

RESEARCH ARTICLE

Cell-Like Portable Biologics-Free Sensors for Stress Diagnostics

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ABSTRACT

Mental health is a pressing and widespread global concern, necessitating accessible, reliable and cost-effective tools for its ongoing monitoring and effective management. Herein, a portable “molecule-probe” platform is presented that integrates a specific chemical reaction within a hydrogel microreactor with *n*-type semiconductor doping for signal amplification. This biologics-free sensing platform enables rapid, sensitive cortisol detection, a key stress biomarker, with superior response time-selectivity compared to conventional antibody-, aptamer-, or chemical-based detection systems. The specific chemical reaction ensures over 50-fold selectivity for cortisol against other biochemicals including cholesterol and glucose. Utilizing non-invasive saliva-based sampling and a biodegradable hydrogel matrix, the device offers low post-waste and high cost-effectiveness. With a short diagnosis time (~ 8 min) and low production cost (~ 7 dollars per unit, projected to drop to 4 dollars at scale), the portable sensor is particularly well-suited for frequent, point-of-care applications in resource-limited or decentralized healthcare settings. By eliminating costly biological recognition elements such as antibodies or aptamers and long diagnosis time, this work introduces a new design paradigm for sustainable biochemical sensing, enhancing accessibility to chronic stress monitoring and mental health assessment across socio-economic boundaries.

1 | Introduction

Stress is a natural physiological and psychological response to situational pressures or demands and constitutes a routine component of everyday life. However, when persistent, chronic stress can significantly contribute to the onset and progression of various mental health disorders and medical conditions, from eating disorders to anxiety disorders, bipolar disorder, post-traumatic stress disorder (PTSD), even self-harm and suicide [1–4]. Despite its clinical relevance, direct assessment of mental health and stress levels remains challenging and often imprecise,

due in part to the subjectivity and variability of core symptoms as well as the limitations of self-reported metrics [5–8].

As a primary biomarker of the hypothalamic-pituitary-adrenal (HPA) axis, cortisol and cortisone with similar chemical structures and properties, are the key biochemical markers associated with the stress of human bodies [9–15]. It can be detected in various biological media including saliva, sweat, hair, and blood (Figure S1, Table S1) [16–19]. However, its concentration fluctuates diurnally and are subject to circadian rhythms and matrix-dependent variation, which complicates accurate,

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real-time assessment [7, 8, 20–22]. To address these complexities, a range of analytical methods has been developed, including DNA/RNA aptamer-based sensors, antibody-based assays, molecularly imprinted polymer (MIP) based sensors, as well as wearable and implantable devices [23, 24]. Despite their high selectivity and accuracy, biosensors utilizing biological recognition elements such as antibodies and DNA/RNA aptamers often incur substantial costs related to production, storage, transportation, and disposal under controlled conditions [25–27]. These factors pose significant challenges to the long-term and multiple stress monitoring of these sensors for individuals. Conversely, MIP-based and wearable chemical sensors utilizing conventional redox systems (e.g., ferricyanide, PEDOT:PSS, and other electroactive chemicals) offer advantages in terms of stability and affordability [21, 28]. Nevertheless, these approaches typically suffer from limited selectivity and signal fidelity in default of targeted reaction and effective signal amplification.

To enable effective, long-term monitoring of chronic stress, several prerequisites in material selection and device design must be met: (i) low cost to facilitate widespread accessibility and multi-testing; (ii) minimal post-consumption waste to support environmental sustainability; (iii) high selectivity, sensitivity, and stability to ensure accurate detection; and (iv) rapid diagnostic turnaround to enable convenient monitoring and decision-making.

To fulfil these criteria, in this study, we developed a distinct class of cell-like “molecule-probe” sensors, in which a specific chemical reaction between cortisol and meta-chloroperoxybenzoic acid (mcpa) is exploited in a PVA hydrogel based microreactor (Figure 1). This reaction mimics the bio-molecular recognition behavior of antibodies or aptamers but without the need for biologics. The reaction triggers an electron transfer that is further amplified by incorporating the narrow bandgap *n*-type metal oxide semiconductive Nb₂O₅. This doping process can reduce the resistance of the hydrogel matrix, significantly improving signal-to-noise ratio (SNR) and overall sensor performance when compared to undoped hydrogel counterparts. The resulting molecule-probe sensors exhibit high specificity toward cortisol in comparison with other biochemicals such as cholesterol and glucose, rapid response (~ 8 min), low production cost (~ 4 dollars per test), excellent operational stability, and portability. Collectively, these features pave a cost-effective and user-friendly solution toward democratizing mental health diagnostics, particularly in underserved populations.

2 | Results and Discussion

The molecule-probe platform was well-designed by integrating a robust hydrogel matrix, a specific chemical reaction, and a dopable semiconductor. To ensure low-cost and minimal post-consumption waste use, polyvinyl alcohol (PVA) hydrogels were employed as the structural framework for the sensing module. Within this matrix, mcpa and *n*-type Nb₂O₅ were incorporated as the chemical recognition agent and the signal amplifier, respectively (Figure 2a). The fabricated sensing module had a compact cylindrical geometry, with a diameter of 5 mm and a height of 3 mm. Scanning electron microscopy (SEM) revealed a three-dimensional porous micro-architecture, which

is expected to facilitate efficient mass transport and information transfer during chemical recognition and signal transduction (Figure 2b). The crystal structure and energy band of Nb₂O₅ were characterized using density function theory (DFT) simulation (Figure 2c). Nb₂O₅ exhibited a monoclinic crystal structure with a P121 space group, exhibited an energy bandgap (EG) is approximately 1.75 eV with the valence band (VB) and conduction band (CB) energies at -6.845 and -5.091 eV. The relatively narrow bandgap suggests efficient electron transition under ambient conditions, which supports its semiconducting behavior when integrated into the hydrogel. Transmission electron microscopy (TEM) and elemental mapping validated the morphology and spatial distribution of Nb₂O₅ particles (Figure 2d, Figure S2). X-ray diffraction (XRD) analysis further confirmed the crystalline nature of Nb₂O₅, consistent with the DFT simulation results (Figure 2e), although minor contributions from a P2(3) space group phase were also observed, indicating slight polymorphism.

To assess the intrinsic semiconductor behavior of Nb₂O₅, a metal-*n*-insulator-*n*-metal (M-*n*-i-*n*-M) structure was fabricated using indium electrodes and compared with a reference device based on *p*-type vanadium dioxide (VO₂) (Figures S3 and S4). The resulting current-voltage characteristics confirmed the formation of a heterojunction between Nb₂O₅ and *n*-Si validating the semiconducting nature of the material. To verify the specific chemical reaction between cortisol and mcpa, Raman and FTIR spectroscopy were performed using equimolar mixtures of both compounds (Figure 2f, Figure S5). In the Raman spectra of mcpa and cortisol mixture, the increasing relative intensity of peaks at ~ 1140 (—C—O—C—), 2900 (—CH₂ influenced by —C—O—), and 3400 (—OH) cm⁻¹ provide strong evidence for the occurrence of a specific chemical reaction between cortisol and mcpa [29]. The detailed reaction products are characterized using NMR and HPLC-MS to further verify the specific reaction between cortisol and mcpa via Baeyer-Villiger oxidation reaction and oxidation reaction of cycloalkenes (Figures S6–S10).

To further investigate the effect of specific chemical reaction on the electrical resistance of the hydrogel system, reciprocal cross-experiments were conducted (Figure 2g,h, Figure S11). Notably, the mcpa solution exhibited intrinsically higher conductivity than the cortisol solution (Figure S11). Two different outcomes were observed depending on the sequence of addition, indicating the presence of either a chemical reaction or a simple dilution effect. In the first scenario, the electrical behavior of Nb₂O₅ was evaluated by sequentially adding a high-conductive mcpa solution followed by an addition of an equal volume of lower-conductivity cortisol solution (Figure 2g). The observed increase in current demonstrated that there is a specific chemical reaction between mcpa and cortisol, producing free electrons that reduced the resistance of Nb₂O₅ by doping. To validate this interpretation, a reciprocal cross experiment was conducted between mcpa and cortisol solutions further verify the reaction-induced current increase (Figure 2h). Generally, in a non-reactive system, this sequence would be expected to result in a net dilution effect, reducing the current. However, the observed increase in current confirmed that a reaction did occur, involving electron transfer during reaction that led to increased conductivity. This supports the hypothesis that electron donation from the mcpa-cortisol interaction contributes directly to resistance modulation. To gain deeper mechanistic insight, the reaction process is presented in

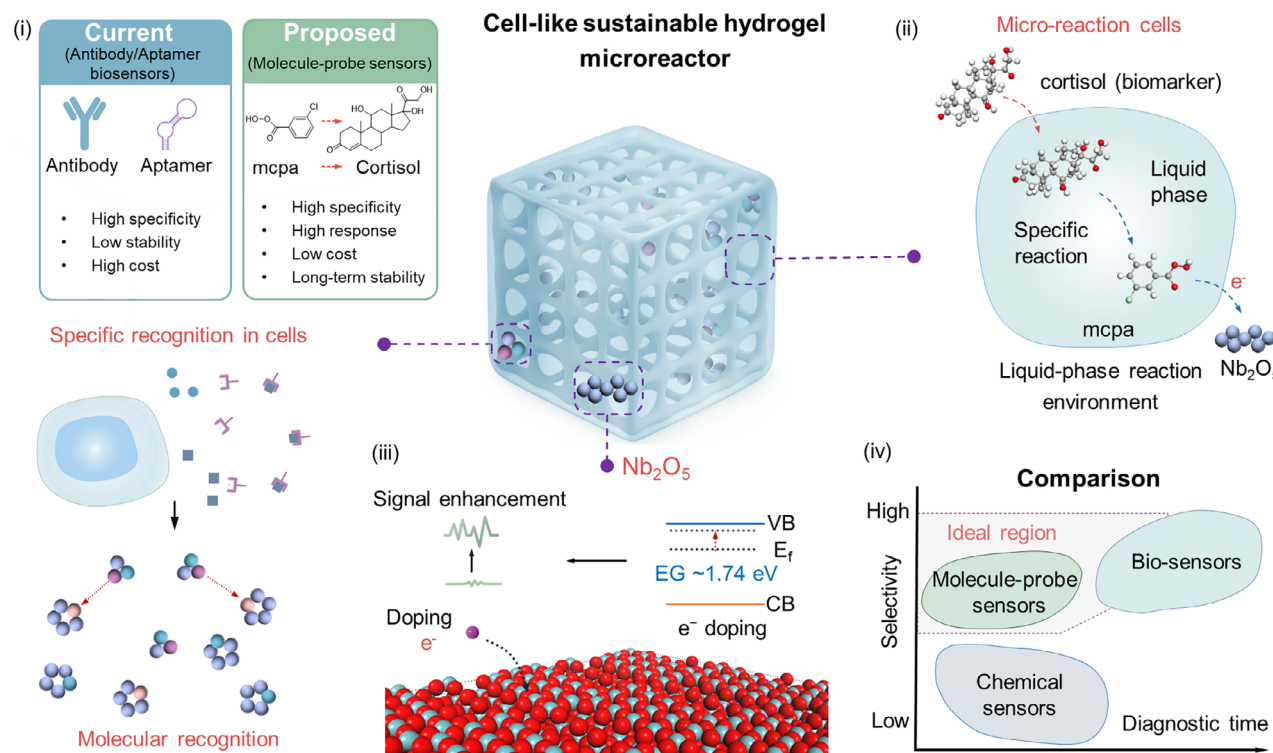


FIGURE 1 | Schematic of design concept and underlying mechanism of cell-like hydrogel microreactor “molecule-probe” sensors. The figure illustrates (i) the comparative mechanism and performance between current antibody/aptamer sensors and the proposed molecule-probe bio-sensors; (ii) cell-like microreactor in which a specific chemical reaction is employed to detect cortisol (stress biomarker); (iii) sensing mechanism of specific molecule-probe sensors where electrons generated from the specific chemical reaction between mcpc and cortisol are transferred into an *n*-type semiconductor to proliferate charge carriers and reduce resistance of the hydrogel-based flexible reactor; (iv) Schematics of benchmarking selectivity and response time of various conventional chemical sensors, biosensors and molecule-probe sensors.

detail using NMR and HPLC-MS results (Figure 2i, Figures S7–S10). The results suggest that a free radical generated from mcpc preferentially reacts with C=O group (at 20 atom) in alkane chain and C=C bond (at 4, 5 atom) of cortisol/cortisone via Baeyer-Villiger oxidation reaction and oxidation reaction of cycloalkenes. This reaction facilitates partial electron transfer into the Nb_2O_5 conduction band, significantly lowering its electrical resistance. This mechanism supports the proposed chemoresponsive sensing pathway and highlights the role of semiconductor doping in signal amplification.

2.1 | Manufacturing of Molecule-Probe Sensors

The molecule-probe sensors were manufactured by integrating a low-cost hydrogel with flexible electrodes to achieve a scalable and practical sensing system. Specifically, each sensing module consisted of flexible poly(styrene-ethylene-butylene-styrene) (PS-*p*-PS) electrodes atop a thin-layer polyethylene terephthalate (PET) substrate, a hydrogel sensing layer, and a PET lid for encapsulation (Figure 3a). The flexible electrodes were prepared using a continuous blade coating process, enabling cost-effective and large-scale manufacturing (Figure 3b). The hydrogel sensing elements were placed directly on top of the electrodes, which presents a strong adhesion between hydrogels and electrodes on PET substrates without the need for additional binders (Figure 3c,d, Figures S12 and S13). The mechanical robustness of the hydrogels was evaluated under cyclic compressive loading

for 10 cycles (Figure 3e), demonstrating excellent mechanical resilience and structural recovery, maintaining mechanical integrity under dynamic repeated deformation. Adhesion between electrodes and hydrogels was further analysed at varying inclination angles and under vigorous vibration. It demonstrated stable and robust contact between hydrogels and electrodes under both static and dynamic conditions, including during strenuous vibration (Figure 3f, Figure S13).

To evaluate the sensitivity of the molecule-probe sensor to low-concentration cortisol, a range of cortisol solutions (0 – 800 ng mL⁻¹), corresponding to total analyte amounts of 0 – 4 ng, was tested using hydrogel-based modules in a two-electrode resistance configuration, as opposed to impedance-based detection (Figure 3g, Figures S14–S18). The relative change in resistance ($\Delta R/R$) was used as the sensing metric, revealing a clear and distinguishable response across the tested range (Figure 3h). Meanwhile, the linear numerical function between $\Delta R/R$ and logarithm of concentration ($\log_{10} C$) of cortisol was built to quantitate concentration of cortisol (Figure 3i). Based on established physiological benchmarks, cortisol concentration in biofluids can be correlated with chronic stress levels [7, 20, 30]. Typically, a concentration range of 2 – 12 ng mL⁻¹ corresponds to low-stress conditions, while higher cortisol levels are indicative of elevated stress and potential mental health deterioration. These results affirm the viability of the molecule-probe sensing system for practical, low-cost, and portable chronic stress monitoring.

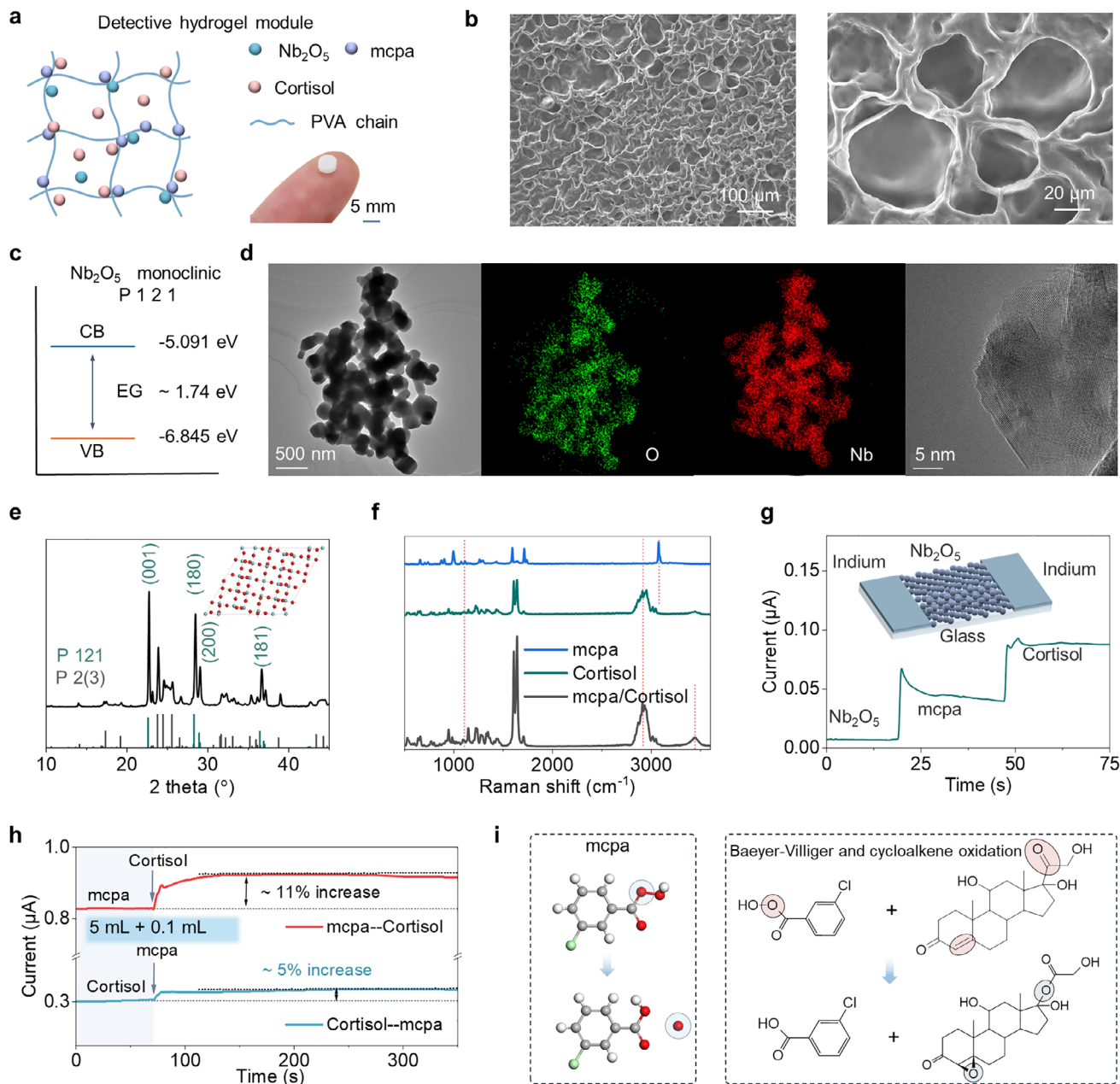


FIGURE 2 | Manufacturing and detection mechanism of hydrogel-based molecule-probe reactor. (a) Schematics and optical images of hydrogels. (b) SEM images of freeze-dried hydrogels, showing porous microstructural features. (c) Crystal structure and energy band diagram of niobium pentoxide (Nb_2O_5). (d) TEM images and element mapping of Nb_2O_5 . (e) XRD pattern of Nb_2O_5 showing crystalline phases. (f) Raman spectra of mcpa, cortisol, and their reactant at equimolar concentrations, indicating chemical interaction. (g) I-t curve of Nb_2O_5 powder on a glass slide with indium electrodes, sequentially exposed to mcpa and cortisol solutions with a bias of 2 V. (h) I-t curves of mcpa and cortisol solutions with a bias of 0.1 V. (i) Schematics of the specific chemical reaction of mcpa and cortisol via Baeyer-Villiger oxidation reaction and oxidation reaction of cycloalkenes.

2.2 | Selectivity of Molecule-Probe Sensors

Given the complexity and high viscosity of saliva, the pristine saliva determinants need to be diluted and purified to minimize the interference from food residues and other biological components [31, 32]. Main components in pristine saliva determinants present diverse molecular weight and size, and the molecular weight of most of components are below 300 Da. (Figure 4a). Since the small molecules species, such as salts and lactic acid, show a certain signal response, which can interfere with

detection of targeted biomarkers (Figure 4b,c), a semi-permeable membrane filtration approach was employed to fractionate saliva based on molecular weight, effectively removing small molecules below 300 Da. (Figure 4d–f, Figure S19). After primary filtration, the retained sample was diluted using a 9:1 (v/v) alcohol-to-water reagent and applied ($\sim 5 \mu\text{L}$) to the hydrogel-based sensing modules (Figure 4e). Thus, this purification ensures improved sensitivity and selectivity performance, supported by the testing result of both artificial saliva and pristine saliva samples, both pre- and post-filtration (Figure 4g,h). To evaluate sensor selectivity,

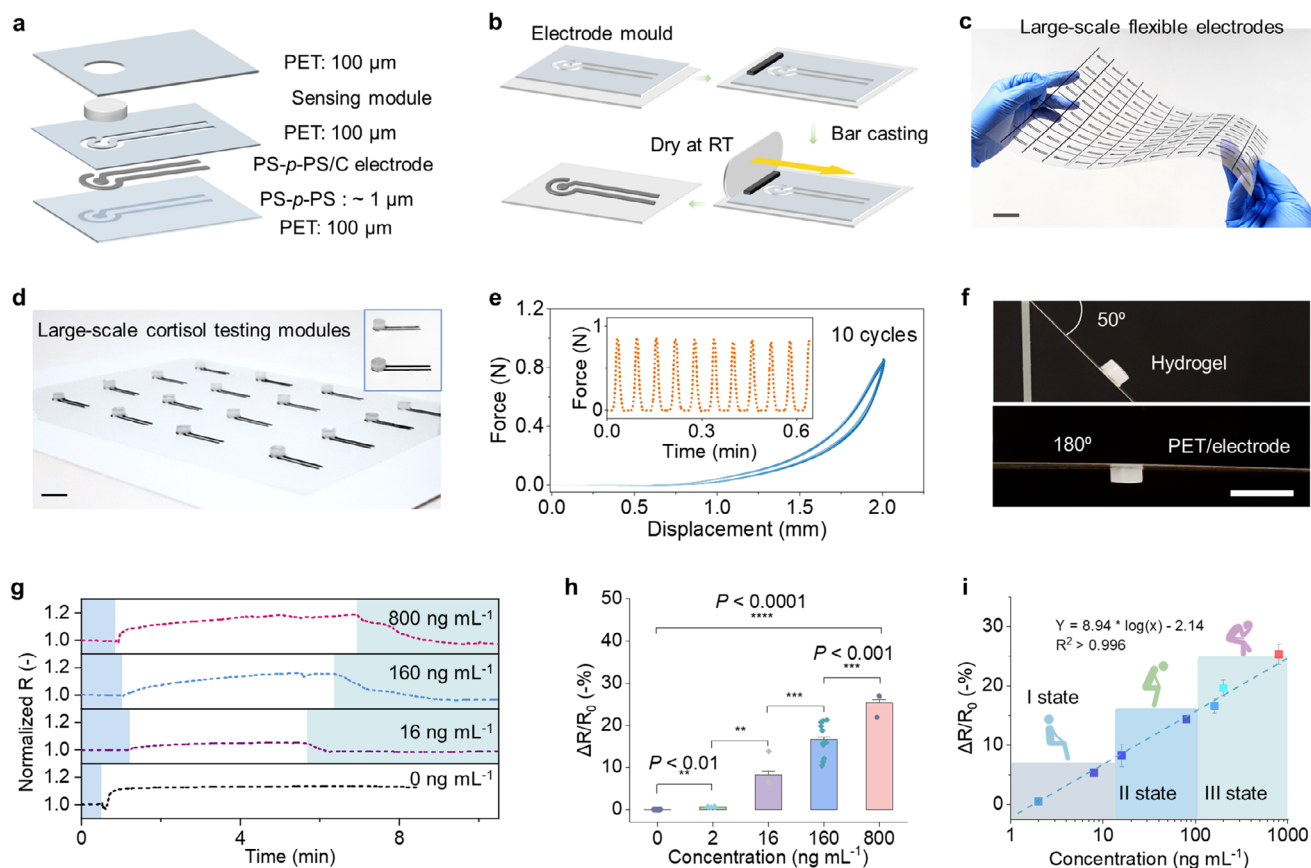


FIGURE 3 | Manufacturing and performance of the cortisol-detecting modules. (a, b) Schematics of the sensor modules comprising the hydrogel reactor, flexible electrodes and substrate. (c) Large-scale production of flexible electrodes. Scale bar: ~ 3 cm. (d) Large-scale view of assembled sensing modules. Scale bar: ~ 2 cm. (e) Compression testing of hydrogel reactor, where the pristine height is approximately 4 mm. (f) Adhesion performance between the hydrogel reactor and flexible electrodes on PET substrate. Scale bar: ~ 1 cm. (g) Cortisol detection at various concentrations. Here, 0 ng mL^{-1} condition represents stimulation with a 9:1 (v/v) ethanol-water mixture. Normalized R is defined as the ratio of resistance to initial resistance. (h) $\Delta R/R_0$ as a function of cortisol concentration (C) with statistical significance. Here, the p -values were analysed by employed one-way ANOVA and one sample t -test. (i) Linear fitting between $\Delta R/R_0$ and logarithm of cortisol concentration ($\log_{10} C$), corresponding to different levels of stress.

a comparative test was conducted using deoxycorticosterone at 60 pg mL^{-1} and cholesterol at 200 ng mL^{-1} , which exhibited a significantly weaker resistance response compared to cortisol at only 16 ng mL^{-1} (Figures S20 and S21). These control experiments using other components further confirmed the high specificity of the molecule-probe sensor, attributed to its targeted chemical reaction mechanism employed (Figure 4i). In comparison with other biochemicals such as cholesterol and glucose, this molecule-probe sensor presented more than 50-fold sensitivity at the same concentrations. In addition, other factors are considered, including high sensitivity of the biosensor toward cortisol/cortisone to other salivary constituents, acceptable recovery rates, long-term stability, and response in different scenarios (Figures S22–S25). These results validate the effectiveness of the purification protocol and the underlying reaction-driven selectivity of the molecule-probe sensing system for cortisol detection in complex biological fluids saliva.

2.3 | Demonstration of Molecule-Probe Sensor

To support the potential commercialization of the molecule-probe sensor, a compact electronic circuit with protective

encapsulation was developed (Figure 5). The electronic system comprises a resistance measurement unit, an STM32F microcontroller (MCU), and a liquid crystal display (LCD) for real-time output (Figure 5a). Schematic diagrams and optical images of the circuit board are illustrated in both exploded and top-view formats (Figure 5b,c, Figure S26, Supporting Information), detailing the layout of electronic components and their respective functions. The testing module, housing the hydrogel sensors is composed of an integrated, multilayer assembly of encapsulation material, a humectant layer, the hydrogel sensing layer, and a flexible polyethylene (PE) lid (Figure S27, Supporting Information). This design helps maintain a stable, controlled temperature and humidity microenvironment, minimizing external variability during sensing (Figure 5c). A proof-of-concept demonstration confirmed the functionality of this low-cost, and portable device, designed for monitoring of chronic stress and mental health in daily life (Figure 5d, Figure S28). In addition, the single-use hydrogel sensing modules can be degraded in soil within a few days with minimal waste (Figure 5e), demonstrating the eco-friendliness of the molecule-probe sensor.

To benchmark the sensor performance, a comparative analysis was conducted by analysing selectivity versus response time for

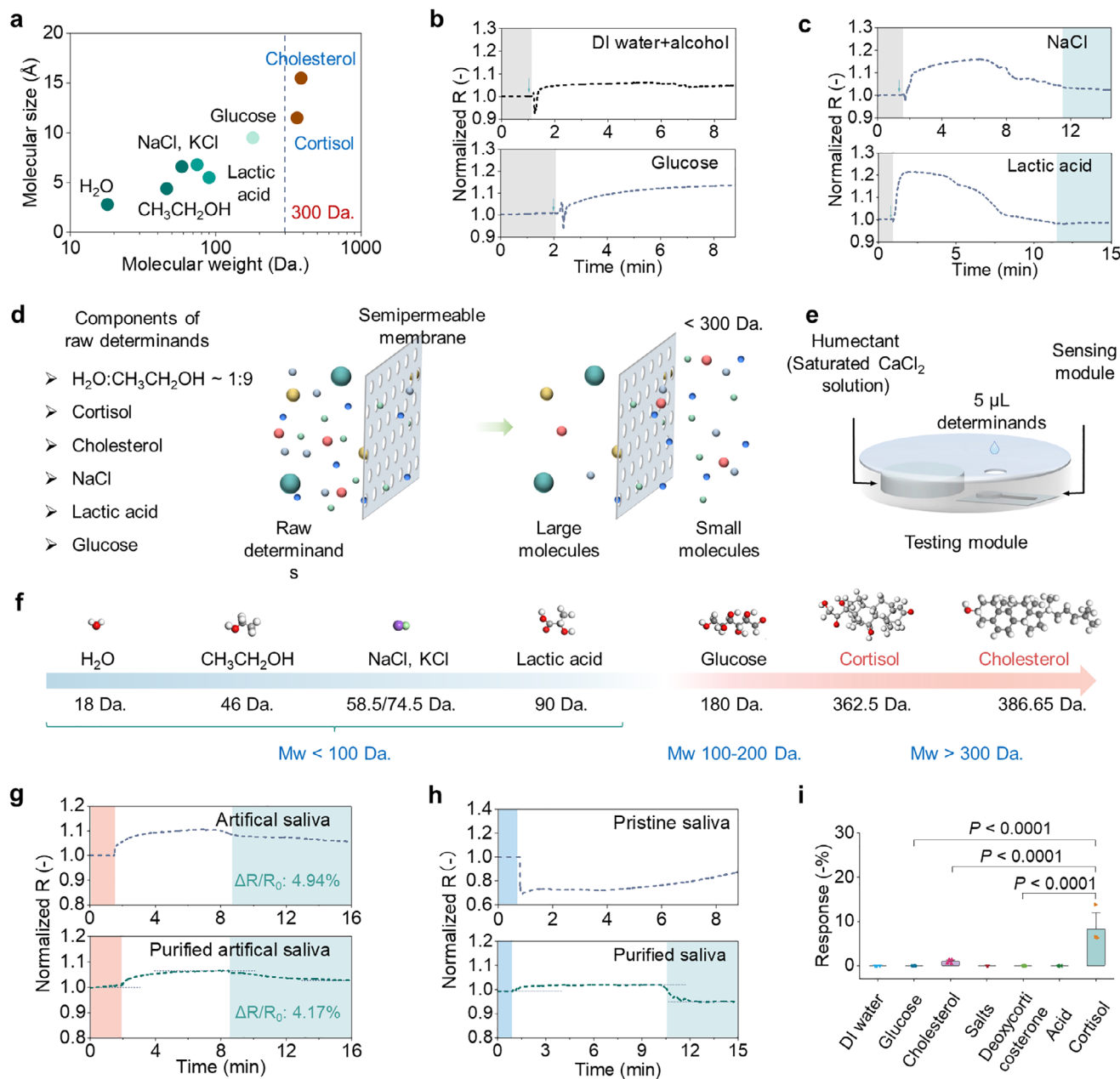


FIGURE 4 | Specificity evaluation of molecule-probe sensors. (a) Molecular size (Å) as a function of molecular weight (Da.) of main components in saliva testing samples. (b, c) Sensitivity of diverse solutions. Here, the concentrations of NaCl, glucose, and lactic acid solutions are 10, 15, and 40 µg mL⁻¹, respectively. Since glucose presented a positive resistance response and NaCl and lactic acid presented a negative response at low concentrations, the signals from these components must be decoupled through purification using semipermeable membrane. (d) Schematics of main components in unprocessed pristine saliva and their purification via semipermeable membrane. (e) Testing module for analyzing salivary constituents after purification. (f) Chemical structures and molecular weight of main components in pristine saliva. (g, h) Sensor response curves of diverse components and artificial and pristine saliva, both pre- and post-filtration after purification. (i) Specificity of the molecule-probe sensor toward cortisol, showing negligible interference from other salivary constituents. Here, the p-values were analysed by employed one-way ANOVA and one sample *t*-test.

our device against previously reported works (Figure 5f, Figures S29 and S30, Note S1) [21, 25–28, 33–37]. The molecule-probe sensor demonstrated a faster response than most antibody or aptamer-based biosensors, while offering superior selectivity over conventional chemical sensors. Furthermore, a cost-performance analysis was conducted by comparing diagnostic time against average detection cost between commercial systems and the present work (Figure 5g, Figure S31, Note S2). Our molecule-probe sensors achieved a rapid diagnosis time (~8 min) and a

low estimated cost (~ 7 dollars per unit, projected to drop to 4 dollars at scale), significantly outperforming most commercial alternatives in terms of affordability and operational efficiency. These findings highlight the favourable cost-to-performance efficiency and commercial viability of portable molecule-probe sensors (Figure 5h). Specifically, this cell-like portable molecule-probe sensors can be manufactured easily in a large scale with low-cost. The ease of operation and rapid-testing enable point-of-care diagnosis and prophylactic therapy. Furthermore, the

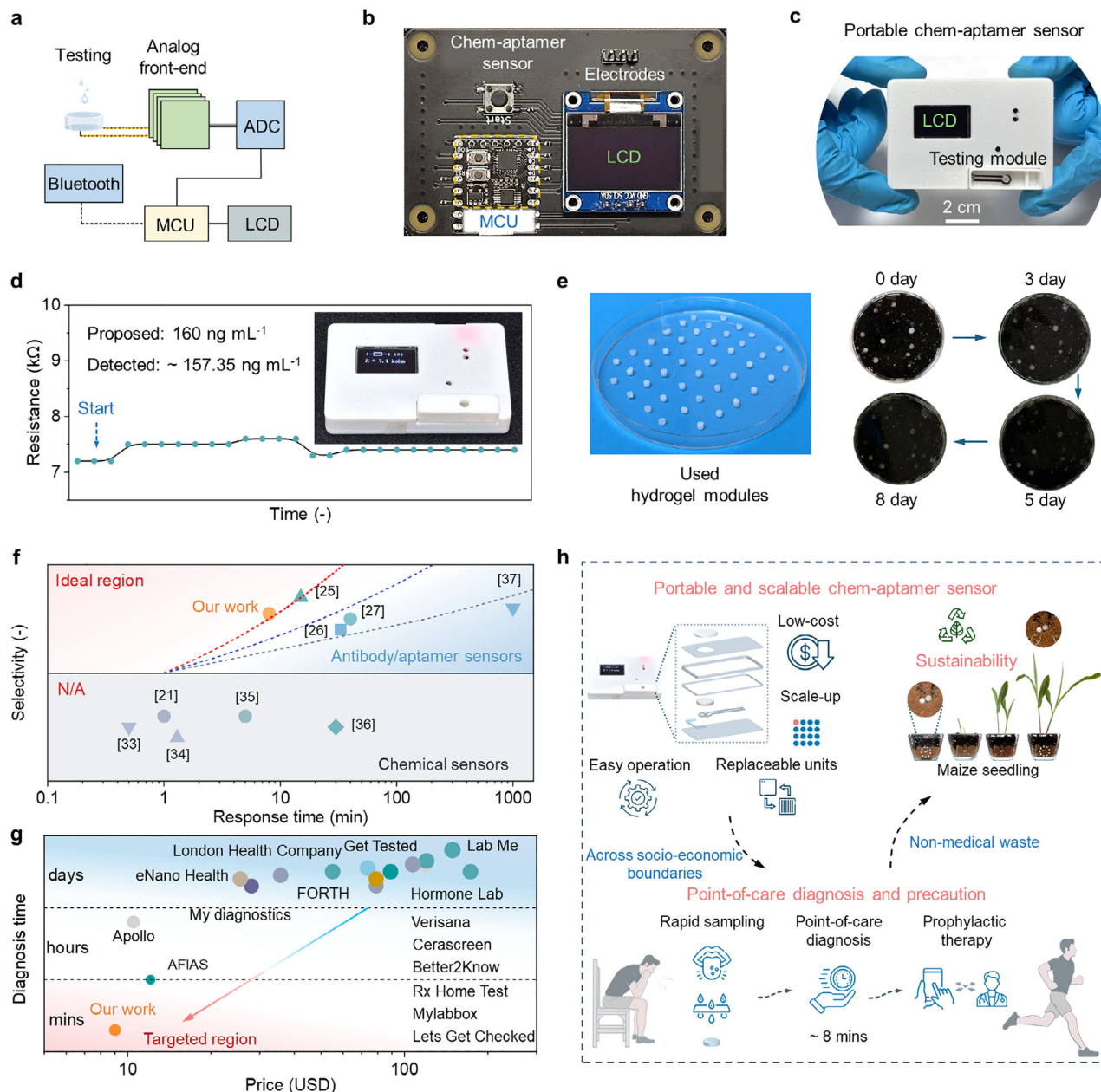


FIGURE 5 | Demonstration and performance comparison of molecule-probe sensor. (a) Electric circuit diagram of molecule-probe sensor (ADC: analog-to-digital converter, LCD: liquid crystal display). Bluetooth is optional in accordance with requirements. (b, c) Optical images of electronic circuit board and molecule-probe sensor. Scale bar: 2 cm. (d) Optical images of the molecule-probe sensor in operation, demonstrating cortisol detection. (e) Optical images of used hydrogel sensing modules and their degradation process in soil. (f) Comparison of selectivity (specificity) and response time of previous works and our work. (g) Comparison of diagnosis time and cost of commercial products and our work. Here, diagnosis time refers to the time taken from sample application to detecting result output. Cost reflects the average price for 20 tests, including the test reagents and sensing devices. (h) Advantages and outlook of molecule-probe sensors.

sustainable replaceable sensing units can be degraded in soil within days, contributing nutrients to plants and supporting eco-friendly deployment.

3 | Conclusions

Cost-effective monitoring of chronic stress is essential for promoting mental health on a global scale. A low-cost portable molecule-probe sensor is developed by integrating a specific

chemical reaction within a hydrogel-based microreactor, coupled with *n*-type semiconductor-based signal amplification mechanism. The sensor demonstrates high selectivity toward cortisol and other relevant biomolecules, along with superior sensitivity and a faster response time compared to previously reported technologies. Notably, this molecule-probe sensor achieves rapid diagnosis at a low cost, significantly more affordable than most commercial detection systems. Its ability to function effectively in realistic biofluid environments establishes a strong foundation for next-generation biochemical sensing. With a modular design,

compatibility with flexible electronics, and environmental robustness, the platform is well-suited for wearable and point-of-care applications. This work presents a sustainable and economically viable approach to biochemical sensing based on rapid response, low-waste design, and chemical specificity, thereby offering an equitable access and a practical solution for monitoring chronic stress and mental health across socio-economic boundaries.

4 | Experimental Section/Methods

Experimental Section/Methods are presented in the Supporting Information.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting the results in this study are included within the paper and the Supplementary Information files and are available from the corresponding author upon request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File: adfm77967-sup-0001-SuppMat.docx.