV) and/or mean absolute error (MAE) for replicate measurements or duplicate sensors on the same patch; (ii) day-to-day reproducibility across multiple wears on the same subject; and (iii) device-to-device variability across nominally identical units. Use concordance-focused metrics, not just correlations, to quantify reproducibility: for example, provide Lin's CCC or intraclass correlation coefficients (ICC) with confidence intervals to directly assess agreement across days and devices [58]. If the device requires calibration, track the stability of the calibration parameters (slope, intercept) over time and rewears; explicitly report how often recalibration was needed and the magnitude of calibration adjustments. Where relevant, contextualize these stability results by comparing them to practices of state-of-the-art continuous monitors (for example, how CGM devices handle calibration and drift) [54] [55]. Taken together, these elements allow readers to distinguish one-off demonstrations from platforms that are stable, serviceable, and manufacturable in the long term.

6.5. Clinical/Physiological Validity: Do Wearable Outputs Track Biology?

For glucose, evidence across battery-powered, NFC-powered, and biofuel-cell platforms shows that patch readouts can mirror blood or ISF trends under controlled protocols when lag and flow-dependence are explicitly handled—either via subject-level calibration or model-based alignment [11] [12] [18] [21]. As a practical yardstick, current clinical CGMs (Dexcom G7, Libre 3) report MARD ≈ 8 - 9%, which is a reasonable benchmark for what "good" free-living tracking looks like [54] [55]. Claims of physiological fidelity should therefore report agreement against a reference (CGM or blood), the lag model used, and whether the mapping holds outside the calibration window. Parallel work in tear glucose (smart contact lenses) reaches the same conclusion: correlation alone is insufficient; correlation plus lag analysis, reproduced across independent cohorts and scenarios, is the minimum evidentiary set before clinical claims [22].

Electrolyte and hydration metrics require physiological context to be interpretable. Studies that relate patch-measured $Na^+/K^+/Cl^-$ and local sweat rate to whole-body electrolyte loss strengthen credibility; whenever feasible, include simple mass-balance checks (pre/post body mass with fluid-intake logs) so that local measurements can be scaled to the organism level [21]. For potentiometric patches, present on-patch readings alongside parallel benchtop assays from co-collected samples; this side-by-side view helps separate true physiology from drift, reference instability, or site effects and shows whether agreement persists across sessions and wear locations [23].

For lactate, emerging trials indicate that sweat-lactate thresholds align with established exercise landmarks (e.g., ventilatory threshold or onset of blood-lactate accumulation) when assessed with Bland-Altman plots, correlation, and threshold-agreement analyses [24]. Robust study designs use ramp or interval protocols, state the threshold definition in advance, and report how often the wearable and reference select the same training zone. Results should also note conditions that degrade concordance—e.g., site-dependent sweat dynamics, temperature stress, or rapid changes in flow—and document whether simple controls (site selection, temperature logging, motion protocols) restore agreement.

Minimum to report for physiological validity: reference method and sampling schedule; lag handling (model or calibration and its stability); flow-aware stratification of accuracy; site and temperature conditions; replication across cohorts or sessions; and agreement metrics that go beyond correlation (e.g., MARD, Bland-Altman limits, threshold agreement) [11] [12] [18] [22]-[24].

Equally important are acknowledging limitations and avoiding over-interpretation. Several reviews caution that sweat-to-blood correlations can be analyte- and context-specific, often requiring per-analyte validation and in some cases even subject-specific calibration for meaningful use [47] [60]. Accordingly, authors should clearly state the assumed physiological model (including any lag, flow, or site correction terms), the reference comparator, and the intended use scenario for their device. Negative or mixed findings (e.g., cases where sweat levels did not correlate well with blood) should be reported as openly as positive results. In summary, clinical validity in lab-on-skin sensing is "earned" through triangulation—combining physiology-aware modeling, appropriate gold-standard comparisons, and rigorous statistics—rather than through any single high correlation value.

6.6. Statistical Analysis & Reporting Checklist

To improve transparency and reproducibility, future studies should adhere to a reporting checklist:

- **Pre-specify endpoints:** Declare the primary outcomes (e.g., MARD, MAE, Bland-Altman bias) and secondary outcomes (e.g., sensitivity/specificity for a threshold event) in advance.
- **Two-stage analysis:** Perform (a) within-subject agreement analysis (how well the wearable tracks everyone) and (b) a mixed-effects or pooled analysis for overall bias while accounting for random effects of subject and site.
- **Agreement, not just correlation:** Always report Bland-Altman statistics and concordance metrics (CCC or ICC with confidence intervals) in addition to any correlation coefficient [53] [57] [58].
- **Stratify by context:** Report performance stratified by sweat rate, ambient temperature, body site, motion state, and day of wear.
- **Calibration handling:** State whether the device was factory-calibrated or

user-calibrated. If calibration was done per user, report the post-calibration accuracy and how calibration drifted (e.g., MARD per day) [54] [55].

- **Missing data & exclusions:** Define failure criteria (e.g., bubbles in channel, sensor saturation, adhesive detachment) and report the exclusion rate and reasons for any data points or sessions omitted.
- **Usability & safety:** Note any skin irritation observed, typical adhesion duration, number of device replacements needed, and whether the device is partially or fully reusable (e.g., disposable patch with reusable electronics) [11] [12].

6.7. Case Exemplars (What "Good" Looks Like)

A few published examples illustrate best-practice validation:

- **Gao *et al.* (2016):** A multiplexed wrist patch measuring Na^+, K^+, glucose, lactate, and temperature with continuous Bluetooth readout. This study incorporated region- and flow-aware calibration, exemplifying multi-analyte validation with physiological context (sweat rate and skin temperature) [18].
- **Bandodkar *et al.* (2019):** A battery-free NFC-powered patch integrating electrochemical and colorimetric assays plus volumetric sweat analysis. The study demonstrated an episodic (on-demand) readout validated with parallel sweat analysis, and highlighted flow-aware design (passive microfluidic "stopwatch" channels) [11] [12].
- **Nyein *et al.* (2018):** A roll-to-roll manufactured microfluidic patch with spiral channels measuring sweat rate and ions (and glucose) across multiple body sites. It featured rigorous regional and flow correlation analysis and even predicted whole-body electrolyte loss, serving as a model for physiology-anchored validation [21].
- **Ursem *et al.* (2025):** A recent comprehensive review focusing on sweat flow rate sensing methods (capacitive and impedimetric) and their limitations due to ionic interference and sensor lifetime. It's a useful reference to justify including flow-aware metrics in validation plans [44].
- **CGM anchors (Dexcom G7 & Libre 3 studies):** Clinical evaluations of these glucose monitors show single-digit MARD and high %20/20 agreement in large cohorts, setting realistic expectations for accuracy in continuous monitoring [54] [55].
- **Tear-glucose lens (Park *et al.* 2024):** A study establishing rigorous methodology for correlating contact lens glucose readings with blood glucose, including lag compensation on-eye. This is directly transferable to sweat/ISF validation where transport delays exist [22].

Table 4 compares peer-reviewed on-body clinical studies of microfluidics-enabled wearables across cohorts, biofluids, sampling sites, protocols, timing behavior, validation metrics, repeatability, artifacts, and wireless/power modes. The comparison emphasizes how flow-aware sampling, explicit lag handling, and standardized reporting shape agreement and generalizability rather than correlation alone.

Table 4. On-body clinical validation studies of microfluidic wearable biosensors.

Ref	Citation (short)	On-body N	Site	Protocol	Response time	Accuracy (MARD/MAE)	Stability/ Repeatability	Exclusion rate/Artifacts	Ethics & Safety	Notes
[11]	Bandodkar *et al.*		Forearm/ back; swimmers & runners	Field trials (indoor exercise, open-ocean swimming); multimodal pH/Lac/Glc/Cl^- + sweat rate/loss			Waterproof operation; colorimetric + electronic mitigate motion/underwater artifacts		IRB approved; human studies	Battery-free wireless; volumetric + colorimetric + EC
[12]	Koh *et al.*	≈2 - 3 (examples)	Wrist	Cycling: 5 min ramp + 30 - 45 min @150 W + 5 min cool-down; vs Macroduct	Onset ~13 - 14 min (channel fill)		Consistent sweat-rate trends across trials	—	IRB approved	Capture & storage; smartphone imaging
[13]	Nyein *et al.*	2+	Wrist	Stationary cycling; Macroduct comparison; Na^+/ K^+/Cl^-/pH + sweat rate	Na^+ ~12 min; sweat-rate later (reservoir volume)		Reproducible across trials	—	IRB approved	EC + impedance for sweat-rate; app readout
[14]	Shitanda *et al.*	1	Back	Exercise test; wireless; compared vs blood lactate (qualitative)	—	—	Bubble trap microchannel improves robustness	—	IRB compliance	Continuous lactate monitoring
[15]	Baker *et al.*	312 athletes	Various sites	Smartphone imaging of microfluidic patches (lab + field)	Within-session	—	Robust across sports and conditions	—	IRB approved	Personalized sweat-rate & sweat loss via imaging
[16]	Baker *et al.*	—	—	ML-assisted meniscus detection for microfluidic patches (image-based)	—	—	Improves reproducibility of image-derived metrics	—	IRB compliance	Method enabling robust remote analytics
[17]	Tu *et al.*	—	Forearm/skin	On-body dynamic profiling of cortisol/ epinephrine/ norepinephrine; stressor tasks	—	—	Multiplexed hormone tracking in real time	—	IRB approved	Iontophoresis sampling; valve-timed chrono-sampling
[18]	Gao *et al.*	—	Forearm/other	On-body exercise; EC sensors for Glc/Lac/Na^+/K^+; temp calibration	Within-session	—	Stable trends during exercise	—	IRB approved	First fully integrated multiplexed array
[19]	Barba *et al.*	—	—	Prototype validation vs portable potentiostat; NFC readout	—	—	Robust to bending; wearer variability characterized	—	IRB compliance	Design/manufacture; limited human cohort

Continued

[21] Nyein *et al.*	Exercise: 3; Fasting: 20 healthy + 28 diabetic	Forehead/ forearm/ underarm/ back; forearm & leg (iontophoresis)	Cycling; iontophoretic sweat at rest; whole-body fluid loss prediction	Onset ~20 min (exercise)	—	Multiple repeats; mass-fabricated patches	—	IRB approved	Regional differences; fasting cohorts
[22] Park *et al.*	Healthy + diabetic (N in Supplementary)	Eye (contact lens)	Continuous wireless tear glucose; basal tears; personalized lag	Sub-minute sampling	High TG-BG correlation (with lag)	Recovered from reflex-tear perturbations	Ethics approved	Wireless NFC smart contact lens	
[23] Parrilla *et al.*	—	Forearm/skin	On-body electrolytes with wearable ion patch	—	—	Stable potentiometric readings; drift characterized	—	IRB compliance	$Na^+/K^+/pH$ on-body demo
[24] Katsumata *et al.*	50 HF patients	Upper arm/skin	Incremental exercise; compare sLT vs VT	—	sLT-VT difference −4.9 ± 15.0 W; Bland-Altman no bias	No device-related adverse events	Prospective clinical trial	Clinical validation of sweat lactate	
[27] Kim *et al.*	—	Arm	Reverse/forward iontophoresis; on-body alcohol sensing vs breathalyzer	—	—	—	—	IRB compliance	Noninvasive alcohol monitoring
[31] Xuan *et al.*	—	—	On-body lactate with microfluidic patch; high-lactate exercise	—	—	Designed to avoid saturation at high lactate	—	IRB compliance	With pH/T compensation
[33] Nyein *et al.*	—	Forearm/skin	At-rest continuous analysis; pH/Cl^-/levodopa + sweat-rate	—	—	Multiplex mitigates pH/ionic confounds	—	IRB approved	Hydrophilic filler for rapid uptake
[34] Wang *et al.*	—	Forearm/skin	Multiplex trace-level metabolites during rest/exercise	—	—	Validated in spiked matrices & on-body trials	—	IRB compliance	Enzyme/ aptamer EC array
[35] Vivaldi *et al.*	—	Forearm/skin	On-body ions/pH demonstration with LIG electrodes	—	—	Selectivity & drift discussed	—	IRB compliance	Laser-induced graphene platform
[36] Emaminejad *et al.*	—	Forearm/skin	Periodic iontophoresis + microfluidic collection; Cl^- diagnostic and glucose demo	—	—	Active extraction reduces contamination	—	IRB approved	Programmable extraction cycles
[37] Bandodkar *et al.*	—	Arm	Reverse iontophoresis + amperometric glucose; on-body OGTT demo	—	—	—	—	IRB compliance	First tattoo-based noninvasive glucose

Continued

[38] Kwon *et al.*	—	Forearm/skin	Real-time wireless during treadmill/cycling & daily activities	—	—	Stable flow sensing with temp compensation	—	IRB approved	On-skin flow, cumulative loss, temperature
[40] Brueck *et al.*	5	—	Indoor/outdoor physical activity; wireless sweat-rate sensor	—	—	Consistent subject-wise profiles	—	IRB compliance	Real-time sweat-rate monitoring
[41] Xuan *et al.*	—	—	Validated vs standard collector; direct-current sensing	—	—	Stable operation during exercise; DC reduces polarization artifacts	—	IRB compliance	Direct-current approach; validation study
[43] Anastasova *et al.*	—	—	Continuous sweat monitoring on-body	—	—	Repeatability reported in tests	—	IRB compliance	Early multisensing wearable patch

Each row corresponds to a human study and lists the cohort/setting, biofluid and target analytes, microfluidic architecture, reference method and synchronization strategy, primary accuracy/agreement metrics (e.g., MARD, %20/20, Bland-Altman bias and limits, CCC), pre-specified stratifications (flow rate, site, temperature, motion, day), and reported exclusions/artifacts plus usability/safety notes. Example contrasts include battery-free NFC patches with hybrid colorimetric/electrochemical readouts versus continuous BLE electrochemical platforms with integrated flow sensing; the aligned outcomes show how architectural choices translate into accuracy, robustness, and user workload.

7. Comparative Analysis

A rigorous comparison of microfluidics-enabled wearables should synthesize evidence across four axes—fluidic reliability, sensing modality, wireless/power, and validation practice—rather than inventorying parts or quoting limits of detection. In practice, deployed systems converge into three archetypes.

(1) Continuous electrochemical + BLE

These devices buffer minute-scale electrochemical streams on-patch and ship bursts when the link is favorable. They are preferred when temporal structure is itself the signal (thresholds, trends, circadian patterns). Microfluidics therefore must keep fresh sample over the sensor for long sessions and prevent bubble-induced dropouts [11] [13] [39]. Validation should use the "trusted minute of trend" as the unit of analysis, apply lag-aware alignment with a capped window, and stratify by rate-of-change, motion/temperature, and flow/site; report MARD, %20/20, and Bland-Altman bias/LOA within these bins, together with availability-aware summaries and dropout/run-length distributions to separate telemetry gaps from sensing errors [5]-[10] [57] [58]. Relating duty cycle and buffering policy to energy per insight (J per trusted minute) makes the energy-accuracy trade-off explicit [51] [52] [59] [61].

(2) Battery-free NFC patches

These favor robust, tap-to-read snapshots via colorimetric lanes and, in some cases, simple electrochemistry. Without a local battery, geometry and microfluidic sequencing act as memory; reliability hinges on priming, evaporation barriers, and readable contrast under variable lighting [11] [13] [39]. Validation benefits from pairing each read with a short reference window and reporting Bland-Altman bias/LOA and short-term repeatability (ICC/CCC). For threshold use-cases (hydration/electrolyte flags), add sensitivity/specificity, decision yield, and time-to-decision; because user-initiated reads can bias timing, include conditional accuracy with respect to read cadence and pre-read conditions (rest vs exercise, site temperature, flow state) [3] [4] [56] [57]. Summarize energy on a Joules-per-correct-decision basis to enable fair comparison to continuous modes [51] [52] [59] [61].

(3) Harvest-assisted platforms

Sensing and telemetry are scheduled to energy plateaus from biofuel cells or thermoelectric; a local scheduler decides when to sample, buffer, and transmit. Success depends on aligning biological dynamics with harvest cycles and on fluidics that tolerate longer idle periods without mixing or dry-out [11] [13] [39]. Validation is naturally episode-based and should report agreement jointly with coverage (availability-weighted MARD, percent time in a "trusted" state), treat gaps as missing-not-at-random when appropriate, and map EPI-accuracy frontiers by sweeping duty cycle and local compute settings; stress across energy states (illumination/field strength, temperature) and document warm-start lag/jitter to make episode timing interpretable [51] [52] [57]-[59] [61].

Across all three, real-world performance ultimately traces back to whether the microfluidic layout stabilizes sampling on skin, the materials/electrode stack keeps bias low at low power, and the analysis reports agreement and reproducibility with correct time alignment and flow awareness. Normalizing results by energy per insight—one minute of trusted trend or one defensible threshold decision—keeps comparisons outcome-focused; studies that state cadence, buffering strategy, alignment window, stratifications, and exclusion rules alongside these metrics are interpretable across architectures [5]-[11] [39] [51] [52] [57]-[59] [61].

7.1. Continuous Electrochemical + BLE: When Dynamics Carry the Meaning

This archetype is appropriate when the shape of the time series is the endpoint: lactate crossing an exercise threshold, electrolytes drifting over long exertion, or minute-scale glucose swings under diet challenges [11] [38]. Local buffering decouples average current draw from RF peaks, enabling small storage elements to support multi-analyte streams without thermal discomfort—provided advertising/connection intervals and retransmission policies match the protocol. A practical design documents buffer depth, burst size, retry logic, and the rules that drop or compress samples when radio windows are missing.

The upstream constraint is microfluidics on skin. At rest or in low-sweat sites, secretion is intermittent, region-dependent, and low volume. Large first-fill volumes or sluggish priming create start-up delays, old-new mixing, and bubble ingress that can masquerade as drift. The most effective countermeasures appear early in the flow path: minimize dead volume, add hydrophilic priming in initial channels, segment with capillary-burst valves, and add bubble traps before the sensing chamber [12] [14]. Good practice is to publish the actual channel map (path lengths, cross-sections, vent locations) and to log priming time and any bypass/overflow flags; these are often more predictive of variance than the nominal sensor limit of detection.

Validation should make transport explicit. Flow-aware analyses that stratify accuracy by sweat rate, body site, and temperature, and that present both raw and lag-corrected error, reveal where improvements truly come from [13] [38] [39] [44]. For example, a report that shows reduced bias at low-flow bins after channel redesign provides stronger causal evidence than a single pooled error. Similarly, publishing site-wise agreement (forearm vs. upper back vs. thigh) and stating which site anchors the main analysis keeps claims tied to physiology rather than to a favorable location.

Materials reinforce these gains. PEDOT: PSS hydrogels and MXene-based electrodes provide low interfacial impedance on compliant substrates, which improves signal-to-noise ratio (SNR) at lower bias and stabilizes minute-resolved currents under motion [5]-[9]. Robust stacks specify the reference (e.g., solid-state Ag/AgCl), encapsulation layers, and adhesive interfaces, and they characterize drift across wear sessions. Reports that include side-by-side benchtop assays on co-collected samples help separate true physiology from reference instability or site effects, and they document how much correction (temperature, motion) is needed for stability.

From the wireless/power side, the decisive choices are cadence control and packet policy. Continuous streams rarely need constant connections; most systems benefit from periodic connection windows and burst uploads tied to buffer thresholds. Publishing the mapping from sensing cadence to radio cadence (including conditions for back-off, drop, or compression) allows others to evaluate energy per insight alongside agreement. Where privacy or user burden matters, designers specify the proportion of time the radio is active, and the number of user interactions required per hour—these become practical limits on free-living use.

Failure modes recur and should be explicitly tested.

- **Priming failures:** long time-to-first-sample, incomplete wetting; test at low-sweat rest conditions and log time to stable baseline.
- **Carryover/mixing:** blurred dynamics across events; test with step changes and report recovery to baseline between steps.
- **Bubble sensitivity:** dropouts during motion/temperature swings; test with controlled shocks/thermal ramps and log up time.
- **Reference drift:** slow bias shifts in long wear; run parallel benchtop assays and publish site-matched comparisons.

  A results section that quantifies uptime, data loss reasons, and post-alignment errors across these scenarios is more informative than a single accuracy figure.

Finally, studies should document user-facing constraints that affect clinical translation: adhesive strategy and wear time, occlusion and skin comfort, charging or swap cadence for any storage elements, and the robustness of smartphone pairing in gyms or clinics. When authors disclose these along with agreement metrics, buffer/radio policies, and flow-aware stratification, readers can compare continuous BLE systems to NFC or harvest-assisted alternatives on equal footing—not just by nominal sensitivity but by delivered, time-aligned information per unit effort [5]-[9] [11]-[14] [38] [39] [44].

7.2. Battery-Free NFC with Colorimetry/Electrochemistry: On-Demand Truth at Near-Zero Idle Power

Battery-free NFC patches concentrate power and data exchange into a few seconds during a smartphone scan, essentially trading time for energy: no power is used until the user initiates a reader. Colorimetric sensing fits naturally here because the microfluidic geometry itself encodes time (which channel filled first, total volume, etc.), and a single smartphone image captures a multi-analyte panel plus volumetric information. Meanwhile, the absence of a battery keeps these patches thin, cool, and low-cost for one-time use [11] [12]. Achieving optical accuracy requires built-in calibration marks on the patch, guided alignment (ensuring consistent camera distance/angle), and color correction algorithms, while volumetric analysis benefits from printed tick marks and parallel validation using standard collectors or gravimetry [12] [13]. Many NFC patches adopt a hybrid strategy: they include one or two electrochemical sensors for analytes requiring high sensitivity (e.g., cortisol, which may be at sub-micromolar levels) that operate only when powered by the NFC field, while maintaining colorimetric channels for robustness and low per-use cost [11] [12] [39]. In practice, this archetype excels when insights are needed only occasionally (hydration or electrolyte checks a few times a day, post-activity assessments). Each tap yields a rich dataset (multiple analytes, cumulative loss) that can drive most decisions without continuous monitoring [11] [12]. From an engineering standpoint, textiles or other large-area coils can mitigate the coupling limitations of small patches, and thin conformal packaging ensures these devices remain comfortable and well-adhered even during movement and sweating [12] [39].

7.3. Harvest-Assisted Systems (Biofuel/Thermoelectric): Letting Physiology Schedule the Radio

Biofuel cells (BFCs) and wearable thermoelectric generators (TEGs) tackle the power supply challenge by drawing energy from the body's chemistry or thermal gradients. The power is variable instantaneously but can be sufficient over tens of minutes or hours to support buffered sensing and periodic BLE transmissions—provided the firmware enforces an energy-aware schedule. In practical terms, this means sampling only when the energy storage is charged above a set threshold, compressing data locally, and transmitting during periods when harvested energy is plentiful (e.g., right after exercise in the case of a sweat-lactate BFC, or during a stable skin-ambient temperature difference for a TEG) [38] [39]. Microfluidic management plays a crucial role here as well: routing sweat through controlled paths and incorporating bubble-tolerant electrode designs can stabilize a BFC's output even during vigorous motion (bubbles or inconsistent fuel flow would disrupt power generation). Similarly, thermal management via heat-spreading textiles can maintain a usable temperature gradient for TEGs while preserving skin comfort, enabling continuous background logging [10] [14]. In documentation, harvest-assisted devices are most convincing when they directly link their performance to their power strategy—e.g., showing that accuracy is maintained at the chosen duty cycle and that the device truly operates "self-powered" within the limits of the use case, rather than just claiming it abstractly.

7.4. Cross-Cutting Dependencies: Fluidics, Materials, Mechanics → System-Level Outcomes

Across all archetypes, microfluidics is often the first amplifier of system performance. Small initial volumes, low-resistance channels, anti-diffusion designs for time-segmentation, and venting/trap features decide whether each data point represents fresh fluid or a blurred mixture that could obscure dynamics [11] [12] [14]. Materials and interfaces form a second amplifier: skin-soft, low-impedance electrodes (PEDOT: PSS gels, MXene coatings) yield higher SNR at lower power, permitting smaller boost converter factors and less heat dissipation; conductive microfibers and serpentine traces keep NFC coils and BLE antennas tuned even as the device stretches and gets wet, which stabilizes communication links [5]-[10]. Mechanics & packaging are a third factor: breathable adhesives, tapered edges, and thin, conformal device stacks with appropriately engineered evaporation barriers can mean the difference between a device that performs beautifully on the bench and one that a person can comfortably wear for hours in the field [12] [39].

7.5. What the Validation Data Show (Agreement over Correlation)

The most rigorous studies treat agreement as the primary outcome and use correlation only as a supplementary descriptor. They report MARD and other error metrics (MAE, root mean square error (RMSE)) for continuous variables, alongside Bland-Altman bias and 95% limits of agreement (to reveal any heteroscedasticity or proportional bias), and they include Lin's CCC or ICC with confidence intervals to quantify reproducibility across multiple days or devices [3] [4] [53] [57] [58]. They stratify results by sweat rate, body site, temperature, motion, and clearly declare the calibration method (factory vs. per-user) up front, then quantify post-calibration accuracy and drift over wear time—practices that have long been standard in both CGM validation and in broader method-comparison communities [12] [51] [52] [54]-[56] [59] [61]. For categorical endpoints (e.g., dehydration flags or threshold crossings), such studies present sensitivity, specificity, ROC-AUC, and time-to-detection, noting that Bland-Altman analysis is not appropriate for binary outcomes [51] [52] [59] [61]. In sweat-specific research, flow-aware analyses (*i.e.*, measuring or controlling for sweat rate and volume) prevent dilution effects from being misinterpreted as sensor chemical drift, especially under low-flow or transitional conditions [13] [38] [44].

7.6. Mapping Archetypes to Use Cases (With Realistic Anchors)

Choosing among the three archetypes works best when the decision is tied to what the study actually needs to decide—how much latency is tolerable, what cadence carries useful information, and what evidence can be shown without hand-waving. When minute-by-minute dynamics carry the value signal, continuous BLE systems make sense. In that setting, the early centimeters of the fluid path matter more than a catalogue of electrode materials: trimming dead volume cuts start-up delay and planning time alignment and flow-rate stratification from day one prevents pooled errors from hiding transport effects. Telemetry should use buffered bursts, and the paper should say plainly how sensing cadence maps to radio cadence (advertising/connection intervals, burst size), what the buffer holds, and what happens when a window is missed—retry, compress, or drop. Thermal spreaders and breathable laminates belong in the methods, not the supplement, since comfort controls compliance in long wear [10] [11] [13] [38].

Battery-free NFC patches are better when a single tap or image answers the question—hydration status at half-time, an electrolyte snapshot before heat exposure. Accuracy here is won or lost on geometry and imaging discipline. Volumetric markings must be readable in ordinary light, and the workflow should be reproducible: note the camera distance and angle used by staff, how white balance was handled, and the phone models that were tested. If a target analyte is poorly served by colorimetry, adding one or two electrochemical channels preserves sensitivity without giving up the zero-idle-power behavior that makes NFC attractive in the first place. Reports that include read range with common phones and per-snapshot agreement against a comparator are easier to trust and easier to reproduce [11] [12] [39].

Harvest-assisted platforms fit longitudinal work with infrequent but consequential reads—stress hormone profiles, extended field campaigns. Here the schedule follows energy availability from biofuel or thermoelectric harvest: sample and transmit on plateaus, and size the storage element only to bridge between plateaus so stiffness and bulk do not creep in. Useful write-ups show the harvest profile beside the sampling plan, the time to the first usable packet after a cold start, and the share of planned windows that were skipped or deferred under real conditions. These details decide whether a design survives outside the lab [38] [39].

Across continuous metrics such as glucose, clinical CGM performance remains the practical anchor: single-digit MARD with high 20/20-zone agreement in large trials sets expectations for free-living use. Until noninvasive fluids meet that bar with strong validation, it is more honest—and more useful—to frame outputs as trend and threshold indicators rather than replacements for blood or ISF values [54]-[56]. Methods from ocular platforms transfer cleanly: on-eye telemetry with explicit tear-to-blood lag modeling shows how to co-register timestamps, estimate lag under defined perturbations, and check that the mapping holds across cohorts—exactly the workflow needed for sweat and ISF devices facing slow transport kinetics [22].

Interpretability improves when context is stated before claims. Give the sweat-rate range and wear site for each analysis, declare whether the goal is trend tracking or a threshold decision, and present outcomes by stratum (flow, site, temperature) rather than as a single pooled figure. That simple discipline makes cross-archetype comparisons possible and shows, at a population level, where devices work and where they fail [60]. Concrete anchors help readers see the stakes. In sports studies, sweat-lactate thresholds line up with ventilatory thresholds only when protocols and threshold definitions are pre-registered and when threshold-agreement appears next to bias and limits of agreement; only then does the result support training-zone decisions [24]. For electrolytes and hydration, ion-selective patches have tracked $Na^+/K^+/Cl^-$ on body under standard comparators; the strongest reports pair site-matched benchtop assays on co-collected samples with simple mass-balance checks, reinforcing broader syntheses that situate sweat sensing in metabolic and clinical contexts [61] [62].

Finally, to make comparisons fair across BLE, NFC, and harvest-assisted systems, keep a common reporting spine: reference method and sampling schedule; the calibration window and whether performance holds beyond it; the way lag is handled; per-stratum outcomes by flow, site, and temperature; threshold-agreement (if relevant) alongside bias and LOA; the radio policy and typical user actions per hour; and an exclusion table with reasons. With those pieces in view, readers can judge delivered, interpretable information—not just limits of detection [18] [22] [54] [61].

8. Challenges & Future Directions

The next phase of skin-interfaced, microfluidic wearable biosensing will be driven by system-level coherence rather than isolated component advances. Sections 3-7 outlined what currently works: fluidic architectures that preserve temporal integrity of samples [12] [18] [21], materials and stretchable interconnects that raise SNR at low bias [5]-[10], radios tailored to information cadence [11] [18], and validation protocols that prioritize agreement over correlation [3] [56] [57]. Rather than recapitulate those findings, this section proposes concrete targets, testable hypotheses, and benchmark tasks that the field can adopt, with expectations anchored by clinical CGM accuracy for continuous analytes [54]-[56] and by transport-aware protocols for non-blood fluids [18] [21] [22] [47] [61].

8.1. A Shared, Flow-Aware Comparability Baseline

Standardize what we report, not just how we report. Future studies should pre-register endpoints and analysis methods (accuracy, agreement, reproducibility); report accuracy stratified by sweat rate, site, temperature, and motion; disclose raw vs. aligned timelines along with the exact alignment method; and quantify repeatability/interchangeability across days and devices using Lin's CCC or ICC in addition to Bland-Altman bias and limits [3] [57] [58]. This level of reporting is already standard in other wearable and clinical device validation domains [51] [52] [59] [61] [62] and should be expected here as well.

Milestone: For each major analyte of interest, publish at least one open dataset containing raw and aligned sensor traces, sweat rate bins, Bland-Altman plots, CCC/ICC with confidence intervals, and a pre-specified exclusion policy.

Why it matters: Such open datasets and thorough reporting turn clever hardware into comparable science, enabling true apples-to-apples synthesis across different labs and devices [23].

8.2. Fluidics Designed "From the Lowest Flow Up"

Decision rule: Design your microfluidic system around the lowest sweat-rate decile of your target user population; everything else will be easier to handle if you can solve for extremely low flow. Use minimal internal volume in the first 1 - 2 cm of the fluid path, include hydrophilic priming coatings, implement capillary-burst valves for chronological segmentation, and add bubble vents or traps near the sensing site [12] [18] [21]. Treat sweat volumetry (via impedance-length calibration or printed volume tick marks) as a primary sensor output, not an afterthought [11] [12].

Key performance gates: (i) Startup delay ≤5 - 7 min at a sweat rate of ~3 $\mu L \cdot min^{-1}$ (forearm site), reported along with the effective channel volume that causes that delay. (ii) Minimum detectable sweat rate ≤0.15 $\mu L \cdot min^{-1} \cdot cm^{-2}$, with a clearly defined failure mode below that threshold (e.g., an indicator that readings are not reliable below the rate). (iii) Bubble tolerance such that ≥90% of data epochs remain valid under scripted perturbations (movement, temperature change).

Falsifiable Hypothesis: Reducing the effective volume in the first 2 cm of the channel network below ~2 - 3 μL will decrease the median startup delay at 3 $\mu L \cdot min^{-1}$ to under 5 min without introducing significant volumetric bias, as tested on N ≥ 15 subjects across at least 2 different body sites with pre-registered acceptance criteria.

Rationale: Variance that appears to be "electrochemical noise" is often rooted in fluidic issues; fixing those upstream (in the microfluidic domain) reduces the burden on downstream algorithms and hardware [12] [21].

8.3. Transduction & Interconnects as System Levers (Not Just Materials Papers)

Decision rule: When introducing new sensor materials or fabrication techniques, report the system-level benefits: for example, the SNR at a given bias current, the stability of wireless link at a given strain or sweat exposure, or the skin temperature increase under a certain transmission duty cycle [5]-[10]. For instance, show that a PEDOT: PSS hydrogel or an MXene laminate interface yields a lower impedance contact that shrinks the required power headroom and reduces heat generation; or that using microfiber/serpentine interconnects maintains antenna tuning under strain and cuts BLE energy per packet by enabling shorter connection events [7] [8] [10].

Key performance gates: (i) Achieve ≥20 dB SNR at the chosen operating bias under motion and simulated sweat for at least two different electrode stack configurations (demonstrating the advantage of the new material). (ii) Ensure NFC/BLE link success rate ≥95% (or RSSI drift ≤3 dB) under 20 - 30% tensile strain and sweat exposure.

Falsifiable Hypothesis: Replacing traditional flat metallic traces with conductive microfibers or serpentine-pattern interconnects will reduce antenna detuning (fractional frequency shift $|\Delta f|/f$) by ≥50% at 20% stretch and will lower the BLE energy per data packet by ≥25% due to shorter re-connection or transmission windows (tested in a controlled strain and sweat simulation).

Rationale: Materials that provide low-bias, high-SNR sensing and mechanical compliance directly improve the energy per insight and user comfort, linking material science innovations to tangible system gains [5]-[8] [10].

8.4. Radios & Power through the Lens of "Energy per Insight"

Decision rule: Let the needed information cadence dictate the radio/power configuration. If a minute-by-minute continuous profile is the answer (as with glucose or lactate kinetics), use continuous electrochemistry with buffered BLE bursts; in that case, tune the system so that average power scales with reporting cadence, not radio overhead (e.g., long BLE intervals) [18]. If information is only needed episodically, go battery-free with NFC: use geometry-as-memory (e.g., colorimetric microchannels) so that one smartphone tap yields a full panel of data at effectively zero idle power [11] [12]. If using harvesters (BFC/TEG), treat them as schedulers for the radio: only sample/transmit when energy has accumulated, and size energy storage just large enough to buffer these intervals [18] [21].

Key performance gates: (i) For BLE systems—energy per minute of "trusted trend" ≤ 150 - 250 mJ per minute for a dual-analyte continuous monitor at 1 min resolution (including any retransmissions). (ii) For NFC systems—energy per complete read (e.g., a four-analyte panel in one tap) ≤ 50 - 80 mJ with ≤ 3 s dwell time in the RF field. (iii) For harvester-powered devices—publish a duty-cycle map that shows sensing/transmission frequency as a function of available energy, including the explicit policies for using energy plateaus.

Falsifiable Hypothesis: In harvest-assisted modes where data transmission is gated to natural energy plateaus, the mean energy per insight (whether defined as a minute of trend data or a single panel read) will be no higher than that of an equivalent battery-powered BLE or NFC system operating under the same conditions, while maintaining non-inferior agreement metrics (to be verified with a pre-registered validation protocol).

Rationale: This reframes radio choices from hardware decisions into decisions about information economy. By quantifying energy per insight, different approaches become directly comparable across use cases [11] [18] [21].

8.5. Modeling & Personalization That Respect Transport

Decision rule: Calibrate and interpret through a transport lens. Fuse on-patch flow, skin temperature, and motion channels with the chemical readout, and judge agreement in rate-of-change categories (rise/flat/fall) rather than only absolute levels, so parameters transfer across sessions with factory or minimal calibration when physiology allows [53] [57] [58]. For glucose-like analytes, use clinical CGM as the bar: single-digit MARD with high 20/20-zone agreement in free-living trials defines credible trend tracking; if lag-aware MARD approaches those anchors, the wearable is delivering clinically useful trends, whereas claims of blood equivalence require multi-cohort evidence and stable lag handling across protocols and sites [54]-[56]. For sweat-centric aims—hydration status, electrolyte balance, lactate threshold—center validation on mass-balance outcomes and threshold detection and make flow-dependence explicit by stating how flow was measured and how results change across flow strata [18] [21] [47] [61].

Key performance gates: (i) Pre-specify the alignment window appropriate to the analyte dynamics (e.g., 5 - 10 min for glucose), then report MARD and %20/20 by rate-of-change bins, both inside and outside the calibration window, with the handling of missed windows or gaps stated plainly [54]-[56]. (ii) Set session-level bounds before data collection (e.g., slope drift ≤ 10% and a small, unit-appropriate intercept bound over 24 h), justify any alternative limits, and disclose where these gates were or were not met; stratify by site/flow/temperature and publish exclusions so missing data is auditable [18] [21] [47] [53] [57] [58] [61].

Falsifiable Hypothesis: Adding sweat flow rate and skin temperature as features to a wearable's calibration model will reduce low-flow MARD by ≥30% without increasing false alarms for threshold-based alerts, compared to a calibration model that does not include these transport-related features.

Rationale: Properly accounting for transport phenomena (fluid generation, diffusion, lag) can turn what appears to be "noisy biology" into a predictable bias or lag that can be modeled and managed, improving accuracy and trust in the wearable outputs [22] [53] [57].

8.6. Translation, Risk, and Sustainability by Design

Decision rule: Map device outputs to recognized clinical or performance anchors—for continuous analytes, think in terms of CGM-style metrics (MARD, %20/20); for threshold-based metrics, think in terms of diagnostic sensitivity/specificity and time-to-detection [54]-[56] [62]. Build IRB-ready packages into the development cycle: assess skin safety (check for erythema, TEWL changes), create thermal maps of the device under operation to ensure any temperature rises are <~1 - 2˚C, and have a data privacy plan separating personal identifiers from physiological data. Favor designs with disposable microfluidic cartridges and reusable electronics and be transparent about materials and end-of-life disposal (particularly for batteries or biohazardous reagents) [11] [60].

Key performance gates: Ensure ≥95% adhesion survival over the intended wear duration under expected movement/heat conditions (e.g., no more than 5% of patches partially peel off within an 8-hour exercise protocol). Limit skin temperature increases to ≤+1.5˚C at electronics or antenna hotspots during worst-case operation. Provide template documents for informed consent and data de-identification if releasing datasets.

Rationale: This approach shifts considerations of ethics, user safety, and device sustainability from afterthoughts to defined engineering goals. By including these in design criteria, researchers can address regulatory and user acceptance factors early, rather than revisiting fundamentals late in the development process.

8.7. Benchmarks & Minimal Reproducibility Package (MRP)

We propose a set of benchmark test scenarios and a minimal reproducibility package for key application areas:

- **BT-1 (Hydration/Electrolytes, episodic):** A battery-free NFC sweat panel with volumetric microfluidics. Benchmark by reporting energy per read, image analysis robustness under different lighting, and agreement with a standard sweat collector and ion analyzer, stratified by sweat rate [11] [12] [23].
- **BT-2 (Lactate, continuous):** A BLE-based two-analyte (e.g., lactate + glucose) electrochemical patch tested across staged exercise workloads. Benchmark by reporting energy per minute, lag-aware MARD, and Bland-Altman bias by body site [18] [21] [24].
- **BT-3 (Stress hormones, sequence-sampling):** A microfluidic patch that collects time-sequenced sweat samples for cortisol/epinephrine, using either periodic NFC reads or harvester-gated BLE bursts. Benchmark by reporting the percentage of valid sample packets, pM-level limits of detection, and the alignment protocol for comparing to serum levels [21] [22].

For each benchmark, the minimal reproducibility package (MRP) should include channel CAD files and measured effective volumes, protocols for any induced perturbations (exercise, temperature changes), data alignment scripts, exclusion rules for data quality (with justifications), anonymized raw and aligned datasets, and analysis notebooks illustrating the key computations [51]-[53] [57]-[59]. The emphasis is on sharing the deliverables and analysis approach, not rehashing the descriptive text of prior sections, so that others can verify and build upon the results.

9. Conclusions

This review has considered skin-interfaced, microfluidic wearable biosensors as complete systems, in which fluidics, interfaces, transducers, power, radios, and validation are tightly coupled rather than interchangeable modules. Three broad lessons emerge. First, microfluidic sample handling is often the primary amplifier of success or failure on skin: start-up volume, chronological segmentation, and bubble control decide whether the sensor sees fresh secretion, a mixed lagged pool, or nothing at all. Second, soft, low-impedance interfaces—hydrogels, conductive elastomers, layered 2D materials—do more than improve comfort: they stabilize potentials at low bias and loosen constraints on power and communication budgets. Third, architecture is clearest to compare when framed in terms of energy per insight: the energy required to obtain a minute of trusted trend, a defensible threshold decision, or a time-stamped biochemical snapshot, rather than isolated figures of merit such as LOD or peak sensitivity.

Two practical design rules follow. The first is to match the radio and power stack to the cadence of information. Buffered BLE suits analytes whose dynamics unfold on the scale of minutes and benefit from continuous time-stamped streams. Battery-free NFC shines when information is needed only episodically and when microfluidic "geometry-as-memory" can compress histories into a tap-to-read panel. Hybrid or harvest-assisted modes become attractive when physiology or the environment naturally gates both energy availability and the need for updates, such as exercise-recovery cycles or repeated clinical encounters. The second rule is to validate for agreement rather than correlation. Agreement-centric analysis—bias and limits, interchangeability metrics, and lag-aware error evaluated across rate-of-change, sweat rate, site, temperature, and motion bins—aligns evaluation with how devices will be used and makes it easier to compare new systems against both established laboratory assays and continuous glucose monitoring benchmarks.

Despite rapid progress, several limitations remain and define the near-term engineering agenda. Low-flow physiology and gland heterogeneity still challenge start-up times and temporal fidelity in sedentary conditions. Evaporation, bubbles, and partial wetting can bias concentration readouts if not fully controlled. Adhesion, reagent stability, and device heating constrain multi-day wear. On the data side, relationships between sweat, tear, or interstitial fluid and blood are analyte- and context-specific; credible models must embed transport, lag, and dilution rather than assuming fixed conversion factors. Privacy, equity, and deployment ethics also move to the foreground as datasets scale across populations, climates, and usage scenarios.

Within this landscape, recent demonstrations already point toward the next generation of lab-on-skin systems. Advanced sweat patches, multiplexed analyte panels, hybrid electrochemical-optical platforms, and population-scale studies of electrolytes, metabolites, and hormones illustrate how microfluidics, soft interfaces, and radios can be co-designed to capture richer physiology on skin [43]-[52]. In parallel, battery-free and harvest-assisted architectures, energy-aware duty cycling strategies, and tightly integrated smartphone or cloud links show how an energy-per-insight mindset can turn disparate power and communication schemes into comparable options along a single axis [50] [53]-[55]. As these threads converge—fluidics that respect transport, interfaces that remain low-bias under motion and perspiration, radios and power stacks tuned to the information cadence, and transparent, agreement-centric validation with reusable datasets—microfluidic wearables can move from bespoke prototypes to robust, clinically anchored tools that deliver interpretable biochemical context outside the clinic and over time.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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