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Integrated individually addressable microneedle arrays for robust glucose monitoring and on-demand insulin releasing

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Abstract

Real-time glucose monitoring and adaptive insulin administration are critical for effective diabetes management. Minimally invasive microneedle-based glucose monitoring sensors offer a promising approach but suffer from signal drift due to tissue reactions, inconsistent implantation, or mechanical damage to their sensitive layers during insertion. Moreover, microneedle-based insulin delivery faces limitations in achieving accurate and quantitatively controlled release due to its passive response mechanism. Here, we report a minimally invasive platform integrating a multiplexed glucose biosensor array with on-demand insulin delivery for precise glycemic control. To prevent the impact of potential individual microneedle failure post-insertion, the system incorporates a redundant sensing array comprising four individually addressable electrodes functionalized with glucose oxidase, providing robust and reliable glucose measurements. Simultaneously, an addressable drug-release array of eight microneedles loaded with insulin within redox-responsive hydrogels enables localized electrochemical triggering for spatiotemporally controlled insulin release. These components are coordinated via a wireless interface leveraging real-time multi-channel ADC data processing and Bluetooth transmission to dynamically activate insulin microneedles based on algorithmic glycemic thresholds. The platform's redundant sensing design enhances system reliability, maintaining accurate glucose monitoring even in case of individual sensor failure, while its on-demand insulin release enables real-time glycemic regulation. Ultimately, in vivo experiments in rats were conducted to verify the system's efficacy. By synergizing multiplexed biosensing, fault tolerance, and programmable drug delivery, this platform addresses critical limitations of current glucose monitoring systems and establishes a demonstration prototype for next-generation closed-loop bioelectronics.

Introduction

Diabetes is a prevalent chronic metabolic disease worldwide, which not only adversely affects patients' quality of life but also leads to numerous complications such as stroke, coronary heart disease, cancer, and liver disorders^{1–5}. A primary need in diabetes management is the timely administration of exogenous insulin in

response to elevated blood glucose levels, in order to maintain glycemic levels within a reasonable physiological range^{6,7}. Therefore, the development of closed-loop systems that can continuously monitor glucose levels and deliver insulin accordingly holds significant clinical importance. In terms of continuous glucose monitoring (CGM), current technologies can be broadly categorized into non-invasive and invasive methods⁸. Non-invasive CGM primarily involves monitoring glucose levels through body surface secretions such as sweat and tears^{9–15}. However, the accuracy of sweat-based glucose sensing does not meet clinical error standards (<15%), and fluctuations in sweat glucose levels significantly lag behind changes in blood glucose levels^{16–18}. As a result,

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non-invasive CGM is currently insufficient to meet the high-precision monitoring requirements of closed-loop diabetes management systems.

Microneedle (MN) technology demonstrates unique advantages in the fields of glucose monitoring and insulin delivery. Its minimally invasive nature significantly reduces patient discomfort, while measurements based on interstitial fluid (ISF) offer higher accuracy compared to completely non-invasive monitoring methods^{19–21}. Current studies have shown that ISF shares similar components with serum and plasma, particularly with respect to glucose^{22,23}. Ribet et al. integrated a miniature electrochemical sensing probe into a hollow microneedle cavity, achieving painless skin penetration and reliable sensor stability, thereby validating the feasibility of microneedle-based CGM systems²⁴. To improve in vivo sensing accuracy and reduce signal interference, Yang et al. designed a differential sensor on a glucose-responsive microneedle array and successfully applied it in human subjects²⁵. Dervisevic et al. developed a high-density silicon-based MN array, where multiple overlapping microneedles enhanced the sensitivity of glucose detection²⁶. Tehrani et al. reported a fully integrated wearable MN system capable of wirelessly monitoring multiple metabolites in ISF in real time. Their system combined a disposable MN array with a reusable electronics module to enable continuous and accurate ISF glucose measurements on human skin²⁷. However, current research efforts face several challenges: Insufficient insertion depth: Most reported MNs are shorter than 1 mm, which limits the effective sensing area and mechanical stability once inserted, due to the natural thickness of the skin; Fragility of glucose-sensitive layers: In many CGM systems based on responsive membrane coatings, the insertion process may damage the sensing layer due to friction with the epidermis; Lack of redundancy: Existing MN-based CGMs typically adopt a single sensing channel. Without independent redundant channels, any degradation in sensitivity of a single MN compromises the functionality of the entire system, leading to poor robustness and limited reliability^{28,29}.

In the domain of therapeutic microneedles, transdermal drug delivery offers pain-free, safe, and highly efficient absorption, making it especially promising for insulin administration^{30–32}. As for minimally invasive closed-loop insulin delivery systems, some chemically responsive (formulation-based) systems have been developed that passively release insulin in response to glucose concentration. Nonetheless, these systems often suffer from imprecise dosage control and are prone to interference from various bodily fluids, limiting their clinical applicability^{33–36}. Wang et al. developed a pH-responsive MN array for insulin release, where the outer layer of the MNs dissolved rapidly upon insertion as the pH changed³⁷. Fu et al. used mesoporous silica nanoparticles to encapsulate

insulin, combined with a ZnO–PBA–2 linker that triggered release upon glucose stimulation, thereby enabling responsive glycemic control³⁸. Yu et al. fabricated hypoxia-responsive nanovesicles for insulin delivery, utilizing the reduction of hydrophobic 2-nitroimidazole groups to hydrophilic 2-aminoimidazole in low-oxygen environments to induce vesicle disassembly³⁹. Nevertheless, in these studies, insulin release was passive and uncontrolled, making it vulnerable to complex physiological conditions and difficult to achieve precise dosing. In an attempt to introduce active control, Lee et al. proposed a thermally responsive insulin MN patch, where embedded heating triggered the degradation of insulin-loaded tips to initiate release⁴⁰. However, this design still lacked accurate quantification of the insulin dose delivered.

To overcome these limitations of existing technologies, here we propose an integrated system for dynamic, real-time blood glucose monitoring and controllable insulin release based on an addressable microneedle array. The closed-loop logic is shown in Fig. 1a. This closed-loop control strategy not only allows continuous monitoring of glucose concentration but also provides precise insulin therapy according to individual metabolic needs, offering a new technological solution for diabetes management. As shown in Fig. 1c, the innovative system consists of three core modules: the redundant multiplexed glucose monitoring microneedle array (Fig. 1c(i)), the addressable electrochemical triggered insulin release microneedle array (Fig. 1c(iii)), and the signal processing and wireless transmission module (Fig. 1c(ii)). The system adopts a unique array design, enabling precise spatiotemporal control of both blood glucose monitoring and insulin delivery. Figure 1b(i) shows the structure of the glucose monitoring microneedle array. The glucose monitoring microneedle array contains four independently addressable sensing electrodes, each coated with glucose-sensitive materials (Fig. 1d(i)), allowing real-time detection of glucose concentration in interstitial fluid. To enhance measurement reliability, the system also integrates four counter electrodes and one reference electrode. Each sensing channel is connected to respective analog-to-digital conversion (ADC) paths of the backend circuit, enabling independent analysis of each channel. Figure 1b(ii) shows the structure of the electrochemical triggered insulin release microneedle array. The electrochemical triggered insulin release microneedle array consists of eight independently addressable drug delivery microneedles, each coated with a hydrogel encapsulating insulin (Fig. 1d(iii)). By selectively applying a -1.5 V reduction voltage to the microneedles (Fig. 1b(ii)), the system enables on-demand drug release from specific microneedles. During system operation, glucose data collected in real-time by the sensing microneedle array is converted through high-precision ADC and wirelessly transmitted to a mobile terminal via a low-power Bluetooth module.

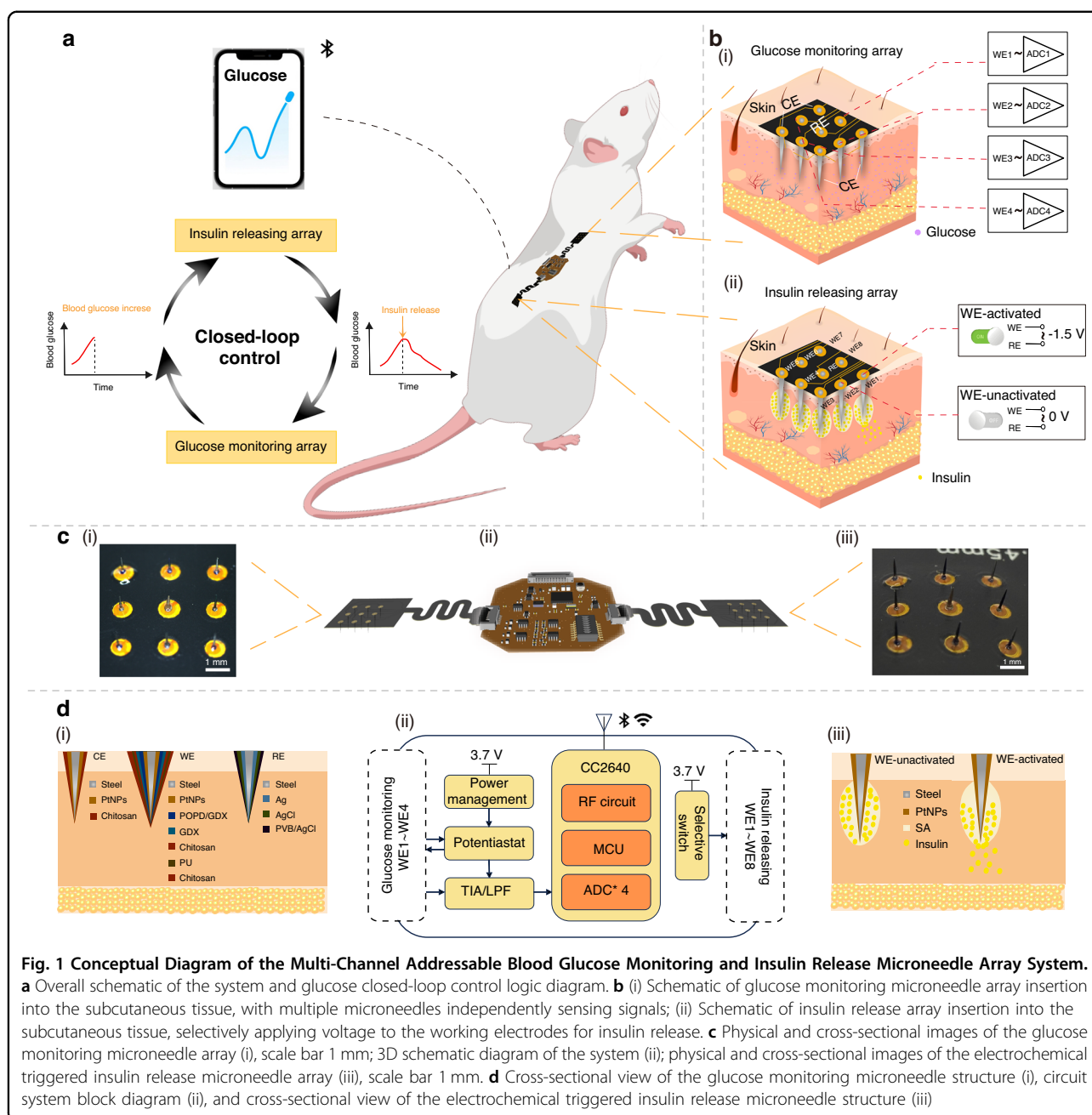


Fig. 1 Conceptual Diagram of the Multi-Channel Addressable Blood Glucose Monitoring and Insulin Release Microneedle Array System.

a Overall schematic of the system and glucose closed-loop control logic diagram. **b** (i) Schematic of glucose monitoring microneedle array insertion into the subcutaneous tissue, with multiple microneedles independently sensing signals; (ii) Schematic of insulin release array insertion into the subcutaneous tissue, selectively applying voltage to the working electrodes for insulin release. **c** Physical and cross-sectional images of the glucose monitoring microneedle array (i), scale bar 1 mm; 3D schematic diagram of the system (ii); Physical and cross-sectional images of the electrochemical triggered insulin release microneedle array (iii), scale bar 1 mm. **d** Cross-sectional view of the glucose monitoring microneedle structure (i), circuit system block diagram (ii), and cross-sectional view of the electrochemical triggered insulin release microneedle structure (iii)

Researchers can monitor dynamic glucose changes through a custom-developed application and, based on preset thresholds or real-time assessments, trigger the release function of specified insulin microneedles.

Results and discussion

Structural configuration of the microneedle array and electronic interface

As shown in Fig. 1d(ii), the electronic sensing architecture of this system adopts a modular design composed of three synergistic functional units: a glucose sensing

unit, a microcontroller and wireless communication unit, and an insulin delivery unit.

In the glucose sensing unit, a classic three-electrode configuration is employed (working electrode WE, counter electrode CE, and reference electrode RE). A total of nine microneedle electrodes are arranged in a 3×3 array to enable multi-channel detection. The array consists of four working electrodes (each with a needle tip length of 1 mm), four counter electrodes, and one reference electrode. A constant potential of 0.5 V is maintained between each working and reference electrode via a

potentiostat. Each working electrode (WE1 to WE4) is equipped with an independent signal acquisition pathway. The resulting current signals are processed through a transimpedance amplifier followed by a low-pass filter (cutoff frequency $f_c = 10$ Hz), and then digitized by a 12-bit analog-to-digital converter (ADC) embedded in the microcontroller unit (MCU). In a three-electrode electrochemical measurement system, the counter electrode serves to form the current path together with the working electrode. To avoid electrode polarization caused by excessively high current density, which may introduce errors in the potential of the working electrode, the surface area of the counter electrode should be maximized. To ensure sufficient surface area and prevent current limitation, the four counter electrodes are electrically connected through a conductive trace. The core of the system is built around the Texas Instruments CC2640R2F, a low-power Bluetooth SoC that integrates an 8-channel 12-bit ADC (sampling rate: 200 kS/s) and a 2.4 GHz RF module. With a customized protocol stack, the system achieves real-time data transmission at 1-second intervals. The insulin delivery unit also adopts a 3×3 array layout, with a central reference electrode and eight surrounding working electrodes. Each working electrode is maintained at a stable potential of -1.5 V through a high-precision voltage divider and voltage follower circuit. The activation of each electrode is independently controlled by an 8-channel DIP switch array.

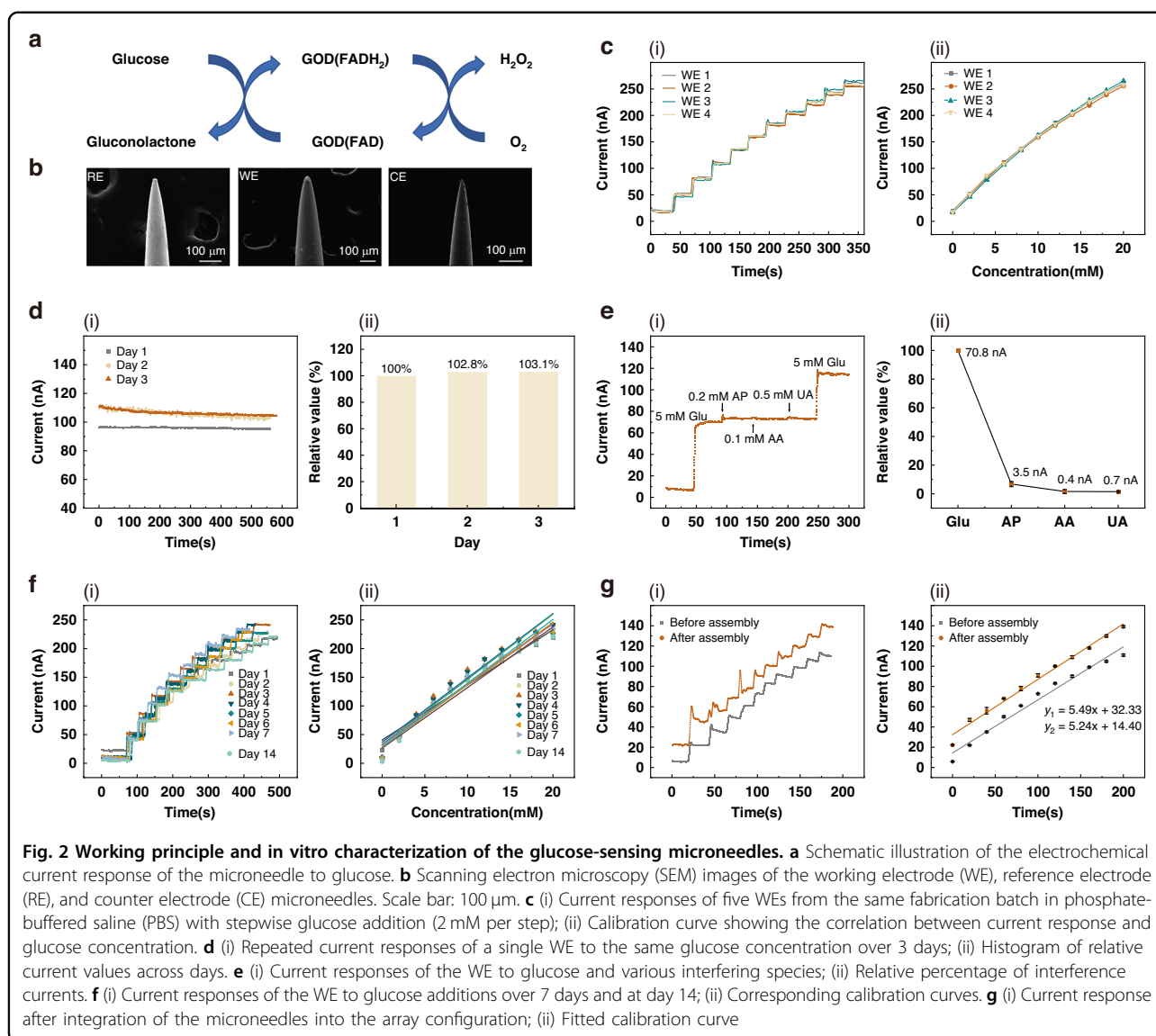
The two functional MN arrays contain sensing and delivery are mechanically and electrically connected to the flexible printed circuit board (FPCB) via 6-pin (sensing) and 9-pin (delivery) edge connectors (“gold fingers”). All interfaces are impedance-matched to a characteristic impedance of 50Ω to ensure signal integrity. The entire system is powered by a 3.7 V lithium-polymer battery, which supplies operating voltages to the respective modules via a high-efficiency DC-DC converter.

Electrochemical surface treatment for glucose-sensing microneedles

The glucose-responsive microneedles developed in this study operate based on an enzyme-catalyzed electrochemical sensing mechanism, as illustrated in Fig. 2a. Glucose molecules undergo oxidation to gluconolactone under the catalytic activity of glucose oxidase (GOD), during which the enzyme cofactor flavin adenine dinucleotide (FAD) is reduced to FADH_2 . The FADH_2 is then reoxidized by dissolved oxygen, yielding hydrogen peroxide (H_2O_2) as a by-product. The H_2O_2 is electrochemically oxidized at the platinum catalytic layer, generating a measurable current signal that is positively correlated with glucose concentration, thereby enabling quantitative glucose detection.

The working electrodes (WEs) of the microneedles were fabricated using a multilayer modification process. First, a porous platinum nanoparticle catalytic layer was electrodeposited on the stainless-steel microneedle surface via potentiostatic deposition in 10 mM $\text{H}_2\text{PtCl}_6/1$ M HCl electrolyte at -0.3 V (vs. Ag/AgCl) for 300 s (see Fig. S3–S4). To enhance selectivity, a permselective interference-resistant membrane was constructed. Experiments revealed that a GOD concentration of 30 mg/mL produced the maximum response current (Fig. S10); thus, the electrodes were immersed in an acetate buffer (pH = 6.0) containing 5 mM o-phenylenediamine (OPD), 10 mg/mL bovine serum albumin (BSA), and 30 mg/mL GOD. Electropolymerization was conducted at $+0.65$ V for 1200 s, forming a poly(o-phenylenediamine) layer that effectively blocks interfering species such as uric acid (UA), ascorbic acid (AA), and acetaminophen (AP), while maintaining high glucose permeability. Enzyme immobilization was achieved using a glutaraldehyde crosslinking process. The microneedles were first incubated in PBS solution (pH = 7.2) containing 10 mg/mL BSA and 30 mg/mL GOD at 4°C for 10 min for pre-adsorption. They were then exposed to saturated glutaraldehyde vapor (50 $\mu\text{L}/250$ mL) at 37°C for 15 min to complete the crosslinking reaction. To ensure biocompatibility and mechanical stability, a “sandwich” encapsulation structure was employed. This consisted of a 5 μm thick hydrophilic inner layer formed by spin-coating 1% chitosan solution, a 2 μm diffusion-limiting intermediate layer of 1% polyurethane (PU, THF:DMF = 98:2), and a second chitosan overlayer for mechanical reinforcement. The presence of the chitosan coating did not adversely affect sensing performance; with chitosan, the microneedles exhibited a sensitivity of 12.32 nA/mM ($R^2 = 0.9926$), compared to 11.65 nA/mM ($R^2 = 0.9743$) without the coating (Fig. S7). In vitro performance remained consistent after repeated implantation into rat skin, indicating that chitosan provides effective protection without compromising sensor function (Figs. S7–S8). SEM images of the modified microneedles are shown in Fig. S9. After platinum nanoparticle deposition, a uniform granular morphology was observed. Following OPD electropolymerization, a dense polymer membrane formed on the surface. GOD immobilization led to the appearance of globular aggregates, and the final PU coating completely encapsulated the inner structures, confirming successful layer-by-layer surface functionalization.

The counter (CE) and reference (RE) electrodes were also carefully engineered. The RE was fabricated by electrodepositing an Ag/AgCl layer on silver-coated microneedles at $+0.6$ V for 40 s in 0.1 M HCl. As shown in Fig. S10, the surface color changed from metallic silver to grayish white, indicating the formation of AgCl. The RE



was then stabilized with a PVB membrane. Testing revealed a stable potential offset of ~ 0.05 V between the Ag/AgCl microneedle and a standard reference electrode (Fig. S11), which is acceptable provided the offset remains stable. For the CE, a platinum layer was electrodeposited at -0.3 V for 600 s in the same 10 mM H_2PtCl_6 / 1 M HCl electrolyte, followed by a protective PU coating. As shown in Fig. S12, increasing deposition time led to greater nanoparticle accumulation and surface darkening; however, cracking was observed at 800 s, so 600 s was selected as the optimal deposition time. The final three-electrode microneedle system exhibited excellent performance in standard H_2O_2 detection, achieving a sensitivity of 11.68 nA/mM with $R^2 = 0.9992$, which fully meets the requirements for physiological glucose monitoring (Fig. S13).

Performance characterization of glucose-sensing microneedles

To comprehensively evaluate the performance of the developed microneedles, we first assessed the linear range and batch-to-batch consistency of the sensors. Four independent microneedles from the same batch were tested by sequentially adding 2 mM glucose standard solutions. As shown in Fig. 2c, all sensors exhibited excellent linear responses over the physiologically relevant range of 0–20 mM glucose, with an average sensitivity of 11.88 nA/mM and a batch-to-batch consistency of 95.53%. The limit of detection (LOD) was determined to be 67 μM . Sensor stability was further verified through continuous testing over three days (Fig. 2d), where the current response to 20 mM glucose fluctuated within $\pm 10\%$ of the initial value, demonstrating high signal

stability. Interference resistance is a critical factor in evaluating biosensor reliability. To assess selectivity, we sequentially introduced 5 mM glucose, 0.2 mM acetaminophen (AP), 0.1 mM ascorbic acid (AA), and 0.5 mM uric acid (UA) into the test solution. As shown in Fig. 2e, the current variations induced by these interfering substances were all below 4% compared to the signal from 5 mM glucose, indicating excellent sensor selectivity. This superior anti-interference capability is attributed to the carefully designed o-phenylenediamine (OPD) selective membrane and the optimized operating potential. For long-term performance evaluation, a 7 day stability test was conducted (Fig. 2f). The microneedles maintained an average sensitivity of 10.73 nA/mM, with an average linear correlation coefficient (R^2) of 0.97, confirming reliable detection performance even after extended use. Importantly, performance testing after integration of the microneedles into the array format (Fig. 2g) showed that, while the baseline current slightly increased, the linear response characteristics remained consistent with those observed in single-electrode tests. This indicates that the array assembly process had a minimal and controllable impact on sensing performance. The complete assemble process for the microneedle array is detailed in Supplementary Figs. S1–S2. These systematic evaluations demonstrate that the developed glucose-sensing microneedle array exhibits outstanding accuracy, stability, and reliability, establishing a solid foundation for its application in CGM.

Mechanism of drug release from insulin-releasing microneedles

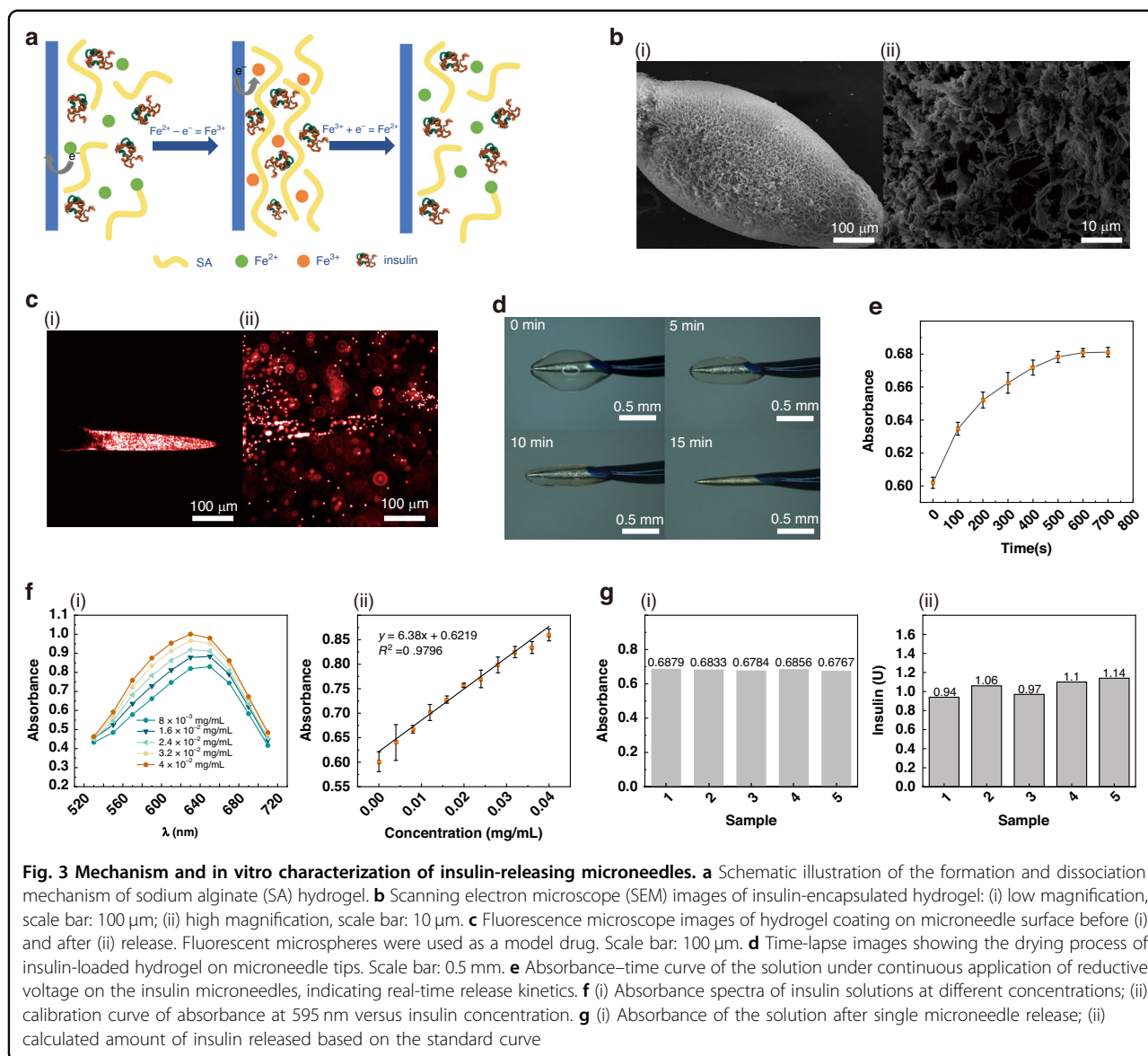
Sodium alginate (SA), a natural polysaccharide extracted from brown seaweed, is composed of β -D-mannuronic acid (M) and α -L-guluronic acid (G) residues. As illustrated in Fig. 3a, the carboxylate groups ($-\text{COONa}$) on the G-blocks can undergo ion exchange with multivalent metal cations. When Fe^{3+} is introduced, it crosslinks with the G-units to form a three-dimensional hydrogel network by coordinating with multiple G-blocks and trapping water molecules. In contrast, Fe^{2+} has a much lower binding affinity to SA and cannot effectively form a stable gel. Leveraging this property, we designed a redox-controlled gelation/dissolution system based on the reversible $\text{Fe}^{3+}/\text{Fe}^{2+}$ transition. Specifically, when an oxidative voltage is applied to the electrode surface, Fe^{2+} in the surrounding solution is oxidized to Fe^{3+} , which rapidly induces gelation by crosslinking with SA. Conversely, applying a reductive voltage reduces Fe^{3+} to Fe^{2+} , leading to dissociation of the hydrogel network. By pre-loading insulin into the SA solution, this electrochemical mechanism enables both encapsulation and on-demand release of insulin via electrochemical redox-triggered gel-sol transitions.

Surface modification of insulin-releasing microneedles

A multilayer surface engineering strategy was employed to construct the insulin-releasing microneedles, consisting of a conductive platinum (Pt) base layer and a functional insulin-loaded hydrogel layer. Stainless steel microneedles were first mechanically polished to increase their surface roughness and effective area, as evidenced by the appearance of surface scratches (Fig. S14). Electrochemical impedance spectroscopy (EIS) before and after polishing (Fig. S15) showed a reduced semicircle diameter in the high-frequency region, indicating enhanced surface area and reduced charge-transfer resistance. Subsequently, the microneedles were electrochemically coated with platinum by immersing them in an electrolyte containing 10 mM H_2PtCl_6 and 1 M HCl, using a constant potential of -0.3 V (vs. Ag/AgCl). Cyclic voltammetry (CV) analysis (Fig. S16) revealed a significant increase in peak current after Pt deposition, confirming enhanced conductivity and favorable electrochemical properties for subsequent hydrogel deposition. The insulin-containing hydrogel layer was formed via constant-current electrodeposition (10 μA , 80 s) in a precursor solution comprising 35 mM FeSO_4 (as crosslinker), 1% (w/v) sodium alginate (SA), and 100 mg/mL insulin. As shown in Fig. S17, 10 μA was selected as the optimal current since deposition at 20 μA resulted in bubble entrapment within the gel. The resulting spherical hydrogel uniformly coated the microneedle surface (Fig. 3d). SEM imaging after freeze-drying (Fig. 3b) revealed a well-defined three-dimensional porous network, while EDX elemental mapping (Fig. S18) confirmed strong nitrogen signals, validating successful insulin encapsulation within the SA matrix. Furthermore, the drying kinetics of the surface hydrogel (Fig. 3d) demonstrated that under ambient conditions, the insulin gel began to shrink within 5 min, showed significant dehydration by 10 min, and was almost completely dried after 15 min, forming a thin residual gel film on the microneedle surface. This rapid drying property ensures mechanical integrity and facilitates effective skin penetration, thereby enabling precise subcutaneous delivery and controlled release of insulin.

Performance characterization of insulin-releasing microneedles

Fluorescent microspheres were used as a model to visualize and characterize the release behavior of the microneedles. A hydrogel precursor solution containing 35 mM FeSO_4 , 1% (w/v) sodium alginate, and fluorescent microspheres was prepared and cast onto the microneedle surface. After drying, the hydrogel-coated microneedles were used as working electrodes, and a constant reduction potential of -1.5 V was applied for 600 s using an electrochemical workstation. As shown in Fig. 3c, fluorescent microspheres were uniformly distributed on the



microneedle surface prior to release (Fig. 3c(i)). After electrochemical triggering, the microspheres were largely released into the surrounding solution, with only a small amount remaining on the microneedle surface (Fig. 3c(ii)), confirming successful electro-triggered release of the encapsulated content. To quantitatively evaluate the insulin released from individual microneedles, the Bradford assay was employed using Coomassie Brilliant Blue G-250 as the chromogenic reagent. In its free state, the dye appears reddish with an absorption maximum at 465 nm; upon binding to protein, it turns blue and the peak shifts to 595 nm. As shown in Fig. 3f(i), the absorbance spectra of insulin solutions at different concentrations exhibited distinguishable differences near 595 nm, which was selected for quantification. The standard calibration curve at 595 nm was established as:

$y = 6.38x + 0.6219$, where y is the absorbance and x is the insulin concentration in U/mL. For quantification, each microneedle was immersed in 4 mL of 0.01 M PBS and subjected to -1.5 V for 600 s. After complete release, the absorbance of the solution was measured at 595 nm. Figure 3g(i) shows the absorbance values of released solutions, and Fig. 3g(ii) presents the calculated insulin content per microneedle, with an average of 1.04 U and a standard deviation of 6.7%, indicating reproducible and quantitative drug release.

Furthermore, Fig. 3e illustrates the time-dependent absorbance profile of insulin release under continuous voltage application. A rapid increase in absorbance was observed at the onset of reduction, indicating a burst release of insulin, which plateaued at 600 s, suggesting near-complete release of insulin from the hydrogel matrix.

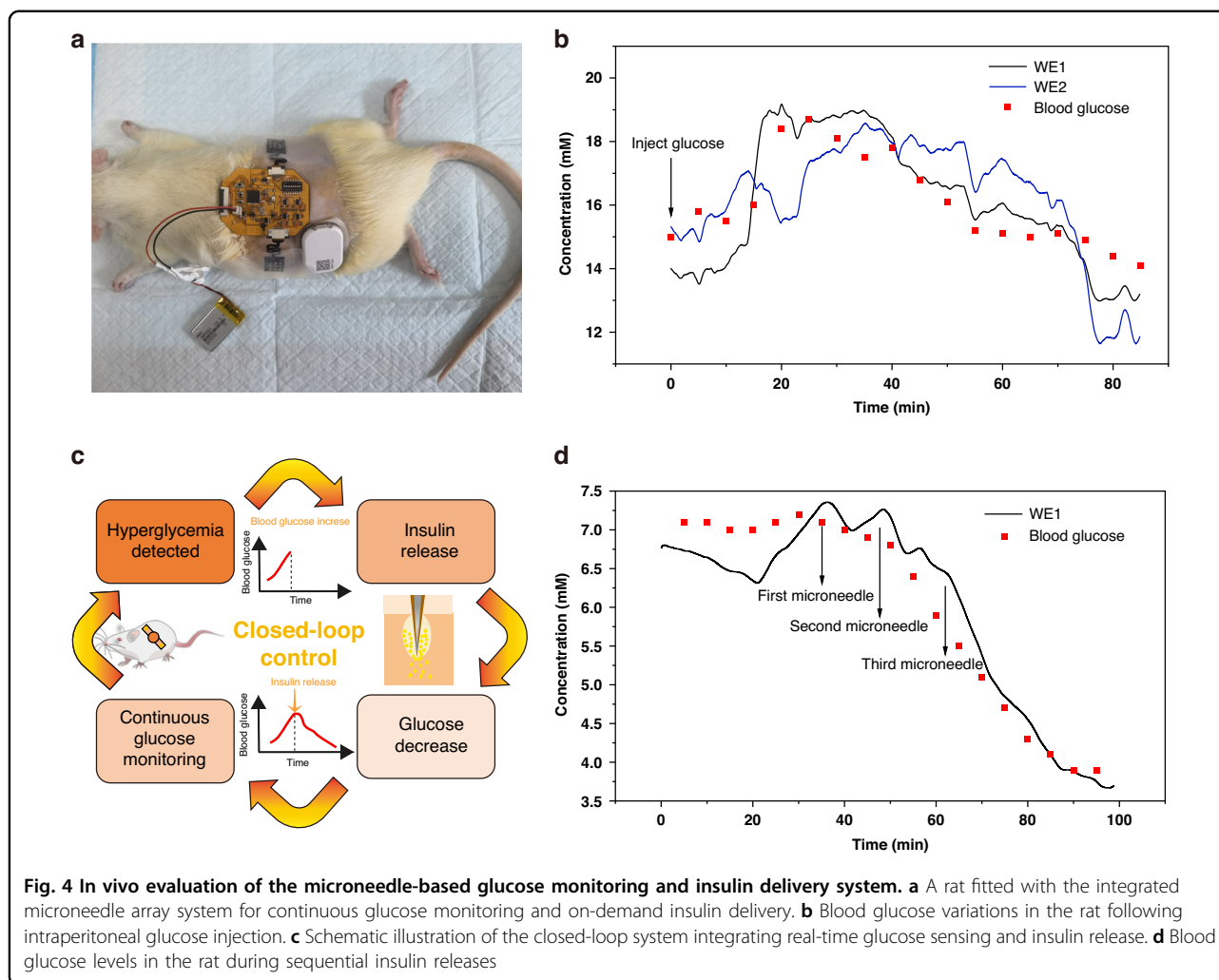


Fig. 4 In vivo evaluation of the microneedle-based glucose monitoring and insulin delivery system. **a** A rat fitted with the integrated microneedle array system for continuous glucose monitoring and on-demand insulin delivery. **b** Blood glucose variations in the rat following intraperitoneal glucose injection. **c** Schematic illustration of the closed-loop system integrating real-time glucose sensing and insulin release. **d** Blood glucose levels in the rat during sequential insulin releases

In vivo evaluation

To assess the biocompatibility of the microneedles (MNs), we first conducted a cytotoxicity assay using microneedle leachates. MNs were immersed in serum-free culture medium to prepare leachates, which were then added to cell culture medium for incubation. The results showed that the cell viability remained above 90% in leachates from the glucose-monitoring microneedle array (WE/CE/RE), while the leachates from the insulin-releasing MNs also supported normal cell survival (Fig. S19), indicating that both types of MNs were non-cytotoxic. Subsequently, skin biocompatibility was evaluated in a rat model. Skin tissues from the MN insertion sites were excised and stained at 7 days after implantation of glucose-monitoring MNs and 24 hours after implantation of insulin MNs. As shown in Fig. S20, HE-stained sections from the RE, CE, WE groups, and the insulin MN group all exhibited localized tissue disruption or damage, corresponding to the MN penetration sites (Fig. S20). Further analysis with Masson's trichrome staining

revealed no significant fibrosis in the WE or insulin MN groups, and only mild fibrosis in the RE and CE groups (Figs. S20–S21), suggesting minimal inflammatory response and good tissue compatibility. Collectively, these findings confirm that the MN system can operate in vivo without eliciting adverse tissue reactions, laying a solid foundation for subsequent glucose monitoring and insulin delivery experiments.

As shown in Fig. 4a, the rat was fitted with the complete microneedle system for both glucose sensing and insulin delivery. First, the performance of the glucose-monitoring microneedles (without insulin release functionality) was evaluated. After subcutaneous insertion, the MN array required approximately 1.5 h to reach a stable baseline, after which formal monitoring began. The commercial “SIBIONICS” CGM system was used as a reference, providing one data point every 5 min. Figure 4b presents MN sensor data processed with a Kalman filter (Fig. S22). During implantation and sensing, two MNs experienced sensitivity loss, while the remaining two maintained stable

responses, demonstrating the robustness and necessity of the redundant addressing design. At the beginning of the test, a 1 mL injection of 20% (w/v) glucose solution was administered intraperitoneally to induce hyperglycemia. The blood glucose level rose rapidly to a peak within 30 min, plateaued with minor fluctuations between 40 and 50 min, and began to decline sharply after 52 min. The MN sensor data closely matched the reference values, accurately capturing dynamic changes in blood glucose levels. Clarke error grid analysis (Fig. S23) showed that 93.6% of data points fell within Zone A and 6.4% within Zone B, confirming the accuracy and clinical reliability of the MN sensor system. The multi-channel design provides valuable redundancy and cross-validation for identifying optimal insulin delivery timing, highlighting the system's strong real-time monitoring capability and translational potential.

The operation of the closed-loop glucose regulation system is illustrated in Fig. 3c. The MN sensor array continuously detects rising glucose levels and transmits real-time data to a smartphone app. Upon receiving the alert, the user can manually activate a switch to trigger on-demand insulin release. Meanwhile, glucose levels continue to be monitored throughout the process. For the insulin delivery experiment, another healthy rat was implanted subcutaneously with the MN array. As shown in Fig. 4d, despite partial signal degradation after insertion, at least one MN retained good sensitivity, again demonstrating the importance of redundant sensor design. The sensor response is plotted as a curve, with red dots indicating reference glucose values. The insulin MN array was controlled by independent switches, each corresponding to a single needle. Insulin was released at 35, 47, and 62 min by activating one needle per event, with each release lasting approximately 10 min. Blood glucose remained stable during the first 45 min and began to drop rapidly at around 50 min, indicating that the first insulin dose took effect within 5 min after complete release. Subsequent doses accelerated the glucose decline. Between 35 and 90 min, glucose levels dropped from 7.2 mM to 3.8 mM. After 90 min, the rate of decline slowed and eventually plateaued, suggesting that the insulin had been fully absorbed and the animal began to self-regulate to prevent hypoglycemia.

These results demonstrate that the microneedle system can achieve precise, controllable insulin release with rapid onset. Each MN carried approximately 1U of insulin, ensuring effective glycemic control while avoiding excessive dosing. Ultimately, the integration of self-developed glucose-monitoring MNs with addressable insulin-releasing MNs achieved dynamic, responsive glucose control, validating the feasibility and practical value of the proposed closed-loop regulation system.

Conclusion

We have developed a minimally invasive platform integrating a multiplexed glucose biosensor array with on-demand insulin delivery for precise glycemic control. This system employs an independently addressable microneedle sensor array for redundant glucose monitoring, coupled with an electrochemically triggered insulin-releasing microneedle array, enabling real-time glycemic regulation via Bluetooth-enabled smartphone interfacing. In vivo validation in a rat model demonstrated robust glycemic control. The system surpasses existing microneedle-based closed-loop systems in two key aspects: (1) Its redundant sensing design ensures enhanced robustness and data reliability against single-point failures; (2) The active on-demand release mechanism achieves spatiotemporally precise insulin administration, thereby optimizing glycemic regulation accuracy. A comparison with previously reported results has also been provided in Tables S2 and S3 of the supplementary materials. Future research can further advance this platform along several key directions. In terms of signal processing, machine learning based multi-channel fusion algorithms may be developed to dynamically calibrate sensor outputs and enhance glucose monitoring accuracy. During clinical validation, multi-center trials are necessary to evaluate the long-term performance and safety of the system across diverse populations of diabetic patients. For control strategies, model predictive control (MPC) algorithms could be introduced to enable autonomous insulin regulation driven by real-time glucose concentrations. Innovations such as anti-fouling coatings and the use of biodegradable materials may further improve system stability and biocompatibility. Collectively, these enhancements will accelerate the development of this system into a fully functional intelligent artificial pancreas, facilitating precision and automation in diabetes care. This work not only offers a potential solution to existing technological bottlenecks but also lays a critical foundation for the future development of personalized and intelligent medical devices.

Materials and methods

Reagents

Glucose oxidase (from *Aspergillus niger*, 180 U/mg), chloroplatinic acid ($\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$), o-phenylenediamine (OPD), chitosan, sodium alginate (viscosity 2000 ± 20 mPa), purchased from Shanghai Aladdin Biochemical Technology Co., Ltd.; polyurethane (PU), purchased from Sigma-Aldrich; tetrahydrofuran (THF), phosphate-buffered saline (PBS, pH = 7.4), dimethylformamide (DMF), glutaraldehyde (25%), bovine serum albumin (BSA), glacial acetic acid, concentrated hydrochloric acid, sodium acetate, concentrated sulfuric acid, potassium ferrocyanide ($\text{K}_3[\text{Fe}(\text{CN})_6]$), potassium

ferricyanide trihydrate ($K_4[Fe(CN)_6] \cdot 3H_2O$), ferrous sulfate heptahydrate ($FeSO_4 \cdot 7H_2O$), anhydrous sodium sulfate (Na_2SO_4), purchased from China National Pharmaceutical Group Chemical Reagents Co., Ltd.; human recombinant insulin (≥ 27.5 units/mg), purchased from Beijing Puxitang Biotechnology Co., Ltd.; poly(3,4-ethylenedioxythiophene)-poly(styrene sulfonate) (PEDOT:PSS) dispersion (Clevious PH1000), purchased from Heraeus Electronic Materials, Germany.

Materials and instruments

Stainless steel needles (0.16×40 mm); silver-plated stainless-steel needles (0.16×40 mm); sandpaper (2000 mesh, 3000 mesh); silver/silver chloride reference electrode; platinum reference electrode; electrochemical workstation (AutoLab); ultrasonic cleaner (power 300 W, frequency 40 kHz); magnetic stirrer (Topolino, Biosharp); field-emission scanning electron microscope (Hitachi, SU8010); SIBIONICS CGM System.

Characterization of glucose monitoring microneedles performance

A standardized three-electrode testing system was established, using the fabricated microneedle as the working electrode, paired with a standard Ag/AgCl reference electrode and a platinum wire counter electrode, for systematic testing in a 0.01 M PBS buffer solution (pH 7.2–7.4). During testing, a constant potential of +0.5 V was applied to the working electrode, and the response signals were recorded using a chronoamperometric method. Four independent microneedles from the same batch were tested. For each test, 2 mM glucose standard solution was added to the system, and the microneedle's linear range, sensitivity, and consistency were evaluated. The microneedles were placed in a 20 mM glucose solution, and the response currents were measured continuously for three days to assess their stability. The microneedles were then placed into the testing system, and glucose (5 mM), ascorbic acid (0.2 mM), uric acid (0.1 mM), and acetaminophen (0.5 mM) were sequentially added to measure the current responses, thus characterizing the selectivity of the microneedles. To evaluate the long-term stability of the microneedles, they were placed into the reaction system, with 2 mM glucose added each time until the glucose concentration in the solution reached 20 mM. The current responses were recorded and measured continuously for seven days. During periods without measurement, the microneedles were stored in PBS (pH 7.2–7.4) for preservation.

For further characterization of the performance of reference and counter microneedle electrodes, the standard Ag/AgCl reference electrode and platinum wire counter electrode in the three-electrode testing system were replaced with microneedle electrodes. Again, 2 mM

glucose standard solution was added to the system each time.

Characterization of insulin-releasing microneedles performance

The microneedles, both before and after polishing, were tested using Electrochemical Impedance Spectroscopy (EIS) in a solution of 5 mM $K_3[Fe(CN)_6]$ and 5 mM $K_4[Fe(CN)_6]$, with an open-circuit voltage for impedance spectrum analysis. The excitation voltage amplitude was set to 10 mV, and the testing frequency range was from 0.1 to 10^6 Hz. The microneedles, both before and after platinum coating, were subjected to EIS testing in the same electrolyte solution (frequency range of 0.1 Hz to 10^6 Hz, with an amplitude of 10 mV). Cyclic voltammetry tests were conducted in a solution of 5 mM $K_3[Fe(CN)_6]$ and 0.01 M KCl within a voltage range of 0–0.5 V to characterize the platinum coating effect. In order to clearly and visually observe the insulin release effect, fluorescent microspheres were used to replace insulin for release characterization. A solution containing 35 mM $FeSO_4$, 1% sodium alginate, and 0.5% PEDOT:PSS was prepared, and after the hydrogel formed on the microneedles, it was dried and observed under a fluorescence microscope. Next, the hydrogel microneedles were used as the working electrode, with Ag/AgCl as the reference electrode and Pt as the counter electrode, immersed in the same PBS solution to form a three-electrode system. A reduction voltage of -1.5 V was applied for 600 s using an electrochemical workstation, after which both the microneedles and the PBS solution were observed under the fluorescence microscope. To characterize the insulin content released from each electrochemical triggered insulin release microneedle, insulin solutions with concentrations of 0, 0.004, 0.008, 0.012, 0.016, 0.020, 0.024, 0.028, 0.032, 0.036, and 0.040 mg/mL were first prepared. Fifty microliters of each solution were placed in a 96-well plate, followed by the addition of 200 μ L of Coomassie Brilliant Blue G-250 dye solution (50 mg Coomassie Brilliant Blue G-250, 25 mL 95% ethanol, 50 mL 85% phosphoric acid, and diluted with water to 500 mL). After staining, the solution was stable within 5–20 min. During this time, the absorbance of the standard solutions was measured using a microplate reader at different wavelengths, and the absorbance at 595 nm was recorded. The electrochemical triggered insulin release microneedles and the Ag/AgCl reference electrode were placed in 4 mL of 0.01 M PBS solution, and a reduction voltage of -1.5 V was applied for 600 s. Fifty microliters of the solution were taken before and after the application of the reduction voltage, and 200 μ L of Coomassie Brilliant Blue G-250 dye was added. The absorbance at 595 nm was measured to analyze the insulin content released by the electrochemical triggered insulin release microneedles.

To explore the insulin content at different release times during the release process, the electrochemical triggered insulin release microneedles and Ag/AgCl reference electrode were placed in 4 mL of 0.01 M PBS solution, with reduction voltages applied for 100 s, 200 s, 300 s, 400 s, 500 s, and 600 s, respectively. Fifty microliters of the solution were taken, and 200 μ L of Coomassie Brilliant Blue G-250 dye was added for absorbance testing at 595 nm.

Microneedle array assembly

To prevent scratching of the modified microneedles during their assembly onto the array, an assembly frame was designed as shown in S1–S2. The microneedles are inserted from the bottom through a 3×3 perforated electrode sheet and placed into the assembly frame. The lower part of the frame is stacked with multiple layers of identical perforated electrode sheets, which support the microneedles in maintaining their vertical orientation during assembly on the electrode sheets. The bottommost layer also contains a 3×3 hole arrangement, where screws of appropriate height are inserted to facilitate adjustment of the microneedles' length exposed on the top layer of the electrode sheet.

After the microneedles are placed, conductive silver paste is used to connect the needle bodies to the electrode pad of the sheet. Once dried, UV-curable adhesive is applied to encapsulate the assembly for insulation. Finally, the excess parts of the microneedles are trimmed to obtain the final assembled microneedle array.

Biocompatibility testing Cell counting kit-8 (CCK-8) test

The 3T3 fibroblast cell line was selected for testing. The 3T3 fibroblasts were revived, cultured, and subcultured until stable cells were obtained. The Ag/AgCl microneedle electrode, Pt microneedle electrode, CGM microneedle electrode, and electrochemical triggered insulin release microneedle were each soaked in serum-free medium to prepare the microneedle extracts. The 3T3 cells, grown stably in culture dishes, were digested, centrifuged, and resuspended in an appropriate amount of culture medium, with cell counting performed using a hemocytometer. Based on the obtained cell concentration, 2×10^4 3T3 fibroblasts were added to each well of a 24-well cell culture plate. Microneedle extracts were then added, and the cells were incubated for 0, 12, 24, 36, and 48 h. After incubation, CCK-8 reagent was added, and the cells were incubated for an additional 1 h. The OD value was measured at 450 nm, and the OD values corresponding to different groups were recorded. The OD value of each group was subtracted by the OD value of the BLANK well, and the average value was calculated to generate a cell viability bar chart.

HE and Masson staining experiments

A healthy SD rat was selected for the experiment. The rat was anesthetized by intraperitoneal injection of 3.5 mL/kg 10% chloral hydrate and depilated using hair removal cream. After depilation, cotton swabs and gauze soaked in water and iodine tincture were used to clean the skin surface from any remaining hair removal cream. To achieve better fixation, the microneedle array was cut into smaller sizes and implanted subcutaneously at an appropriate site on the rat's back. The array was then fixed with multiple layers of 3 M medical adhesive tape. To prevent the rat from gnawing on the microneedle array, each implanted rat was housed individually in a cage.

After 7 days of glucose microneedle array implantation and 24 h of electrochemical triggered insulin release microneedle array implantation, the skin at the insertion site of the respective arrays was excised. The needle puncture sites were marked with a marker pen for easier sectioning. The skin tissue was fixed in 4% paraformaldehyde for 24 h and then sectioned for HE and Masson staining. The tissue inflammation response around the microneedle puncture sites was compared and analyzed.

In-vivo experiments

A healthy SD rat was selected for the experiment. The animal was anesthetized using either a gas anesthesia machine or an injectable anesthetic. The rat's limbs were then fixed to a board using adhesive tape. The back fur of the rat was moistened, and long hairs were trimmed with scissors. The majority of the fur was shaved using an electric clipper, and further cleaning was performed with a razor. Finally, hair removal cream was applied to the targeted area and left for 8 minutes before being wiped off. At this point, the skin was thoroughly clean. It is essential to wipe off the hair removal cream completely and apply iodine tincture to avoid skin irritation, bleeding, and scabbing, which could affect subsequent experiments.

The dorsal region of the rat/rabbit was chosen as the site for microneedle insertion (an area with few organs and less tendency to gnaw). After applying iodine tincture and allowing it to dry, a commercially available silicone-based dynamic glucose meter was applied to the skin. The skin was gently stretched using both hands, and the prepared microneedle array was pressed onto the skin. Multiple adjustments and pressures were applied to ensure that the microneedles were properly inserted subcutaneously. The microneedle array patch was then covered with a dressing to secure it in place. The circuit part was connected to the microneedle array electrode via an interface. Glucose monitoring data was collected through Bluetooth on a mobile phone.

Ethics declarations

The animal experiments were approved by the Laboratory Animal Welfare Ethics Committee of Zhejiang University (Approval No. ZJU20220149) and performed in compliance with ethical standards.

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Author contributions

B.L. and Y.W. designed the overall study; Y.W., W.C., Y.M., Y.Z., Z.D., and H.L. performed the experiments; Y.W., W.C., Y.M., Y.Z., S.Z., and Y.Z. analyzed the results with assistance from B.L. and X.Y.; Y.W. and W.C. wrote the paper with assistance from B.L. and X.Y.; B.L. and X.Y. revised the paper; B.L. conceived the idea and led the project. All authors provided feedback on the results and the paper.

Conflict of interest

The authors declare no competing interests.

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