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Microneedle Sensors for Subcutaneous Biomarker Detection

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Abstract. Continuous monitoring of body chemistry is crucial for the management of chronic diseases such as diabetes, but blood draws and implanted sensor wires remain invasive, uncomfortable, and expensive for everyday use. The microneedle sensor is a micrometer-scale projection array that can penetrate the stratum corneum and the interstitial fluid (ISF) of the sample without touching the pain-sensing nerve endings, and it is a minimally invasive method for detecting subcutaneous biomarkers. This paper follows the thread that actually decides how such a device performs. The materials read like a trade-off table. Metal and silicon give dense, conductive arrays but stay rigid and pricey; polymers are cheap enough to throw away after use, yet bend; hydrogels load enzymes and dyes straight into the matrix, but respond slowly. The chemistry maps onto targets, not the other way around. Enzymatic amperometry still owns glucose and lactate; potentiometric membranes handle ions; aptamers and antibodies open the door to proteins and narrow-window drugs; fluorescent biodegradable patches let a smartphone read through the skin with nothing left behind. Building on these schemes, integrated patches now measure two metabolites at once in volunteers, dual glucose-and-metformin platforms report pharmacokinetic and pharmacodynamic feedback in diabetic animals, and disposable cartridges separate cheap consumables from reusable electronics. The remaining barrier is no longer device chemistry but longitudinal patient-grade validation and regulatory standardization. Closing this gap could turn microneedle patches into everyday closed-loop tools for personalized disease management.

Keywords: Microneedle sensors, interstitial fluid, wearable biosensors, biomarker detection, diabetes management

1. Introduction

The continuous monitoring of physiological markers has been gradually transferred from hospital wards to everyday life, with diabetes being the clearest example. Patients measure glucose many times a day, but each return blood stick reading only records a snapshot of a concentration that varies continuously with feeding, exercise and physiological stress. Commercial continuous glucose monitors (CGMs) solved part of this problem, but they still rely on a rigid sensor wire that stays in the subcutaneous tissue for days, causes local irritation, and costs more than many health systems can sustain [1]. The gap between what clinicians want, a painless and affordable window into the

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body's chemistry, and what current devices deliver keeps driving research toward less invasive sampling.

Interstitial fluid (ISF) is the natural intermediate compartment. It fills the extracellular spaces surrounding dermal cells and lies just a few hundred micrometres beneath the skin's surface. ISF small molecule concentrations are tightly correlated to blood for glucose, lactate, electrolytes and many drugs [2]. The composition of ISF is very much like that of blood plasma but with substantially lower protein level. Thus, lower matrix and easier sample handling is expected for small-molecule targets [3]. Low barrier to reach ISF, needles need not be long. Microneedle sensors consist of micro-projections of hundreds of micrometres in length; hollow variants function as micropipettes, piercing the stratum corneum without reaching pain-sensitive nerve endings. They present an easy alternative to directly tapping ISF without incurring hemorrhage or unnecessary pain [3].

The field has grown quickly. Both solid microneedles, coated with enzymes to be read amperometrically, and hollow designs that could extract the ISF for subsequent off-line analysis were demonstrated as early as 2010 [2]. A whirlwind of rapid diversification rather than convergence followed: researchers introduced a wide range of new materials—some silicon, then metal, some polymer and hydrogel; and fastened disparate transduction schemes to them—for both electrochemical, optical and immunoassay-based detection approaches [1-3]. Meanwhile, target analytes have expanded beyond glucose to include lactate, electrolytes, protein biomarkers, nucleic acids and therapeutic drugs [4]. Recent technology focuses on integrating everything along the system pathway in terms of wireless electronics, smartphone readout and closed-loop coupling to therapeutic release where sensing and treatment can share the same patch [5].

But what continues to hold the field back is often that these advances are reported in isolation. A typical paper describing a new hydrogel microneedle may barely touch on the transduction chemistry required to read out the signal from a protein biomarker of interest. Conversely, a paper demonstrating an elegant aptamer based sensor for a single drug will say little about how that patch might perform over days of wear. Review articles tend to focus on one of these aspects to the exclusion of others, forcing the reader to stitch together material properties, transduction mechanisms, targets, and system-level design considerations from several disparate literatures. Therefore, to facilitate understanding, this review is divided into paths that actually control the performance of devices; device materials and geometry (Section 2.1), transduction mechanisms (Section 2.2), classes of biomarkers that have been demonstrated and what the measurement of each dictates from the sensor (Section 2.3), and complete system integration together with clinical data where available (Section 2.4). rticular emphasis is given to publications appearing from 2021 onward, when integrated, wirelessly connected microneedle platforms first became available for human studies [1, 6].

2. Microneedle sensors for subcutaneous biomarker detection

2.1. Materials and structural designs

The choice of material for a microneedle influences its subsequent properties such as its penetration into the skin, the amount of fluid it can collect, its reusability and its interaction with the transduction layer. Four main groups of materials are commonly studied in the literature: metal, silicon, polymer and hydrogel. Each has its own advantages and disadvantages [3].

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Metal microneedles are typically stainless steel or titanium, materials that can withstand repeated use and insertions under laboratory conditions and allow for direct electrical contact, greatly simplifying the wiring up to the readout electronics. However, their rigidity is a primary limitation, necessitating individual fabrication or small arrays and thereby restricting the density of sensing sites to very low levels. Silicon is the other extreme. Arrays of silicon microneedles, fabricated using deep reactive-ion etching and metallized with gold or platinum, have been demonstrated for transdermal glucose sensing as well as protein immunodetection using a single patch [7, 8]. The capability to pack hundreds of needles per square centimeter is a significant advantage for multiplexing. Still, because silicon breaks easily and costs a lot to produce, the majority of these silicon patches remain experimental.

Polymer microneedles solve the cost issue. The molding process using biocompatible resins enables polymer microneedles to possess sharp tips and high aspect ratios, and their low cost makes them suitable for disposable applications. Their downfall is mechanical. Unlike metals, polymers tend to bend or snap more readily, and adding a conductive layer requires a separate step, which entails additional processing steps. Different fabrication methods exist: from laser cutting through micromolding up to 3D printing, which impacts tip sharpness, batch consistency, and ease of iteration on a design [3]. In contrast are hydrogel microneedles that swell upon contacting ISF, drawing fluid into their needle bodies via swelling and capillary forces, which they may subsequently remove for analysis or read optically whilst still inserted [9]. As the matrix is mostly water, it allows direct loading of enzymes and fluorophores during polymerization. This comes at the cost of slow response and poor mechanical strength; hence hydrogels tend towards sampling or optical sensing as opposed to fast amperometric readout.

As much geometry as chemistry: needle height has to be greater than the stratum corneum thickness (~10-20 um) yet less than the dense nerve layer (around 300-500 um), or else it ceases to be painless; tip sharpness, spacing, and number of needles per patch control penetration reliability on skin sites varying in thickness and elasticity; devices used in clinical-grade studies have uniform arrays with controlled heights since uneven insertion leads to noisy signals and patient discomfort – both failure modes visible immediately during human testing [1, 2].

2.2. Sensing mechanisms

Most microneedle sensors change a chemical signal into an electrical current or potential: their conversion mechanism influences the information they can detect and the response speed of the sensor. The oldest and most mature scheme is enzymatic amperometry, where an oxidase (typically glucose oxidase or lactate oxidase) is immobilized onto the needle electrode, consuming its substrate while producing hydrogen peroxide, which gets oxidized at the electrode surface at a fixed potential. Current scales with substrate concentration and the sensor may be read continuously as long as the enzyme stays active: this is the principle of most glucose microneedle patches, such as silicon arrays reporting stable transdermal glucose tracking in animal models [6, 8]. Enzymatic sensors offer selectivity and speed. However, enzymes gradually denature under skin temperature and interfacial contamination, limiting the maximum wearable duration; additionally, the peroxide signal can be confounded by electroactive species in ISF, requiring permselective membranes to eliminate interference.

A different approach to ions uses potentiometric sensing instead of an enzyme: an ion-selective membrane is put onto the electrode; the open-circuit potential difference between the working and reference electrodes varies according to the activity of the target ion. Since there's no consumption

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of the receptor, these sensors are intrinsically stable and reversible – ideal for continuous monitoring of electrolytes. Solid-state potentiometric microneedle patches were reported in the literature for simultaneous pH and ion monitoring during wear [3]. Resolution is usually worse than amperometry and interference from other ions requires careful membrane formulation, however the stability is a real advantage for long-term wear.

Affinity-based transduction serves as the major non-enzymatic strategy for large biomolecules. Both antibodies and aptamers bind their targets with high specificity, and this binding induces an electrochemical signal via a redox reporter attached to the receptor. As the binding process is reversible, affinity sensors may be reused throughout one wear session, and the same platform can be adapted to various targets simply by changing the receptor sequence. A wearable microneedle patch using electrochemical aptamer sensors showed continuous monitoring of two antibiotics with narrow therapeutic windows in humans, whose readings followed drug concentrations throughout the whole dosing interval [10]. Sensitivity at low concentrations is challenging as affinity sensors need some fraction of receptors to be bound, and fouling of the receptor layer over time still needs solving.

Optical transduction (fluorescence, colorimetry, or Raman) does not rely on any electrode. In particular, fluorescent microneedles are very attractive as the fluorophore could be embedded in a biodegradable matrix so that the whole patch dissolves upon use. A fully biodegradable fluorescent microneedle array was used for tether-free continuous glucose monitoring, reading the glucose-dependent fluorescence intensity through the skin with a smartphone accessory [9]. Optical readouts do not suffer from electrical interference and do not require wiring, although an external light source and detector are needed, and photobleaching limits long-term stability.

2.3. Biomarker spectrum

Biomarkers chosen by microneedle sensors relate directly to how accessible ISF is and the maturation of each transduction scheme. Glucose is ubiquitous for obvious reasons – it's small, abundant, and clinically essential; enzymatic amperometry performs well at its physiological concentrations. A review of wearable glucose sensing outlines the evolution from fingerstick meters to CGM towards multiplexed, closed-loop systems [6]. Other classes have been demonstrated in vivo, each posing different challenges to the sensor. Small metabolites like lactate extend naturally from the enzymatic approach.

Microneedle patches using lactate oxidase have monitored lactate in ISF continuously over exercise protocols whose dynamics follow those seen in blood lactate with a short lag [1]. Electrolytes work better with potentiometric designs (as discussed above) and multiple potentiometric patches report simultaneous measurements of pH and ions in vivo [3]. All of these molecules are electroactive or have specific enzymes, mapping easily to electrochemical transduction.

Large protein biomarkers face detection barriers due to slow diffusion across skin layers and low physiological concentrations for most tumour-specific and disease-specific markers. Immunosensing via antibody-modified silicon microneedles was demonstrated for breast cancer biomarkers in both buffer and biological samples with detection limits in the sub-nanomolar range, though the response time is long due to the need for the protein to diffuse to the capture layer [7]. The capture surface needs to be resistant to fouling from the small amount of protein that does cross the skin; hence, surface chemistry, blocking layers, and receptor orientation are common themes in these reports. Nucleic acid targets encounter comparable mass-transport limitations because large nucleic acid

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fragments diffuse slowly within the ISF matrix, raising requirements for highly sensitive recognition probes. Narrow window drugs, however, have proven a practical target since their therapeutic concentrations are relatively high, relaxing the sensitivity requirements. Aptamer-based microneedle sensors have tracked antibiotics in humans, paving the way for personalized dosing [10].

Multiplexing comes up repeatedly among these demonstrations. With a patch containing many needles, there is no structural reason not to monitor more than just one analyte, and several groups have advocated measuring panels of diabetes related markers, glucose along with lactate, ketones or inflammatory proteins, capturing metabolic state instead of a single number [4]. Integrated arrays reported in human studies already measure two metabolites simultaneously [1] and the roadmap calls for multi-biomarker panels informing drug dosing decisions [5].

2.4. System integration and clinical translation

Moving from a basic sensor to a wearable device needs electronics, power, wireless communication and packaging to function well when in contact with skin, sweat and movements. This is usually the difficulty in developing new sensors, and it is also the area which has been improved greatly by recent research.

The reference example is the microneedle array fully integrated for continuous detection of several biological markers in interstitial fluid (ISF) during daily activities. This system integrates reusable electronics with a disposable microneedle array, transmits data wirelessly to a smartphone program and determines the concentrations of lactate and glucose at the same time in the volunteers who do daily work [1]. The advantage of the disposable cartridge in commercial aspect is that it separates the costly electronics from the inexpensive consumables, just as it made continuous glucose monitoring (CGM) systems practicable. Similar integration is shown in the Chinese research groups, where a dual-sensor microneedle device is used to measure glucose and metformin at the same time in the ISF of diabetic rats and send both signals to a smartphone for pharmacokinetic and pharmacodynamic analysis, which is a clear direction towards individualized treatment in diabetes [5].

Biodegradable designs lead to a new approach of integration. When the microneedles and the sensor chemistry disappear after application, the device does not leave any residue in the skin and thus avoids the removal step, thereby decreasing the long-term foreign-body response. The biodegradable fluorescent glucose patch has shown this idea in animal experiments, where the array absorbed gradually while the reading was still conducted through the skin [9]. The main disadvantage is that dissolution imposes a strict restriction on the device's lifetime, hence biodegradable systems are suitable for medium-term monitoring instead of permanent use.

Clinical evidence remains the bottleneck. Most microneedle sensors are validated in vitro or in animal models, and only a handful of human studies exist. The studies reported to date show acceptable tolerability, no serious adverse events, and good correlation with blood measurements for glucose, lactate, and antibiotics, but they are small, short, and performed in healthy volunteers rather than patients [1, 10]. Sensor-to-sensor reproducibility is another unresolved point: microneedles are handmade in most labs, so calibration curves rarely transfer between batches without re-measurement, and regulatory agencies have not yet established dedicated, standardized evaluation pathways for this category of wearable biosensors [4]. Open questions include how sensors drift over the full wear period, how skin-to-skin variability affects calibration, and whether the ISF-to-blood lag, minutes for many analytes, is clinically acceptable for the intended decision [4].

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Taken together, the field has assembled most of the pieces: materials that are cheap and safe, transduction schemes that cover the main biomarker classes, and integration architectures that work in ambulatory settings. What is missing is longitudinal evidence at scale and regulatory-grade studies that connect sensor output to clinical outcomes. The next phase of microneedle sensor research will likely be defined less by new chemistry and more by disciplined clinical validation and by closed-loop systems in which the same patch senses and delivers therapeutic agents [3].

3. Conclusion

Microneedle sensors have turned the dermis from a barrier into a window, giving minimally invasive access to subcutaneous chemistry that once required blood draws. Across materials, no single design dominates. Metal and silicon yield dense, conductive arrays but stay rigid and expensive; polymers are cheap enough to be disposable but bend more easily; and hydrogels load enzymes and fluorophores directly while trading response speed for softness. Transduction follows the analyte: enzymatic amperometry covers glucose and lactate, potentiometric membranes cover ions, affinity receptors extend sensing to proteins and narrow-window drugs, and optical schemes enable biodegradable patches that read through the skin. On targets, glucose remains the anchor, but lactate, electrolytes, cancer markers, nucleic acids, and antibiotics have all been demonstrated in vivo, and multiplexed panels rather than single analytes now set the development direction. Integration has caught up with materials: reusable electronics paired with disposable cartridges, wireless smartphone readout, and dual glucose-metformin pharmacokinetic platforms show that sensing can feed dosing decisions directly. Together, these advances move microneedle sensing from a laboratory exercise toward affordable everyday diagnostics and frame a practical path to closed-loop systems that both measure and treat. Why, then, are these patches not yet on every wrist? The human data are thin. The studies are short, run in healthy volunteers, and rarely follow a patient through a full treatment cycle. Enzymes denature, receptor layers foul, and handmade arrays mean a calibration curve from one lab does not transfer to the next. Regulators have no dedicated pathway for this device category, and the minutes-long ISF-to-blood lag still needs clinical justification. The next phase will not be won with a cleverer molecule. It will be won with longitudinal trials in real patients, standardized fabrication, longer-lasting recognition layers, and patches that sense and deliver in one closed loop. Whether they finally leave the bench depends on that discipline, not on more chemistry.

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