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A self-powered closed-loop brain-machine-interface system for real-time detecting and rapidly adjusting blood glucose concentration

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Abstract:	The traditional methods of detecting and adjusting blood glucose concentration, such as blood analysis and insulin injection, may delay the treatment of metabolic disease. Here, a new self-powered closed-loop brain-machine-interface system for real-time detecting and rapidly adjusting blood glucose concentration has been fabricated. The system can work without external power supply and be self-powered by the body motion itself, which can meet the requirement of immediate treatment. The system mainly consists of active blood glucose sensor, energy harvester, micro-control unit and brain stimulator. The blood glucose sensor made of enzyme/ZnO nanowire arrays can output piezoelectric voltage under the driving of body motion, and the output can be treated as the glucose-detecting signal through the biosensing-piezoelectric coupling effect. A piezoelectric ceramic device as the energy harvester can convert the body mechanical energy into electricity for powering the whole system. The micro-control unit outputs brain stimulation pulse to the dorsomedial part of the ventromedial hypothalamus (VMHdm) in the brain upon abnormal blood glucose concentration. In mouse samples, the brain stimulator connected to the VMHdm augments the expression of regulatory nerve receptors to achieve rapid increase of blood glucose concentration (39% within 10 minutes). Thus, a closed loop is formed among the body, brain and system. This self-powered closed-loop approach improves the accessibility of physiological insights and extends brain-machine-interface application in precision medicine for metabolic diseases.

Dear Editor,

We are very grateful to the Editor for the comments. We have carefully revised our manuscript according to the reports.

Sincerely yours,

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Research Highlights:

-A novel closed-loop system for rapidly adjusting the blood glucose concentration.

-The self-powered blood glucose sensor can be driven by the body itself.

-These blood glucose sensing signals can be converted into brain stimulation signals.

-The brain-computer interface system successfully adjusts the blood glucose concentration of mice.

Correction List (NANOEN-D-21-03804R1)

We are very grateful to the Editor for the comments. We have carefully revised our manuscript according to the reports. The details are shown as follows:

Editor：

1. Please follow the format of the journal as given online to strictly formulate the style of the text, especially about the reference style of the journal,otherwise your manuscript may be returned for further revision.

Response:

This is a very useful suggestion and we thank the editor. We have modified these errors. *Refs. 1-61* have been modified.

A self-powered closed-loop brain-machine-interface system for real-time detecting and rapidly adjusting blood glucose concentration

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Abstract

The traditional methods of detecting and adjusting blood glucose concentration, such as blood analysis and insulin injection, may delay the treatment of metabolic disease. Here, a new self-powered closed-loop brain-machine-interface system for real-time detecting and rapidly adjusting blood glucose concentration has been fabricated. The system can work without external power supply and be self-powered by the body motion itself, which can meet the requirement of immediate treatment. The system mainly consists of active blood glucose sensor, energy harvester, micro-control unit and brain stimulator. The blood glucose sensor made of enzyme/ZnO nanowire arrays can output piezoelectric voltage under the driving of body motion, and the output can be treated as the glucose-detecting signal through the biosensing-piezoelectric coupling effect. A piezoelectric ceramic device as the energy harvester can convert the body mechanical energy into electricity for powering the whole system. The micro-control unit outputs brain stimulation pulse to the dorsomedial part of the ventromedial hypothalamus (VMHdm) in the brain upon abnormal blood glucose concentration. In mouse samples, the brain stimulator connected to the VMHdm augments the expression of regulatory nerve receptors to achieve rapid increase of blood glucose concentration (39% within 10 minutes). Thus, a closed loop is formed among the body, brain and system. This self-powered closed-loop approach improves the accessibility of physiological insights and extends brain-machine-interface application in precision medicine for metabolic diseases.

Keywords: self-powered; closed-loop; brain-machine-interface; glucose concentration

1. Introduction

Blood glucose concentration is an important indicator that relates to the physiological health of human body. People with low blood glucose level will suffer from sweating, hand trembling, palpitation, rapid heartbeat and limb weakness [1-2]. People with high blood glucose level may take high risk of diabetes and other metabolic diseases with symptoms of polydipsia, polyphagia, polyuria and obvious weight loss [3-4]. As the patients with glucose metabolic diseases cannot use their own physiological system to adjust blood glucose level, they demand to inject glucose or insulin to avoid hypoglycemia or hyperglycemia as the traditional treatment [5-7]. The difficulty of traditional diagnosis (blood collection/analysis) is that the patients cannot care about their blood glucose concentration at anytime and anywhere. These traditional methods of detecting and adjusting blood glucose concentration may delay the treatment [8-13]. Thus, real-time detecting and rapidly adjusting blood glucose concentration are highly expected for the prevention of abnormal blood glucose symptoms.

Widespread research has shown that glucose concentration in saliva (before meals or after meals) can reflect blood glucose concentration [14-17], and saliva glucose detection is much more convenient compared with blood sampling. Recently, various self-powered wearable biosensing techniques have been developed for monitoring the physiological conditions in real time [18-26]. Thus, a self-powered wearable saliva glucose detector can probably realize real-time monitoring the blood glucose concentration. For adjusting body physiological parameters (such as body temperature, blood glucose concentration, heart beat rate and etc.), the nerve/brain stimulation has been confirmed to be a very promising method [27-33]. For example, stimulating the ventromedial hypothalamus in brain can influence the transmission of nerve receptors and can rapidly adjust blood glucose concentration [34-39]. The neuromodulation of activating SF1 neurons (a major

subset of VMH neurons) to release synaptic glutamate [40] or opening K_{ATP} channel of glucose-sensing neurons [41-43] can promote neuronal communication and ultimately avoid hypoglycemia. It can be assumed that an integrated wearable brain-machine-interface system with the combination of self-powered glucose sensors and brain stimulator may achieve real-time detecting and rapidly adjusting blood glucose concentration.

Here, a new self-powered brain-machine-interface system for real-time detecting and rapidly adjusting blood glucose concentration has been fabricated from active blood glucose sensor, energy harvester, micro-control unit and brain stimulator. The system can work under the driving of the body motion itself, and no external power supply is needed [44-46]. The sensor unit in the system can actively monitor the salivary glucose level in real time through the biosensing-piezoelectric coupling effect [47-49]. The micro-control and brain stimulator units can transmit brain stimulation pulse to the dorsomedial part of the ventromedial hypothalamus (VMHdm) for adjusting blood glucose concentration. A closed loop is formed among the body, brain and system. This self-powered closed-loop strategy can extend the application of brain-machine-interface systems in precision medicine.

2. Experimental Section

2.1 Synthesis of ZnO nanowire arrays

A titanium sheet (1 × 3 cm in area, 150 μm in thickness) as the substrate for supporting zinc oxide (ZnO) nanowire arrays was pre-cleaned with anhydrous ethanol and deionized water. 0.0219 g of $Zn(H_3COO_2)\cdot 2H_2O$ was stirred and dissolved in 10 mL of ethanol, and the solution was evenly dropped on the titanium substrate. After drying naturally, the titanium substrate was annealed at 350°C in air for 20 minutes, and the seed layer for the growth of ZnO was formed on the substrate [50]. 0.416 g of $Zn(NO_3)_2\cdot 6H_2O$ was dissolved in 38 mL of deionized water and stirred for 10 min

at room temperature. Under continuous stirring, 2.5 mL of $NH_3 \cdot H_2O$ was added to the solution. The solution was transferred into a polytetrafluoroethylene reactor, and the titanium substrate with the seed layer was immersed in the solution. The reactor was sealed and kept at 83°C for 24 h. After cooling down to room temperature, the substrate (with ZnO nanowire arrays) was taken out, washed with absolute ethanol/deionized water, and dried at 60°C.

2.2 Modifying GOx on the surface of ZnO

0.01 mL of glucose oxidase (GOx) aqueous solution (10 $mg \cdot mL^{-1}$) was slowly dropped onto the surface of ZnO nanowire arrays [51], and the substrate was completely dried. This process was repeated for 3 times to ensure the adsorption of GOx. Finally, the substrate was washed with deionized water to remove the non-absorbed GOx.

2.3 Characterization and measurements

The structure and morphology of the system were studied by scanning electron microscope (SEM, Zeiss Gemini 300). A hammer (controlled by a program motor) provided a force that can be adjusted in magnitude and frequency. The force sensor was used to measure the magnitude of the force. The output voltage and current were respectively measured by a low noise voltage preamplifier (Stanford Research Systems Model SR 560) and a low noise current preamplifier (Stanford Research Systems Model SR570). The output signal of the brain stimulator was measured by an oscilloscope (Uni-T UTD4102C Digital Storage Oscilloscope). A commercial electrochemical blood glucose monitor (Data Sciences International, 47160) was used to measure the glucose concentration.

2.4 Animal preparation and surgery

All of the procedures in this study conformed to the regulations for the administration of affairs concerning experimental animals and were approved by Animal Care and Use Committee of

Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences. 23-27 g C57BL6J mice were induced to general anesthesia with 3% isoflurane air, then they were used a 1% isoflurane air maintenance dose. A self-made bifilar bind tungsten wires (ADVENT W558411) as stimulating electrode was stereotactically implanted in the ventromedial hypothalamus (VMH) (AP = - 1.30 mm, mL = + 0.20 mm, DV = - 5.40 mm). Depth anesthesia was performed with Ketamine hydrochloride (100 mg kg-1 Zhong Mu Bei Kang animal health products CO.,LTD) and Xylazine Hydrochloride (10 mg kg-1 Ji Lin Hua Mu animal health products CO.,LTD) on mouse by perfusion of a 4% paraformaldehyde solution of (Aladdin C104190) for determining the electrode position. Coronal 35 μm brain parts cryogenic thermostat was cut on a frozen cryostat (Leica CM1950). The images were observed with a microscope (Olympus BX61VS).

2.5 Mouse blood glucose adjustment

Mice were put into a blood glucose monitoring equipment (patent: ZL201611245698.9), and was connected to the micro-control unit and stimulators on the electrode. Their tails were disinfected with 75% alcohol and dried with sterile dry cotton, 1-2 mm tail was cut off with sterilized scissors. After 40 minutes, we squeezed and wiped the first blood, sucked the second blood, and measured the blood glucose concentration with an electrochemical blood glucose meter (Sinocare An Wen Plus). Non-electrically stimulated group: the blood of the tail of the mouse was measured every 5 minutes, a total of 4 times without stimulation is performed. Electrically stimulated group: the blood of the mouse's tail was measured every 5 minutes (the first two times without stimulation, the following with stimulation current: forward pulse width of 0.1 ms, frequency of 50 Hz, constant current of 300 μA, "on" for 0.4 s, "off" for 0.6 s).

3. Results and Discussion

3.1. Experimental design

The self-powered closed-loop brain-machine-interface system for real-time detecting and rapidly adjusting blood glucose concentration is designed to be wearable and implantable on various parts of human body, as shown in Fig. 1a. Fig. 1b shows the components of the system. The flexible glucose sensor can actively monitor the saliva glucose concentration in real time and send signal to the micro-control unit [52]. The sensing mechanism is based on the biosensing-piezoelectric coupling effect, and the sensor is self-powered by the body motion. The energy harvester can realize energy conversion and storage, and provide electrical power for micro-control unit and brain stimulator. The micro-control unit can judge the glucose concentration, and transmit the stimulation current to the electrode of the brain stimulator, and rapidly increase the blood glucose concentration. Fig. 1c reveals the circuit diagram of the system. The optical photographs of the functional units are shown in Fig. 1d. The size of the glucose sensor is 3 × 1 cm; the size of the micro-control unit is 2 × 1 cm; and the size of the energy harvester is 4 × 2 cm. The entire system is flexible and wearable.

3.2. Performance of the sensor

Figure 2 shows the performance of the flexible glucose sensor. It has been reported that the glucose concentration in different body fluids is different. For examples, the concentration in blood, urine and tear is 0.86–2.33, 0.273–0.858 and 0.010–0.083 g/L, respectively [53-55]. And the concentration in outside-body fluids, such as sweat and saliva, is lower than that inside the body. For the noninvasive examination of outside-body fluids, the oxidase amount modified on the nanowires in our work is adjusted to test low glucose concentration. The sensor is completely immersed in glucose solution with certain concentration. A hammer (controlled by a program motor) can provide a force on the sensor. A low-noise voltage preamplifier (Stanford Research Systems Model SR 560) is used to measure the output piezoelectric voltage of the sensor under

different glucose concentration. The response of the flexible sensor is tested in a series of glucose concentration gradients (0-4.1 mg/L). Under the applied pressure of 35 N, the output of the sensor has a great correlation with the glucose concentration in aqueous solution (Fig. 2a). From 0 to 2 minutes, the piezoelectric voltage stabilizes at 160 mV in pure water. After changing glucose concentration to 2 mg/L, the piezoelectric voltage decreases to 120 mV within 2 minutes. Fig. 4b-d show that as the glucose concentration is 0, 1.3 and 2.9 mg/L, the output piezoelectric voltage of the sensor is 160, 130, and 90 mV, respectively. Obviously, the piezoelectric voltage has a negative correlation with the glucose concentration. As the glucose concentration increases, the output piezoelectric voltage decreases. According to the definition of response [56]:

$$R\% = \left|\frac{V_0 - V_i}{V_i}\right| \times 100 \quad (1)$$

, the sensor has a response of 116% against the glucose concentration of 4.1 mg/L (Fig. 2e).

The stability is an important parameter for biosensors in practical applications. Fig. 2f shows the high mechanical durability of the sensor. Under the pressure of 35 N, the output of the sensor can maintain around 0.16 V during bending for 5000 times. The output response of the sensor under 0.5, 1, 2 and 3 Hz deformation (35 N) is shown in Fig. 2g. It can be seen that the output peak value of the sensor does not change under different deformation frequencies. Fig. 2h explicates the piezoelectric output of the nanowires with and without GOx modification, indicating that GOx has little effect on the output of the sensor in pure water. It is well known that some electroactive substances may affect the performance of glucose biosensors. As a control experiment, 0.5 mg urea is continuously added to the measurement solution to study the anti-interference ability of the glucose biosensor. As shown in Fig. 2i, urea has not obvious effect on the sensing performance of the biosensor. From the above data, it can be concluded that the sensor has good sensitivity, stability and selectivity.

3.3. The sensing mechanism.

Fig. 3 shows the working mechanism of the sensing process. Fig. 3a-c show the scanning electron microscope (SEM) images of ZnO nanowire arrays on titanium substrate. With the same growth direction, the nanowires are vertically arranged on the surface of the substrate. Fig. 3a shows the side view of the nanowire arrays, and the lengths of the vertically arranged nanowires are almost the same (~22 μm). The top view of ZnO nanowire arrays is shown in Fig. 3b. The uniformly distributed nanowires facilitate the adsorption of glucose oxidase. Fig. 3c shows a cross-sectional view of a single nanowire, exhibiting a hexagonal structure with a diameter of ~391 nm. Fig. 3d reveals the structure of the glucose sensor. The core material is GOx@ZnO nanowire array. The titanium sheet and copper sheet with good flexibility are used as the two electrodes, respectively. The copper is selected as the electrode material due to the high conductivity and flexibility. But as a heavy metal, it is not suitable for the practical application on the human body due to the instability. In the near future, alternative electrode materials with biocompatible and flexible features (e.g. the emerging conductive polymer) can be developed. The electrodes are connected to external circuit with two copper leads, and the outermost layer is encapsulated with Kapton boards (with many small holes). This sensor has a good flexibility. The sensing mechanism is based on the coupling of biosensing (enzymatic reaction) and piezoelectric effect, as shown in Fig. 3e and f. Owing to the stress on the c-axis, the nanowire can output piezoelectric pulses. With no enzymatic reactions, the surface carrier density of the nanowires is low (Fig. 3e). The piezoelectric shielding effect is weak, and the output piezoelectric voltage is high. After contacting with glucose solution, an enzymatic reaction can occur between GOx and glucose. The GOx on ZnO nanowires as the catalyst plays a key role for specific recognition in the biosensing process. The GOx has succeeded in converting glucose, water and oxygen into gluconic acid and hydrogen

peroxide [57-58]. During the decomposition of H_2O_2, H^+ can be adsorbed on the surface of the nanowire, and e^- will be transferred to ZnO nanowire, increasing the surface carrier density (Fig. 3f). As a result of the strong piezoelectric shielding effect of a large amount of H^+ and e^- on the surface of the nanowires, the output piezoelectric voltage of ZnO nanowires is low [59-60].

3.4. The performance of the system.

The sensor can be used to test the glucose concentration of real saliva. Fig. 4a-b show the sensing performance of the sensor upon testing the glucose concentration in the saliva of six persons (three males and three females). The operation on the sensor is similar to that in Section 3.2. The saliva is diluted with 10 times (volume) PBS because the amount of saliva is too small. Before meal, as the glucose concentration in diluted saliva of the six persons is 2.16, 2.2, 1.81, 2.31, 2.12 and 1.75 mg/L, the output of the sensors is 0.099, 0.089, 0.11, 0.087, 0.93 and 0.1 V, and the response (compared with the output in pure water) is 20.4%, 34.8%, 9.1%, 37.9%, 29% and 17.7%, respectively. After meal, as the glucose concentration in diluted saliva of the six persons is 3.6, 2.4, 3.32, 3.5, 3.4 and 3.38 mg/L, the output of the sensors is 0.067, 0.081, 0.076, 0.068, 0.07 and 0.07 V, and the response is 78.2%, 48.2%, 57.9%, 76.5%, 71.4% and 71.4%, respectively. The piezoelectric voltage signal can be treated as a glucose concentration sensing signal for real-time detection. The reaction between glucose and oxygen is irreversible, and the glucose oxidase only acts as the catalyst with very limited consumption. In the first few measurements, the sensor response decreases with measurement times due to the washing loss of the not-firmly-bonded oxidase. After that, the response tends to be stable in the long-term measurements (Fig. S2). The enzyme on the sensor can be replenished after the sensor being used for several times. The pressure on the sensor needs to keep constant in practical application. Thus

in the near future, a mechanical device needs to be added in this system for providing constant pressure on the sensor.

Fig. 4c exposits the PZT device worn on the knee as an energy harvester. The commercial PZT device is usually rigid and cannot be conformably attached on human body. The PZT device in our experiment is packaged with flexible PDMS film, and can be attached on the movable joints of human body. The both sides of PZT film (4 × 2 × 0.06 cm) is deposited with Ag as the electrodes. After connecting the leads, the PZT film is packaged with two pieces of PDMS film (5 × 3 × 0.3 cm). With a large piezoelectric constant [61], it can efficiently convert the mechanical energy of the human body into electrical energy. Under the natural bending state of the knee during walking, the output voltage and current of the energy harvester is measured (Fig. 4d). The average output voltage peak (open circuit) is about 20 V, and the output current peak (short circuit) is about 150 μA. The output power of the PZT energy harvester is related to the resistive load, as shown in Fig. 4e. The maximum value is ~1 mW as the resistive load is 100 KΩ. Fig. 4f illustrates the charging performance of the energy harvester. As the energy harvester directly charges the 100 μF capacitor through the rectifier bridge for 50 s, the voltage across the capacitor can reach 13 V. This clearly shows that the energy harvester can effectively power the entire system as a power source. In practical applications, the energy harvester can be placed on specific position of human body, such as ankles, shoulders, elbows and etc. The energy harvester is connected to the energy storage in the micro-control unit via leads attaching on the body. Fig. 4g reveals the micro-control unit. If the sensor inputs a piezoelectric signal higher than 0.1 V, the micro-control unit will output the stimulation signal for five seconds (Fig. 4h). The micro-control unit outputs a positive square wave voltage (pulse width is 0.1 ms; frequency is 50 Hz; “on” for 0.4 s, “off” for 0.6 s) as the brain stimulation signal (Fig. 4h-j). In our experiments, the stimulation signal is calibrated in vitro before

the device is implanted in mice, and the implanted brain stimulator can output the same stimulation signal in vivo.

3.5. Electrical stimulation experiment on mice for adjusting blood glucose concentration.

Fig. 5a shows electrical stimulation adjusting the blood glucose concentration of mice. A self-made bifilar bind tungsten wires as the brain stimulating electrode is stereotactically implanted in the VMH of mice. The electrical stimulation signal is inputted into the brain region through a micro-control unit to rapidly adjust blood glucose concentration. The glucose concentration of mouse tail blood is tested with a commercial electrochemical blood glucose meter. The animal experimental details can be found in the Section 2.4-2.5. When the blood glucose level of the mice becomes lower than the normal range, the blood glucose concentration can be quickly increased by electrical stimulation. The mice ($n=4$) are implanted with microneedle electrode at the VMHdm position. The micro-control unit connects to the electrode and the brain stimulator is worn on the head of mouse (Fig. 5b). Fig. 5c shows that the tail tip blood glucose concentration of four mice is measured without and with electrical stimulation. Without electrical stimulation, the blood glucose concentration of the mice does not change significantly. Then the electrical stimulation is continuously performed for ten minutes. Obviously, after receiving electrical stimulation, the blood glucose concentration rises sharply and rapidly. Fig. 5d shows the increase percentage of blood glucose concentration upon five and ten minutes of electrical stimulation. After five minutes of stimulation, the maximum increase percentage is 28%, and after ten minutes of stimulation, the maximum increase percentage is 56%. It can be seen that electrical stimulation can continuously and effectively increase blood glucose concentration. Without electrical stimulation, the blood glucose concentration fluctuates steadily in a small range (Fig. 5e). Fig. 5f shows that after 5 minutes of electrical stimulation, the average increase of glucose concentration is 1.8 mmol/L, and

the average increase percentage is 20%. After 10 minutes of electrical stimulation, the average increase of glucose concentration is 3.5 mmol/L, and the average increase percentage is 39%. The electrical stimulation in VMHdm can induce a rapid increase in blood glucose concentration. Fig. 5g shows a brain slice of a mouse. It can be clearly seen that the electrical stimulation position is basically consistent with the expected position (VMHdm).

4. Conclusion

In summary, a new self-powered brain-machine-interface system has been fabricated for real-time detecting and rapidly adjusting blood glucose concentration. The system made from active blood glucose sensor, energy harvester, micro-control unit and brain stimulator can function without external power supply. The sensor unit can actively monitor the saliva glucose level in real time, and the working mechanism is based on the biosensing-piezoelectric coupling effect. The micro-control and brain stimulator units can transmit brain stimulation pulse to the dorsomedial part of the ventromedial hypothalamus (VMHdm) for adjusting blood glucose concentration. In mouse samples, we achieve rapid increase of blood glucose concentration (39% within 10 minutes). This self-powered closed-loop strategy can extend the application of brain-machine-interface systems in precision medicine.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

X.X. and Y.Z. conceived and initiated the project. G.Y, Y.T. and T.L. designed the experiments. G.Y. and T.L. performed perception sensing experiments. G.Y. and Y.T. performed mouse

stimulation experiments. X.X., G.Y., Y.T., Y.Z., Y.F., T.Z., Y.Z. and L.X. wrote the manuscript with comments from all authors.

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Supporting Information.

Figure S1. The circuit simulation diagram of the micro-control unit.

Figure S2. The influence of measurement times on response.

Movie S1. Input signal triggers stimulation signal output experiment.

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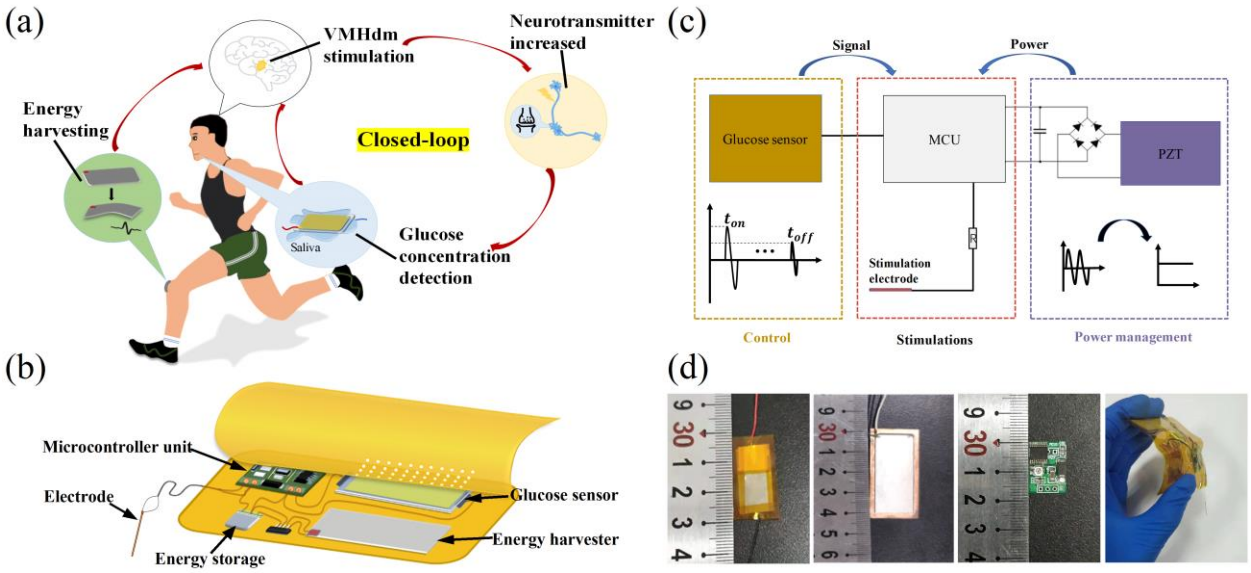

Fig. 1. Experimental design. (a) A self-powered glucometer combined with a brain-machine interface for constructing closed loop. (b) The components of the system. (c) Electrical circuit diagram of the overall signal regulation system. (d) Optical images of the devices.

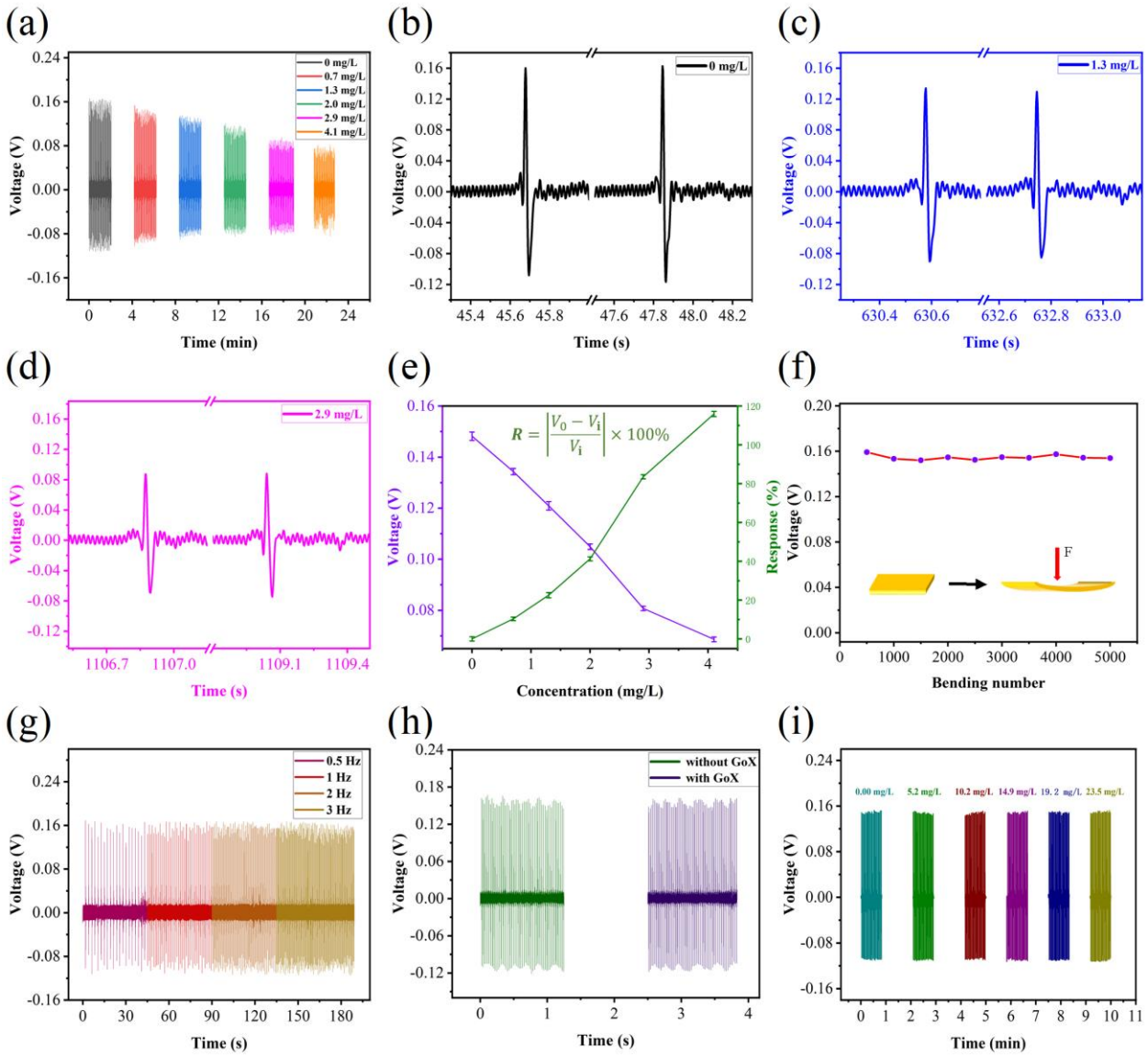

Fig. 2. Performance of the sensor. (a) The output piezoelectric voltage of the sensor against different glucose concentrations. (b), (c) and (d) Magnified view of output piezoelectric voltage under different glucose concentrations. (e) The output piezoelectric voltage and corresponding response under different glucose concentrations. (f) The durability of the sensor. (g) The output piezoelectric voltage of the sensor at different frequencies. (h) The output piezoelectric voltage with and without glucose oxidase modification on the nanowire in pure water. (i) The influence of urea on output piezoelectric voltage.

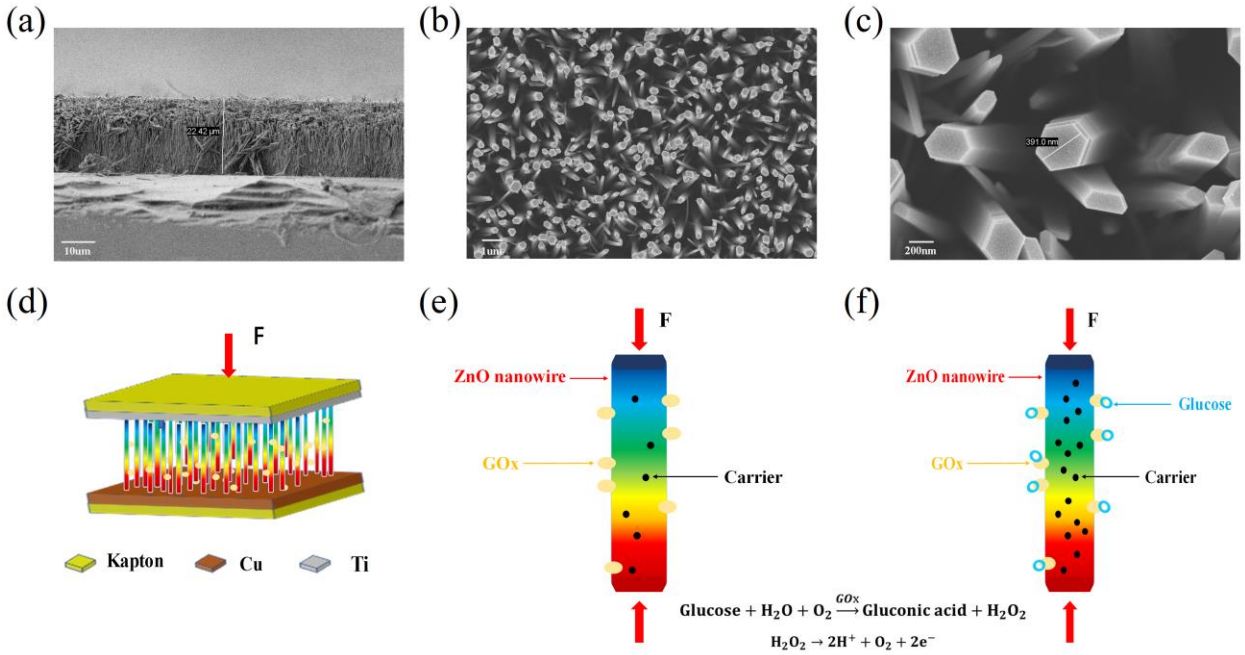

Fig. 3. The sensing mechanism. (a) Side view of ZnO nanowires. (b) Top view of ZnO nanowires. (c) a cross-sectional view of a single nanowire. (d) The structure of the glucose sensor. (e) and (f) The sensing mechanism.

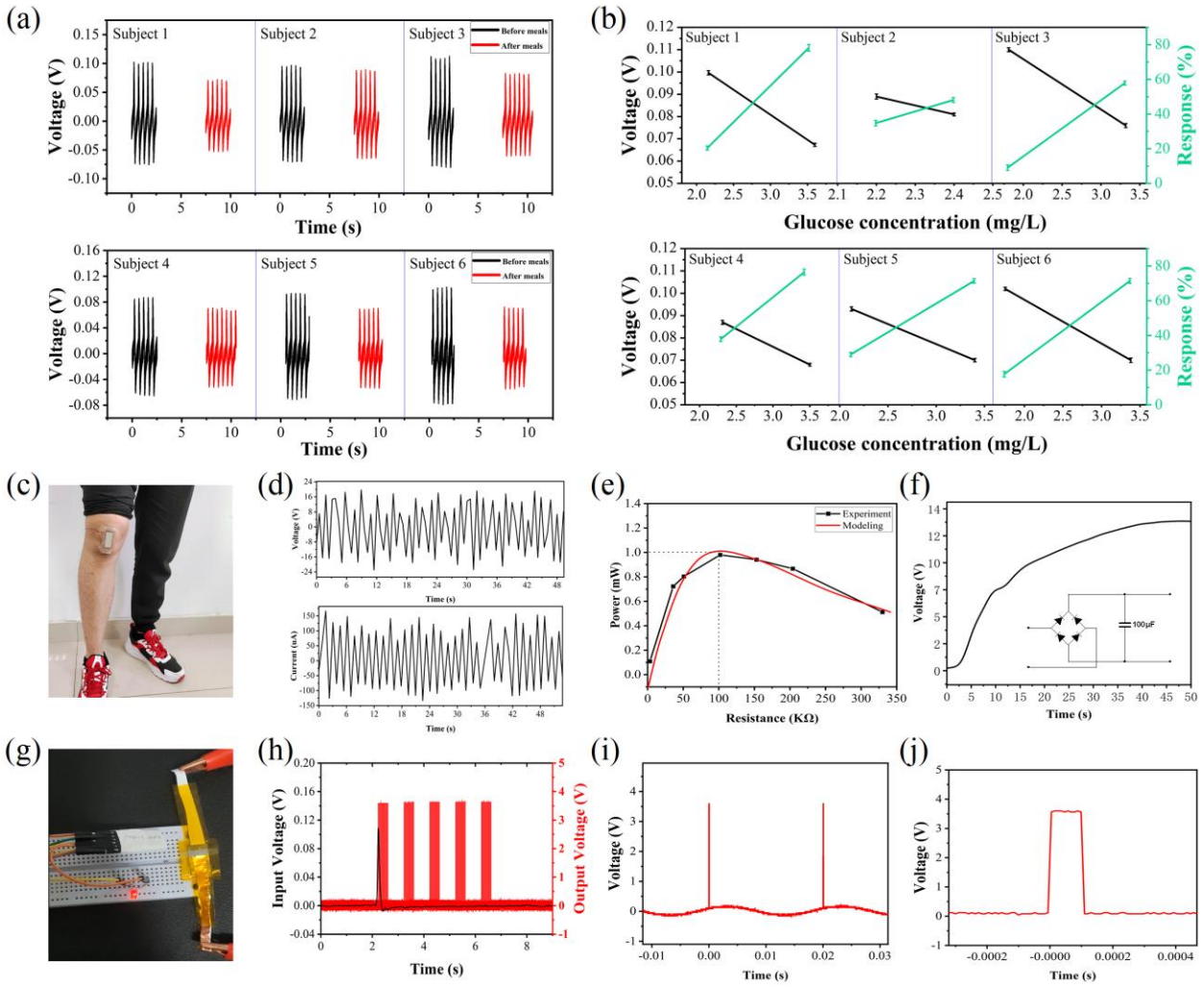

Fig. 4. The performance of the system. (a) The output of the sensor in the saliva of six persons (three males: Subject 1-3; three females: Subject 4-6) before and after meals. (b) The response of the sensor in the saliva of six persons (three males and three females) before and after meals. (c) The PZT device worn on the knee. (d) The output voltage and current of PZT device. (e) The output power of the PZT device with resistive load. (f) Charging curve. (g) The micro-control unit. (h), (i) and (j) Stimulation signals.

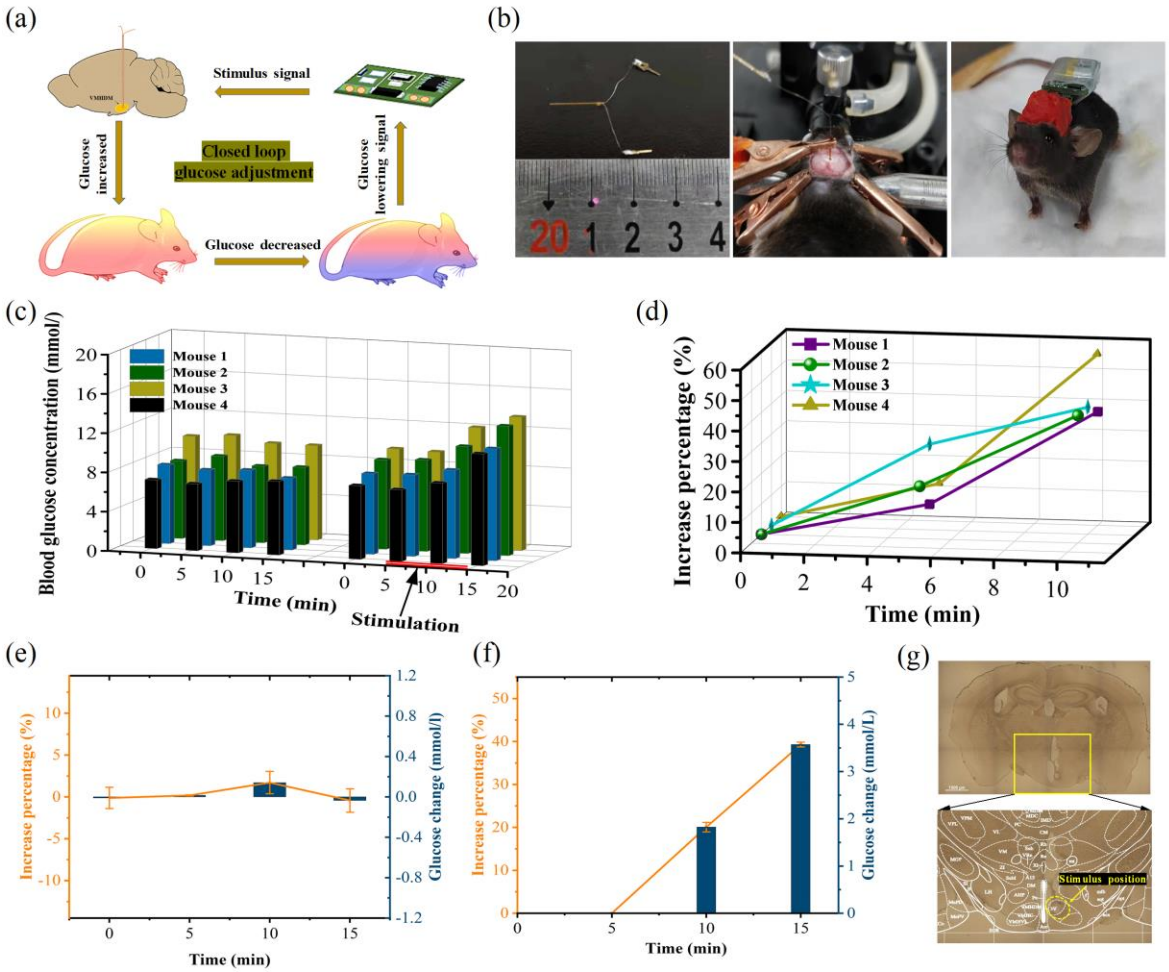

Fig. 5. Electrical stimulation experiment on mice for adjusting blood glucose concentration. (a) The closed loop of electrical stimulation adjusting the blood glucose concentration of mice. (b) Electrode implantation and electrical stimulation experiment. (c) The tail tip blood glucose concentration of four mice without and with electrical stimulation. (d) The increase percentage of blood glucose concentration with electrical stimulation. (e) The average change and increase percentage of glucose concentration without electrical stimulation. (f) The average change and increase percentage of glucose concentration with electrical stimulation. (g) A brain slice of a mouse.

Vitae

Guangyou Yang is currently studying for the master degree in the School of Physics, University of Electronic Science and Technology of China, China. Now his research interests include nanogenerators and self-powered systems.

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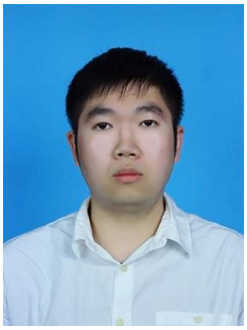
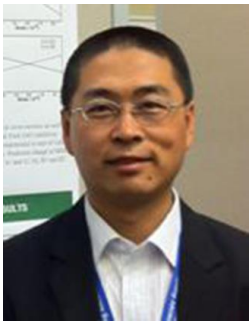
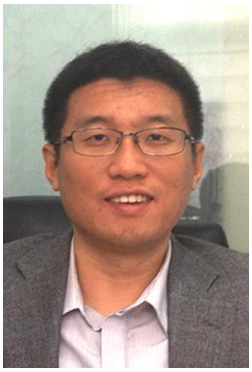


Yan Zhang is a professor at University of Electronic Science and Technology of China, China. His research interests include self-powered nano/micro system, piezotronic and modeling of nonlinear dynamics of NEMS.



Lili Xing is a Professor at University of Electronic Science and Technology of China, China. She mainly focuses on the synthesis of metal oxide nanostructures.

Xinyu Xue is a Professor at University of Electronic Science and Technology of China, China. Currently he is working on the next generation of sensors and batteries, such as self-powered active sensors and self-charging lithium battery.



Yang Zhan is a Professor at Brain Cognition and Brain Disease Institute, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, China. His main research interests focus on the neural circuit and behavior of rodents.

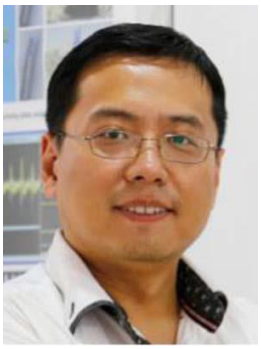


Figure1

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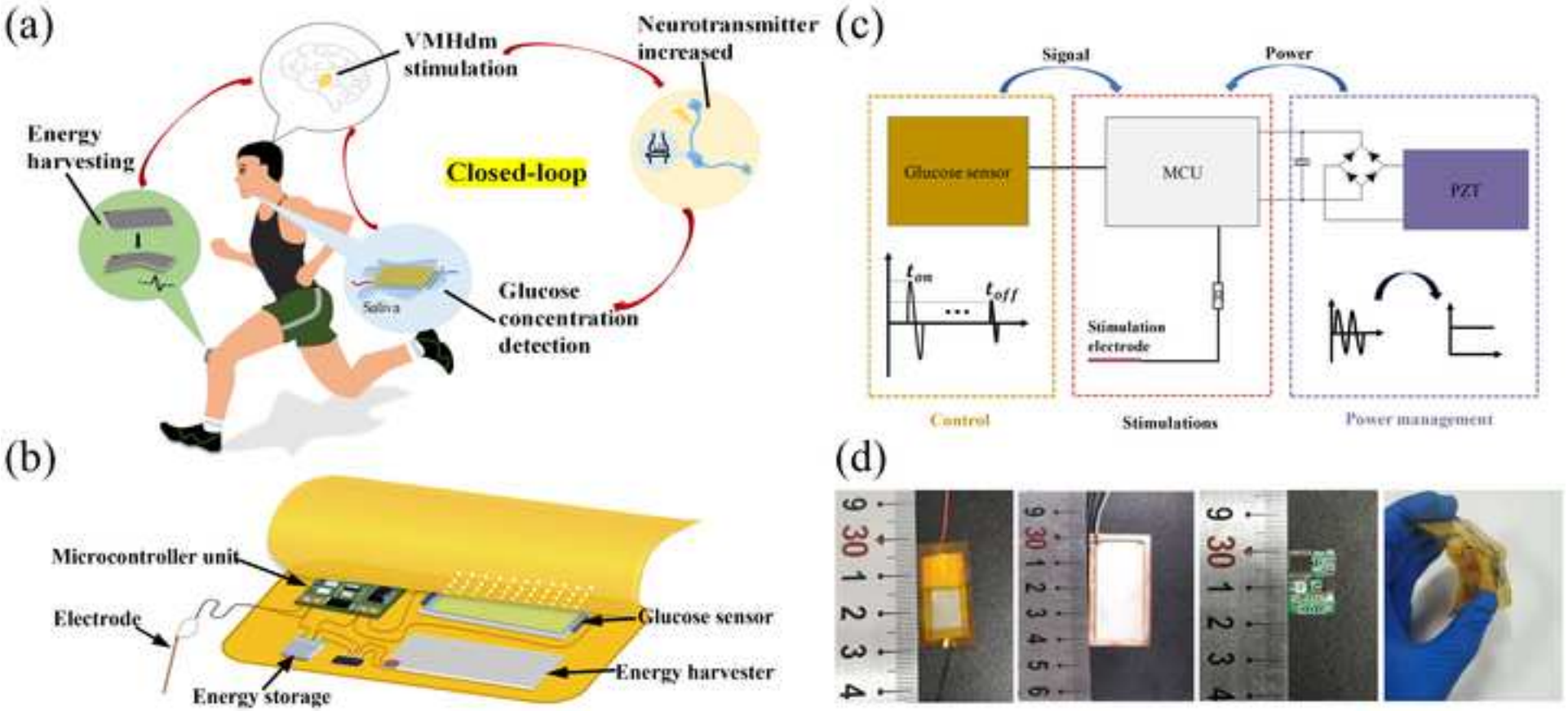

Figure2

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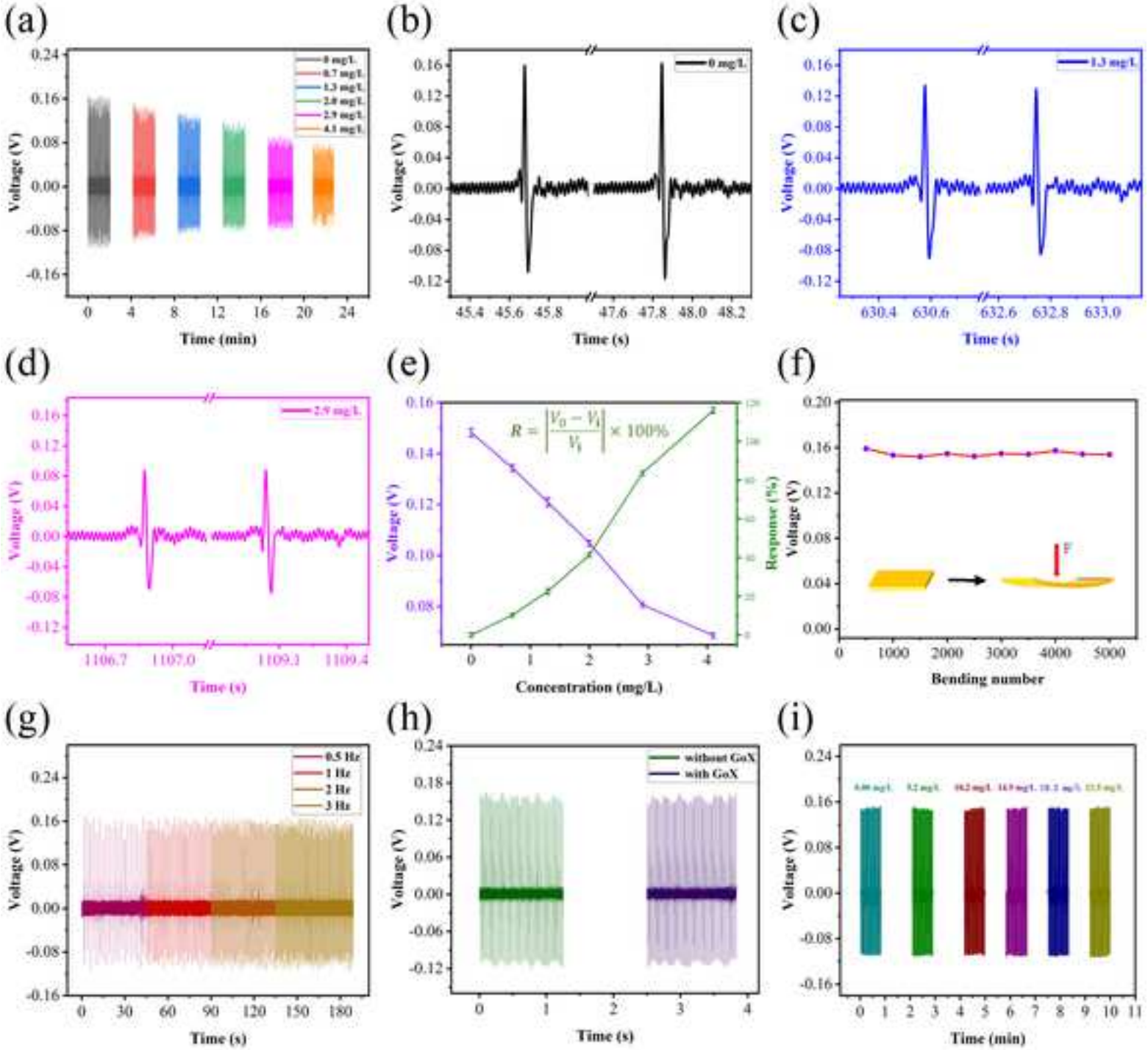

Figure3

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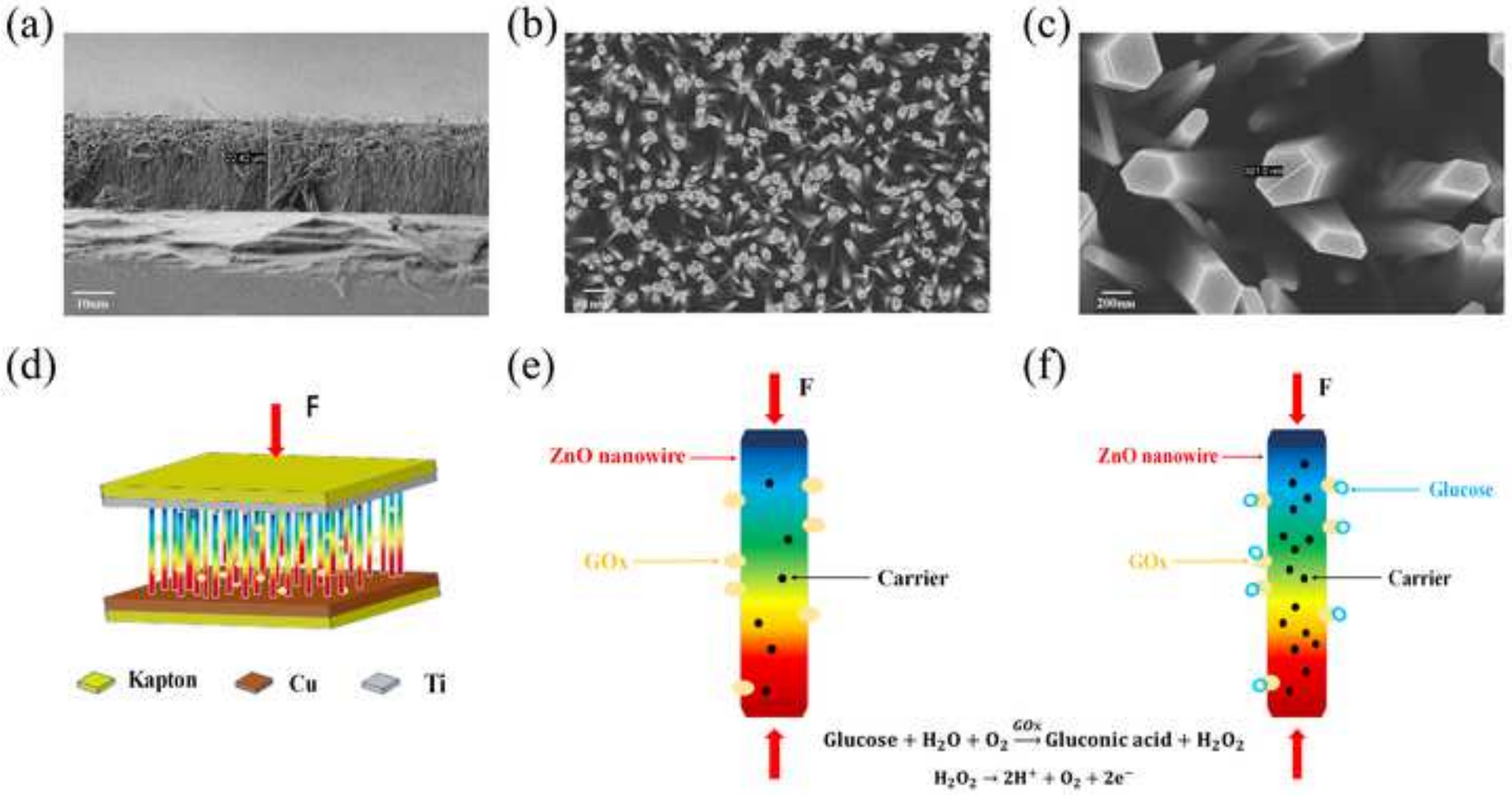

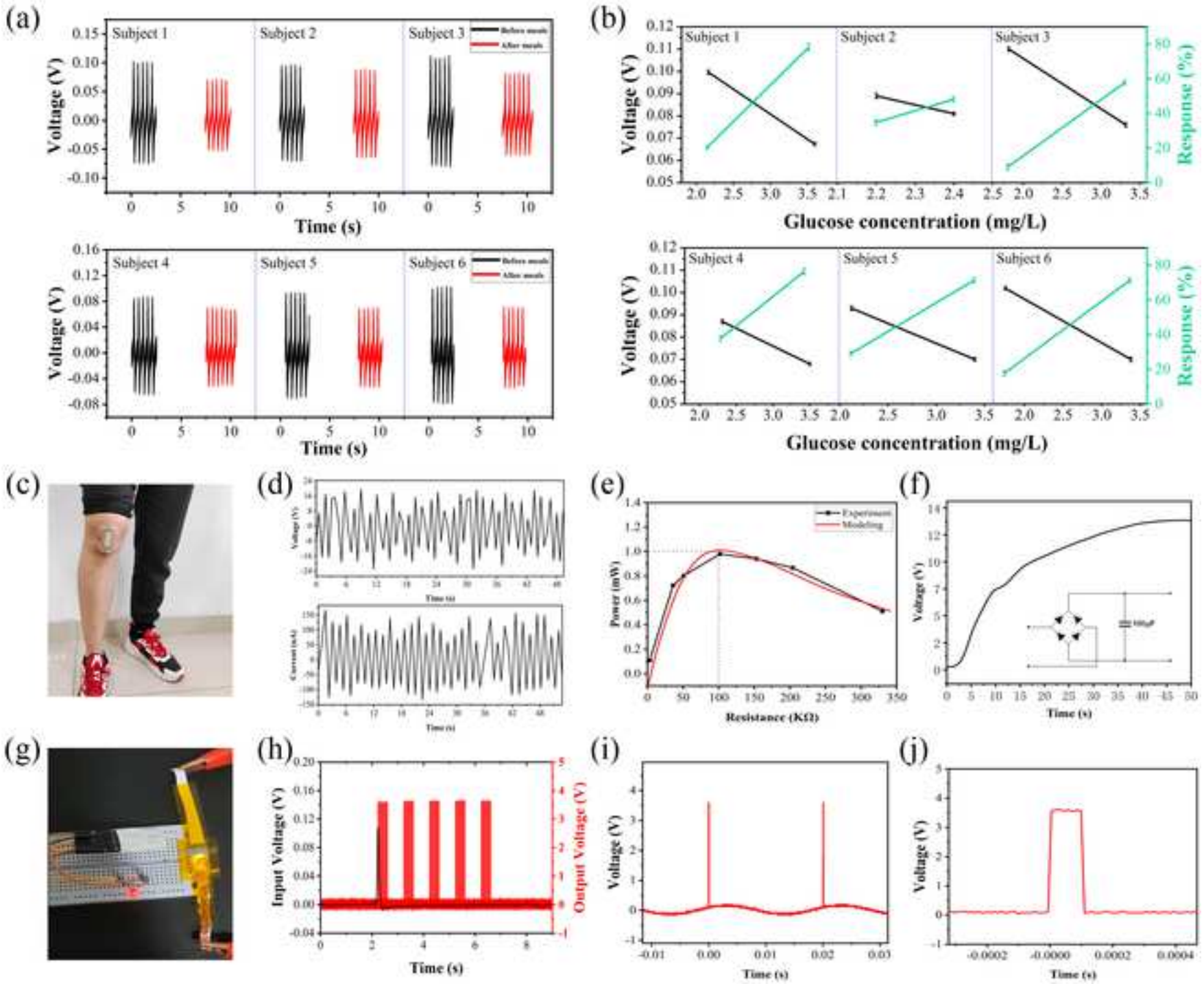

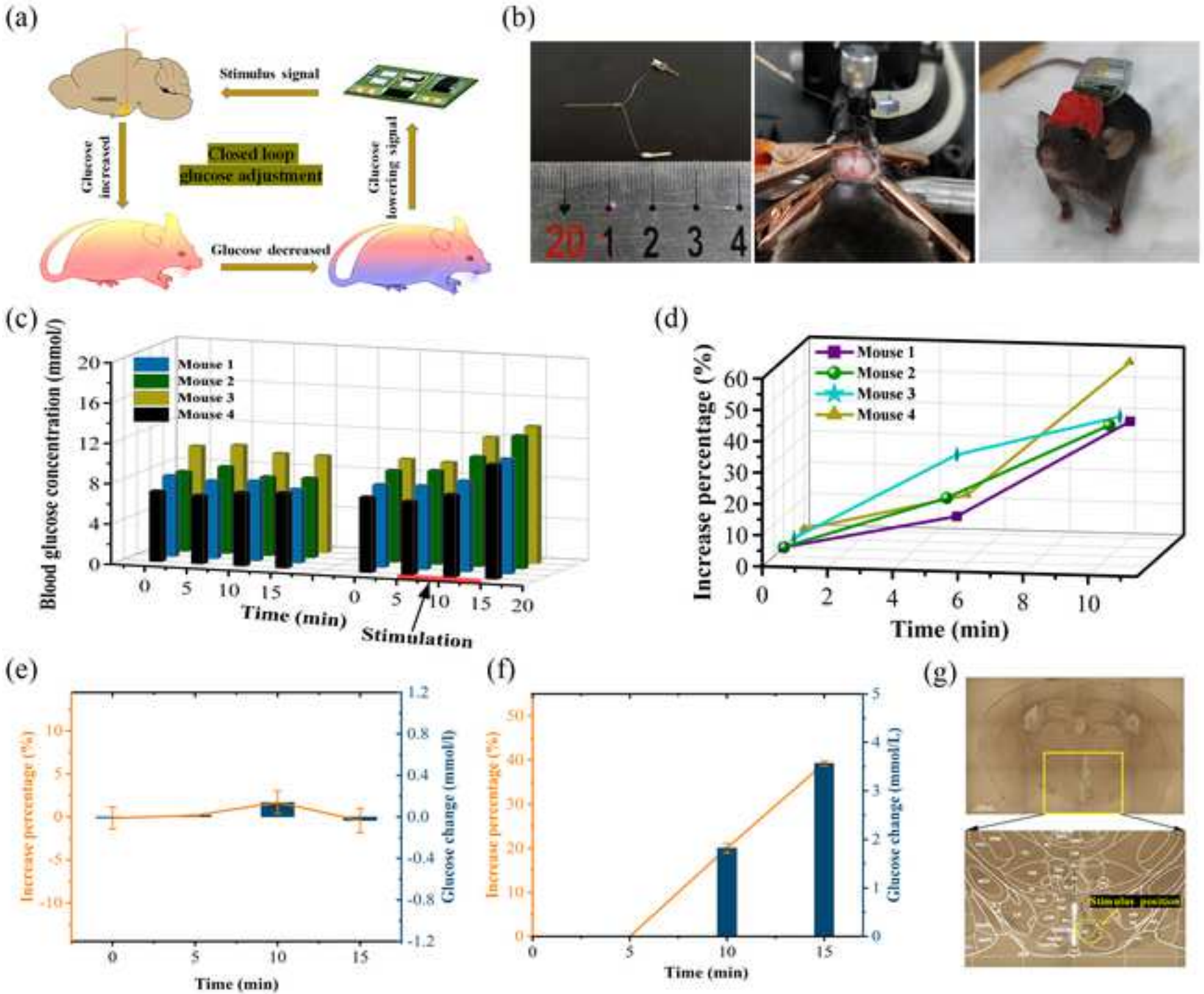

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Graphical Abstract

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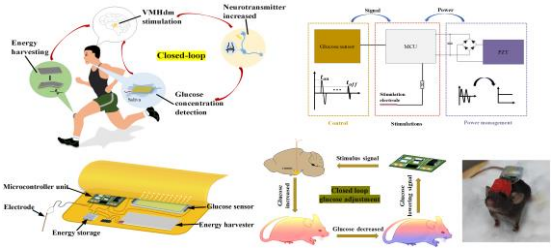

A self-powered closed-loop brain-machine-interface system for real-time detecting and rapidly adjusting blood glucose concentration has been realized. The blood glucose sensor made of enzyme/ZnO nanowire arrays can output piezoelectric voltage under the driving of body motion, and the output can be treated as the glucose-detecting signal through the biosensing-piezoelectric coupling effect. The micro-control unit outputs brain stimulation pulse to the dorsomedial part of the ventromedial hypothalamus (VMHdm) in the brain, and in mouse samples, we achieve rapid increase of blood glucose concentration (an average increase of 39% within 10 minutes).

Declaration of interests

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

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Credit Author Statement

Guangyou Yang: Investigation, Writing - Original Draft; Yong Tang: Investigation, Writing - Original Draft; Tao Lin: Investigation; Tianyan Zhong: Writing - Original Draft; Yaowei Fan: Writing - Original Draft; Yan Zhang: Methodology; Lili Xing: Methodology, Conceptualization; Xinyu Xue: Conceptualization, Writing - Review & Editing, Supervision; Yang Zhan: Conceptualization, Supervision.