A chemically mediated artificial neuron

Ting Wang[1,2,8], Ming Wang[2,3,8], Jianwu Wang[2], Le Yang[4], Xueyang Ren[5], Gang Song[6,7], Shisheng Chen[5], Yuehui Yuan[5], Ruiqing Liu[5], Liang Pan[2], Zheng Li[2], Wan Ru Leow[4], Yifei Luo[2,4], Shaobo Ji[2], Zequn Cui[2], Ke He[2], Feilong Zhang[2], Fengting Lv[6], Yuanyuan Tian[1], Kaiyu Cai[1], Bowen Yang[1], Jingyi Niu[1], Haochen Zou[1], Songrui Liu[1], Guoliang Xu[1], Xing Fan[1], Benhui Hu[5], Xian Jun Loh[4], Lianhui Wang[1], and Xiaodong Chen[2,4*]*

[1]State Key Laboratory of Organic Electronics and Information Displays & Jiangsu Key Laboratory for Biosensors, Institute of Advanced Materials (IAM), Jiangsu National Synergetic Innovation Center for Advanced Materials (SICAM), Nanjing University of Posts and Telecommunications, 9 Wenyuan Road, Nanjing 210023, China

[2]Innovative Center for Flexible Devices (iFLEX), Max Planck – NTU Joint Lab for Artificial Senses, School of Materials Science and Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798, Singapore

[3]Frontier Institute of Chip and System, Fudan University, Shanghai 200433, China

[4]Institute of Materials Research and Engineering, Agency for Science Technology and Research (A*STAR), Fusionopolis Way, Singapore 138634, Singapore

[5]School of Biomedical Engineering and Informatics, Nanjing Medical University, Nanjing 211166, China

[6]Beijing National Laboratory for Molecular Sciences, Key Laboratory of Organic Solids, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100910, China

[7]College of Chemistry, University of Chinese Academy of Sciences, Beijing 100049, China

[8]These authors contributed equally: Ting Wang, Ming Wang.

*Corresponding author. E-mail: chenxd@ntu.edu.sg, hubenhui@njmu.edu.cn

Brain–machine interfaces typically rely on electrophysiological signals to interpret and transmit neurological information. In biological systems, however, neurotransmitters are chemical-based inter-neuron messengers. This mismatch can potentially lead to incorrect interpretation of transmitted neuron information. Here we report a chemically mediated artificial neuron that can receive and release the neurotransmitter dopamine. The artificial neuron detects dopamine using a carbon-based electrochemical sensor and then processes the sensory signals using a memristor with synaptic plasticity, before stimulating dopamine release through a heat-responsive hydrogel. The system responds to dopamine exocytosis from rat pheochromocytoma cells and also releases dopamine to activate pheochromocytoma cells, forming a chemical communication loop similar to interneurons. To illustrate the potential of the approach, we show that the artificial neuron can trigger the controllable movement of a mouse leg and a robotic hand.

Brain–machine interfaces (BMIs) can bridge the gap between humans and machines through the interpretation and transmission of neurological information. This is a critical process in neuron rehabilitation, cyborg construction and ultimately consciousness detection and control.[1-3] Current state-of-the-art BMI technologies rely on the translation of electrophysiological signals,[4-6] such as surface (ex-vivo) or intracellular (in-vivo) bioelectrical potentials.[7-9] However, in biological neuron-networks a large portion of intelligent information — including memory and emotion

— are encoded in or conveyed by chemical molecules like neurotransmitters.[10-13] This raises the question of whether electrophysiological signal-based BMIs can comprehensively interpret human consciousness. This problem could be mitigated by building a neurotransmitter-mediated BMI that has chemical communication capabilities and can complement current BMI approaches.

In the human brain, neurons communicate with one another at junctions known as synapses (Fig. 1a). Neurotransmitters in the synaptic cleft mediate neural synaptic plasticity, and give rise to emotional and intelligent behaviors.[14-16] To chemically communicate with biological neurons, bioelectronics should at least possess three basic functionalities: neurotransmitter recognition, synaptic plasticity, firing of action potentials and releasing of neurotransmitters. Many neuromorphic devices have been developed with the aim of constructing intelligent systems,[17-25] such as phase-change neurons,[26] artificial afferent nerves,[27] artificial nociceptors,[28] and optoelectronic sensorimotor synapses[29]. These systems are only responsive to physical or electrical signals — such as pressure, temperature, and optical stimuli — and cannot directly interface with biological neurons and are incapable of direct neurotransmitter sensing (Supplementary Table 1). Recently, an organic synaptic transistor has been reported that can provide neurotransmitter sensing where neurotransmitter driven oxidation tuned the conductance of the postsynaptic channel.[30] However, build a complete neurotransmitter communication loop with biological neurons remains a challenge due to the lack of threshold spiking and neurotransmitter-releasing functionalities.

In this Article, we report a chemically mediated artificial neuron that can be used

for bi-directional communication in a BMI, including both receiving and sending chemical information with neurotransmitters as the interfacial messengers. The artificial neuron fulfils the essential functionalities of neurotransmitter recognition, synaptic plasticity, threshold firing and neurotransmitter release. Dopamine (DA) — the motivational stimulus in reward-driven learning[11, 31-32] — is used as the neurotransmitter model in our system. Our artificial neuron is a fully integrated sequentially operating system comprised of three main components: a DA electrochemical sensor that uses carbon nanomaterials with a linear detection range from 1 μM to 1.5 mM spanning the DA concentration in the bio-synaptic cleft, and a sensitivity of 419.9 μA cm^{-2} mM^{-1}; a memristor device with both long-term and short-term plasticity; and a DA-encapsulated heat-responsive hydrogel that releases DA in a temperature window from 37.5 °C to 43.5 °C. The chemical message flow in the artificial neuron follows three steps: activation of the sensor by DA molecules with a current signal response as the output; adaptable modulation of the internal resistance state of the memristor by current signals; and heater switch-on when the memristor resistance reaches a target value, thereby triggering the release of DA from the hydrogel.

The artificial neuron provides the fundamental functionalities of a biological interneuron, being sensitive to tens of μM of DA and capable of releasing DA in the same concentration range with adaptability. We show that the artificial neuron can respond to the DA exocytosis from PC12 cells and release DA to activate PC12 cells, achieving chemical communication similar to interneurons. We also demonstrate that the artificial neuron can enable DA stimuli to trigger the controllable feedback of a

mouse leg or a robotic hand. Our approach provides a step towards chemical BMIs and offering new avenues for development in neuro-prosthetics,[33] human-machine interactions,[34] and interactive Internet of Things (IoT) systems.

Building blocks of the chemical-mediated artificial neuron

To achieve a chemical-mediated artificial neuron (Fig. 1b), three building blocks—DA electrochemical sensor, resistive switching memristor, and heat-induced DA-releasing hydrogel — are considered. The nanomaterial synthesis and device fabrication procedures are shown in Supplementary Text 1-5 and Supplementary Fig. 1 in detail. For DA recognition, an electrochemical sensor is selected because of its low cost, ease of operation, and facile integration with memristors.[35-36] The electrochemical sensor transduces chemical signals to electrical signals which can stimulate a subsequent memristor. The internal resistance state of the memristor is modulated by the history of DA stimuli, emulating the short-term and long-term plasticity of synapses in biological counterparts[37-38]. Here, the electrochemical sensor and the memristor together imitate a bio-synapse, which exhibits in-sensing memory function for DA recognition and adaptive synaptic plasticity. A hydrogel with temperature-dependent polymer-chain mobility is adopted to simulate the DA-releasing behavior of an interneuron. Once sensor-memristor hybrid synapse is activated, it will convey the electrical signals to the releasing component which consists of a heater and a temperature-sensitive hydrogel. The increase in temperature enhances the mobility of the hydrogel polymer chains, and thus induces the release of encapsulated DA. Each

building block of the artificial neuron will be respectively discussed *vide infra*, followed by the entire artificial neuron system.

To obtain a DA electrochemical sensor with high selectivity and sensitivity, a carbon nanotube/graphene oxide (CNT/GO) nanocomposite-modified electrode is exploited (Fig. 2a). Detailed information for DA sensing mechanism, performance, and materials characterization are shown in the Supplementary Text 6 and Supplementary Fig. 2-5. GO modification causes a negative shift of the DA peak potential and positive shift of ascorbic acid (AA) oxidation peak in the cyclic voltammetry (CV) curves (Supplementary Fig. 2). This is because negatively charged GO (Zeta potential characterization in Supplementary Fig. 3) attracts positively charged DA and repels the negatively charged AA, which enhances DA sensing selectivity even with abundant interferences (at ~ hundreds of μM) present in the biofluid[39-40]. CNTs modification enhances the peak current density of DA oxidation (Supplementary Fig. 2c). This is because CNTs with good conductivity provide a three-dimensional cross-linked conductive network (micromorphology characterization in Supplementary Fig. 4, Supplementary Fig. 5 and electrochemical impedance spectra (EIS) in Supplementary Fig. 6), which facilitates the electron transfer and increases the electrochemical sensing sensitivity. To achieve both high sensitivity (conductive CNT is used for high sensitivity) and selectivity (negative charged GO contributes to high selectivity), the optimized CNT to GO ratio of 1:1 ($CNT/GO_{1:1}$) is used. $CNT/GO_{1:1}$ modified Au electrode achieves a linear DA detection range from 1 μM to 1.5 mM with a sensitivity of 419.9 $\mu A\ cm^{-2}\ mM^{-1}$ and a detection limit of 0.2 μM, as characterized by amperometry with

a constant potential at 0.2 V (Fig. 2c). It is noteworthy that CNT/$GO_{1:1}$/Au shows even higher sensing sensitivity than pure CNT/Au or GO/Au electrode owing to the synergistic effect of both carbon materials.

We further test the performance of CNT/$GO_{1:1}$-based sensors including the sensor-to-sensor variation, selectivity, and repeatability (Supplementary Fig. 7). DA sensing sensitivity of 12 sensors shows a variation of 8.1%, indicating the reliable stability of device (Supplementary Fig. 7a). The DA sensor shows good anti-interference capability (or selectivity) in the presence of ions that are abundant in the biofluid, including Na^+, K^+, Mg^{2+}, CO_3^{2-} and Cl^- (Supplementary Fig. 7b). No obvious performance deterioration (a variation of 6.7%) is observed after 8 cyclic testing (Supplementary Fig. 7c). The sensor shows good linear response in the detecting range whenever the DA concentration increases or decreases (Supplementary Fig. 7d), which enable the sensors to accurately detect time-dependent signals in the linear-responsive range. Hence, the CNT/$GO_{1:1}$-based DA sensor whose detection range covers the DA concentration range in the synaptic cleft (tens of μM)[30] is competent for constructing a neurotransmitter-responsive artificial neuron.

The memristor was fabricated using a crossbar structure with the configuration of Ag/Ag nanoparticles (Ag NPs)-silk fibroin/Au (Fig. 2d). Here, silk fibroin was chosen as the resistive switching dielectric owing to its good biocompatibility and mechanical flexibility[41]. The procedures for silk fibroin extraction are given in Supplementary Text 4. Ag NPs with a size of around 45 nm (Supplementary Fig. 8, Methods) were mixed into the silk fibroin to improve the resistive switching performance of the memristor

via mediating the formation and rupture of nanoscale Ag conductive filaments. Detailed information for memristor characterization is given in Supplementary Text 7. In brief, the memristor device after an electroforming process could exhibit both nonvolatile memory switching behaviors under a high compliance current (CC) of 1 mA, and volatile threshold switching behaviors under a low CC of 10 μA (Fig. 2e and Supplementary Fig. 9a). The phenomena that resistive switching characteristics depend on CC can be explained by a surface-limited self-diffusion mechanism of nanoscale conductive filaments whose size is governed by the value of CC[42-43]. The memristor device sustained 50 consecutive direct current (DC) cycles for both memory and threshold switching, validating the consistent stability of the memristor device (Supplementary Fig. 9b and 9c) under repeated operation. We also examined the memory switching variability for a total of ten memristors showing a good device-to-device uniformity (Supplementary Fig. 10). In addition, a fast switching response (~ 75 ns) is achieved in the memristor device (Supplementary Fig. 11).

Such resistive switching characteristics can be used to imitate the synaptic plasticity, such as short-term plasticity (STP) and long-term plasticity (LTP) (related concepts are briefly described in Supplementary Notes). Under a weak electrical stimulus (Stimulus 1, pulse: 1.2 V, 100 μs), the programmed resistance state of the memristor cannot be maintained, indicating a STP behavior (top left panel of Fig. 2f), which could be further verified by a relaxation measurement (Supplementary Fig. 12). Under a strong stimulus (Stimulus 2, pulse: 2 V, 100 μs), the memristor shows a nonvolatile LTP behavior (top right panel of Fig. 2f). These resistance states obtained

under strong stimuli could be maintained for over 10^4 s (Supplementary Fig. 13). Moreover, the resistance state of the memristor can be continuously tuned under a series of pulse stimuli (0.7 V with pulse width of 2 ms in the bottom panel of Fig. 2f), indicating a good paired pulse facilitation (PPF) behavior. These results demonstrate the memristor could process external stimuli with synaptic plasticity via adaptively modulating its internal resistance state, and would form LTP to allow firing the release of DA.

Heat-triggered DA-releasing hydrogels are used to mimic the release of neurotransmitters in the axon vesicles. Here, we chose the temperature-sensitive poly(vinyl alcohol) (PVA) hydrogels which were prepared via the cyclic freeze-thaw method without initiators or oxidants for gelation, preventing the oxidative polymerization of DA during gelation. It is expected that at sufficiently high temperatures, PVA chain segments gain enough kinetic energy leading to the dissociation of crosslinking hydrogen bonds. The disrupted polymer network loses its encapsulation capability, which causes DA release. An ideal releasing temperature should be within 37.2 ^{o}C to 45 ^{o}C to ensure the integrity of hydrogel structure at physiological temperatures and prevent heat-burns to human tissues. We tuned the releasing temperature of PVA hydrogels by adjusting PVA molecular weight and composition. PVA with lower molecular weight dissolve more easily in aqueous solution due to a greater chain mobility and the ease of breaking inter/intra molecular hydrogen bonds,[44-45] leading to a lower network dissociation temperature of PVA hydrogels. Thus, we combined PVA of low molecular weight (13~26 kDa, PVA_{LW}) and

high molecular weight (140~160 kDa, PVA_{HW}) to control the releasing temperature of hydrogels. Tensile tests show that reducing the PVA_{HW} weight ratio below 1 wt%, e.g., 0.5 wt%, results in the formation of a fragile hydrogel (Supplementary Fig. 14). Hence, PVA hydrogels with PVA_{HW} weight ratio no less than 1 wt% were investigated using rheology tests to find out the optimal composition. An optimal PVA hydrogel for the DA-releasing system contains 1 wt% PVA_{HW} and 16 wt% PVA_{LW}, which shows a temperature-dependent gel-solution transition process when temperature is higher than 37.7 °C, as confirmed by the decrease in shear storage modulus[46] (Fig. 2h). To prevent the undesirable DA diffusion out of hydrogels at low temperatures, we synthesized porous SiO_2 particles with a mean pore size of 1.93 nm and a specific surface area of 870.36 $m^2\ g^{-1}$ as the carrier matrix for DA (Supplementary Fig. 15, Methods). These pores serve to retain DA within the matrix. We characterized the amount of released DA from the PVA/SiO_2/DA hydrogel using the Linear Sweep Voltammetry (LSV) method based on the working curve, as shown in Supplementary Fig. 16 and Supplementary Text 8. We observed that a gradual increase in temperature from 37.5 to 43.5 °C induces the release of DA, from a concentration of 0.7 μM to 11.9 μM, showing successful temperature-triggered DA-release with temperature window suitable for heat-induced DA release in-vivo (Fig. 2i).

Artificial synapse with in-sensing memory ability

In the artificial neuron, the DA electrochemical sensor incorporated with the memristor constitutes a neurotransmitter-mediated artificial synapse (Fig. 3a), which

can implement both the recognition and memory functionalities of neurotransmitters. To validate the in-sensing memory ability, we used different concentrations of DA as presynaptic stimuli and monitored the electrical response of the artificial synapse.

The circuit scheme and testing setup are shown in Supplementary Fig. 17-19. To simulate the DA solution flow in a biological system, we used two peristaltic pumps and a beaker with constant stirring to achieve continuous solution flow with controlled DA concentrations (Supplementary Fig. 18 and 19). For a period (tens of seconds) of DA stimulus with a low concentration of 10 μM, the sensor exhibits an increase in current to 5.21 μA (upper panel of Fig. 3b) while the memristor device shows a negligible change in current (lower panel of Fig. 3b) as the stimulus is too weak to form Ag conductive filaments in the memristor. When the DA concentration increases to 40 μM, the current of sensor increases to 22.82 μA and the memristor device exhibits a similar current increase but returns to its original high resistance state (HRS) after removing this stimulus, implying that a moderate DA signal induces unstable conductive filaments with STP behaviors. When the DA concentration is further increased to 200 μM, the current in the memristor device exhibits a synchronous increase as that of the sensor. Even when the DA stimulus is removed, the current does not return to its original state, indicating the LTP behavior of the memristor due to the formation of stable conductive filaments. This memorized low resistance state (LRS) induced by a strong DA stimulus can trigger the subsequent DA release, signaling the firing of the artificial neuron.

Besides a period of DA, we also used continuous DA stimuli with stepwise increase

in concentrations from 0 to 100 μM to activate the artificial synapse. When the memristor is in the HRS, with successive increase of DA concentration from 0 to 4 μM, steady-state current of the sensor shows stepwise increase from 0.18 to 2.53 μA (upper panel of Fig. 3c). Meanwhile, negligible changes are observed in the memristor device (lower panel of Fig. 3c) as the weak stimulus cannot induce the formation of Ag conductive filaments. With further injection of 20 μM DA, the current of the sensor increases to 6.64 μA. The current of the memristor device abruptly increases after continuous DA stimulation for tens of seconds, indicating that the memristor has been switched from HRS to LRS under these accumulated stimuli (lower panel of Fig. 3c). Once the nonvolatile resistive switching behavior is activated, the memristor has the capability for the long-term retention of memory of the DA stimulus. Hereafter, the memristor exhibits similar stepwise current increase as that of the sensor when the system is exposed to DA (Fig. 3d), even under weak stimulus (the inset in lower panel of Fig. 3d). The successive DA stimuli experiment corroborates with the DA period experiment, confirming the in-sensing memory ability of the chemical-mediated artificial synapse.

Memristor-mediated DA release behavior

The memristor is connected in series with a heater covered by a DA-encapsulated hydrogel, where the memristor controls the releasing behavior of the hydrogel (Fig. 3e). To clearly observe heat-responsive properties of the hydrogel, we used an infrared camera (Fluke Ti450) to record the temperature of the heater and simultaneously

employ a microscope to monitor the change in the hydrogel morphology. For the memristor in HRS initially, a low potential applied on the device could not cause too much change of both temperature and morphology of the hydrogel. When the applied potential exceeds a certain threshold value, the memristor will be programmed to a nonvolatile LRS, thus triggering an increase in heater temperature and hydrogel deformation, showing an obvious threshold firing (Fig. 3g and 3f). When the memristor is in LRS initially, the heater temperature increases with the increasing potential. And visible hydrogel deformation is triggered by a smaller potential (~0.5 V) compared with the case when the memristor is in HRS initially (~1.5 V). The deformation of PVA hydrogel means that accumulated joule heat induces the breaking of the hydrogen bonding and melting of the crystallites in PVA hydrogels,[46] allowing the DA to diffuse out of the PVA hydrogel, which emulates the controllable neurotransmitter-releasing behavior in the axon vesicles. These results reveal that according to the lower (higher) resistance state of memristor, the system can release DA at a smaller (larger) voltage. Hence, the memristor can mediate the releasing behavior of hydrogels by its resistance value, which is affected by the previous stimuli. Such behavior is like the memory function of biological counterparts.

Artificial interneuron and motor neuron for neuro-interfaces

In the biological system, neurotransmitter communication is one of the most important channels for neuron connections in both central and peripheral nervous systems. In the central nervous system, interneurons capable of neurotransmitter

recognition and releasing function form a neural network which serves as a decision maker (Fig. 4a). In the peripheral nervous system, based on neurotransmitter recognition capability, motor neurons can electrically activate the contraction of muscle cell, contributing to motion feedback. Here, we demonstrate the functionalities of interneurons and motor neurons with our artificial neuron.

To mimic interneurons, the DA sensor, the memristor, and the heat-responsive DA hydrogel are integrated, executing or exhibiting pre-neurotransmitter recognition, synaptic plasticity, and post-neurotransmitter release functions, respectively (Fig. 4b). To guide the flow of released neurotransmitters, polydimethylsiloxane (PDMS) film with microfluidic channels of 220 μm in width are further integrated with the chip. A digital image of the integrated chip structure is shown in the inset of Fig. 4c. All the functional layers have been integrated on a flexible polyethylene terephthalate (PET) substrate, endowing the chip with flexibility for bio-interfacing applications.

We apply DA stimulus with concentration stepwise increasing from 0 to 50 μM to the system. We simultaneously monitor the sensor response (Supplementary Fig. 20) and detect the concentration of DA released from the hydrogel (Fig. 4c). When there is no DA stimulus, the sensor shows background current (< 1 μA) and negligible amount of DA is released. When being exposed to DA stimuli, the sensor shows current increases synchronously with the increase of stimuli concentration. In contrast, DA release is only triggered when the stimuli concentration reaches a certain threshold. Subsequently, the released DA concentration rises with the stimulating concentration simultaneously. To visualize the flow of substance released by the hydrogel in

microfluidics, we encapsulate methyl blue in the hydrogel (Fig. 4d, Supplementary Video 1). When we apply a continuous DA stimulus of 20 μM, a continuous flow of dye solution into the microfluidics was observed, confirming the stimulus-triggered releasing behavior. This process corresponds to the firing of action potential and releasing of neurotransmitter to the synaptic cleft in biological neurons.

We also observe that the memristor state can affect the concentration threshold for triggering DA release. When the memristor is in initial HRS, a higher concentration of DA stimulus (≥20 μM) is required to activate DA release than that (>5 μM) when memristor is in initial LRS. For memristor in HRS, the accumulation of DA stimuli is needed to trigger the conductive filament formation in the memristor for switching the memristor from HRS to LRS. After that, the heater is switched on and the release from the hydrogel is subsequently triggered. For memristor in LRS (memristor has been triggered by previous stimuli already), the release behavior is more easily activated. That means the system has formed a stronger connection with repeated stimuli and will be more sensitive to familiar stimuli compared with fresh ones. In biological system, alterations in neuronal connectivity are regarded as the basic mechanisms of memory and learning.[47] Dopamine-modulated plasticity in the artificial neuron is similar to the adaptivity of biological neurons, contributing to the systematic intelligent behaviors.

The dopamine-responsive artificial neuron is further connected to biological neuron cells to demonstrate its applicability for chemical BMIs. Here we use catecholamine-containing rat pheochromocytoma cell (PC12) for validation (details given in the Supplementary Text 9-11). The cytotoxicity of materials including

CNT/GO, PVA hydrogel, and SiO_2 are qualitatively and quantitatively assessed by live/dead cell staining and Cell Counting Kit 8 (CCK8). Dead cells were barely seen in both CNT/GO/Au electrode and PVA/SiO_2 hydrogel. Incubated with these materials for 48 h, PC12 cells show viability larger than 90%, indicating the acceptable biocompatibility (Supplementary Fig. 21 and 22).

We further investigate the bi-directional communication including receiving and sending chemical information from/to neuron cells (details shown in Supplementary Text 9 and Supplementary Fig. 23a). The phosphate buffer saline (PBS) solutions with different K^+ (that elicit DA exocytosis) are incubated with the cells for 3 min. Then the PBS solution is pumped across the sensor with peristatic pumps. Amperometric *i-t* curves of sensor are recorded (Supplementary Fig. 23b). The control experiment without the presence of cells (blue line) confirms the addition of K^+ did not cause obvious current change. In the presence of cells, an obvious current response (red line) is observed which reflects that our sensor is responsive to the DA released from living cells. The current also increases with the K^+ concentration increasing from 10 to 50 mM due to K^+-induced DA exocytosis (Supplementary Fig. 23c). Based on the current response, the released amount of DA is estimated to be 0.35 μM per $1\times10^5/cm^2$ cells. It is observed that the current response can be used to further trigger memristor and heater by current-potential signal transformation after systematic optimizations.

To illustrate the ability of sending information to biological neuron cells, we use the DA released by our devices to activate PC12 cells. The testing setup is shown in Fig. 5a where the artificial neuron is exposed to DA stimuli and the DA released by

artificial neuron contact with PC12 cells. It is reported that DA can enhance the intracellular calcium release and activate the K^+ ion channels of neuron cells based on the natural coupling of the dopamine receptors to G protein_ENREF_10[48-50]. Hence, Ca^{2+} fluorescence imaging and K^+ ion current of PC12 cells are characterized by confocal microscopy and patch clamping, respectively. Here we select a strong stimulus with DA concentration of 100 μM that could switch the memristor to LRS and trigger the DA releasing based on previous testing results. When the artificial neuron is exposed to DA stimuli of 100 μM, we observed an increase in both relative fluorescence intensity (Fig. 5b, c and Video S2) and K^+ current (Fig. 5d, Supplementary Fig. 24) of PC12 cells, indicating that the released DA by our artificial system successfully triggers PC12 cells. In contrast, when artificial neuron is exposed to blank control with DA concentration of 0 μM, no obvious increase in fluorescence intensity and K^+ current is observed. These results indicate that the artificial neuron acts as a chemical messenger bridge capable of transmitting information to PC12 cells.

Besides interneurons, this system can also mimic the neurotransmitter-triggered motor neuron to control the muscle contraction feedback. To illustrate the function, we use DA stimulus to activate the motion of either robotic hand (Supplementary Fig. 25) or mouse sciatic leg (Fig. 5e). Explicitly, DA concentration linearly effects the potential dropped on the resistance (in series with the memristor), which is utilized to regulate the motion of both robotic hand or mouse leg. The results show that without DA stimulus, both robotic hand and mouse leg cannot provide any feedback, due to low input signals. In the case of strong DA stimulus (≥20 μM), the robotic hand is

successfully activated to perform a handshake (Supplementary Fig. 25c and Supplementary Video 3). Similar results are further demonstrated in the case of mouse sciatic nerves. The movement angle of the mouse leg gradually increases from 0 to 8.1° ± 3.9° when DA stimuli stepwise increases from 25 to 60 μM (Fig. 5 f-h). These results indicate that the artificial neuron successfully transmits neurotransmitter information to an afferent nerve which further controls the feedback.

Our research has demonstrated chemical neurotransmitter-mediated artificial neuron with functionalities of DA recognition, synaptic plasticity, and DA release/motion feedback, which enables the bi-directional communication with biological neurons. For practical application, system-level performance such as response time, power consumption, and systematic encapsulation[51], remains to be explored. We expect that biomodification of sensor surface such as aptamers that can enhance the affinity of sensing interface to neurotransmitter can improve the response speed of system.[36] Downscaling of sensor[52] and memristor[53], and optimization of memristor with multilayer-stacked structures[54] would reduce the energy consumption of system. Selecting energy-efficient electrochemical transistor-based sensors[55] that would eliminate the amplifier can further reduce the energy consumption. Moreover, encapsulation is also believed to be necessary to achieve high device stability for integration of a complex and large-scale neural network.

Conclusions

We have reported a chemical-mediated artificial neuron capable of receiving and

releasing DA with synaptic plasticity. These functions are realized using an integrated system comprised of three building blocks: a CNT/GO nanocomposite-based DA electrochemical sensor, an Au/Ag NPs-silk fibroin/Ag memristor, and a temperature sensitive PVA/SiO_2/DA hydrogel. The artificial neuron responds to the DA exocytosis from PC12 cells and releases DA to activate PC12 cells, forming a neuromorphic chemical communication loop like interneurons. The artificial neuron can controllably trigger the motion of a mouse leg and a robotic hand, demonstrating chemical information transmission to an afferent nerve. The neurotransmitter-mediated neuromorphic communication capability enables seamless connection with biological neurons using neurotransmitter as the interfacial messengers. Such chemical BMIs could complement electrical BMIs, potentially allowing neuronal information to be correctly and comprehensively interpreted for use in neuro-prosthetics, human–machine interactions, and cyborg construction.

Methods.

The GO aqueous solution (~12 mg/mL) prepared by a modified Hummers' method was purchased from Hangzhou Gaoxi Technology Co., Ltd (www. gaoxitech.com). CNT powders (Bu-202 Bucky USA) were used without further purification. Chemicals including $AgNO_3$, Na_2S, poly(vinyl pyrrolidone) (PVP), tetraethylorthosilicate (TEOS), poly(vinyl alcohol) (PVA), (3-aminopropyl)triethoxysilane (APTES), ethylene glycol (EG), cetyltrimethylammonium bromide (CTAB) and DA were purchased from Sigma. Silk fibroin solution was extracted from commercial available Bombyx mori silkworm

silk with similar procedures used in our previous research[41].

Synthesis of Ag nanoparticles for memristor.

The Ag nanoparticles were prepared by sulfide-mediated polyol method in which Ag^+ is reduced to Ag by EG in the presence of PVP as the capping agent and a trace amount of Na_2S as the catalyst.[56] Details are given in the Supplementary Text 1.

Preparation of poly(vinyl alcohol) (PVA) hydrogels and SiO_2 nanoparticles .

PVA hydrogels were prepared via three freeze-thaw cycles based on physically cross-link effect. Porous SiO_2 nanoparticles were prepared by a CTAB-assisted precipitation method followed by calcination at 600 ^oC for 6 hours in ambient atmosphere. Details are given in the Supplementary Text 2-3.

Fabrication procedures of artificial neurons.

PET film with surface washed by ethanol was used as the flexible substrate for the artificial neurons. Patterned electrodes with optimized thickness were deposited on the PET film by thermal evaporation using a shadow mask (Supplementary Fig. 1 i). 3 nm Cr / 70 nm Au electrode was used as the working and counter electrode of the sensor, bottom electrode of the memristor, and all circuit connection parts. Reference electrode was prepared via evaporation of 150 nm Ag followed by electrochemical chlorination[57]. 3 nm Cr / 30 nm Au with a width of 100 μm and length of 22 mm was used as the resistor (1 KΩ ± 50 Ω) for sensor signal readout. 100 nm Au with a width of 90 μm and length of 44 mm was used as the heater for hydrogels.

Surface modification was then performed to functionalize each part. GO and CNT mixture solution was firstly ultrasonicated for 30 mins to improve dispersibility. 5 μL

CNT/GO solution was drop-casted on the working electrode, producing CNT/GO modified sensors (Supplementary Fig. 1 ii). Ag NPs/silk fibroin solution was ultrasonicated for 20 mins and then spin-coated onto the bottom Au electrode of the memristor (Supplementary Fig. 1 iii). Next, 70 nm Ag was thermally evaporated on the insulator, which served as the top electrode, producing the crossbar Au (bottom)/Ag NPs-silk fibroin (insulator)/Ag (top) memristor (Supplementary Fig. 1 iv).

To prepare the PVA/SiO_2/DA hydrogel, 1 mg of porous SiO_2 was first dispersed in 10 mL of distilled water under ultrasonication for 30 min. The SiO_2-dispersed solution was de-oxygenated by bubbling in N_2 for 30 min and 100 mg of DA powder was then added. After complete dissolution, the tube containing the mixture solution was sealed to avoid DA polymerization and placed under vigorous stirring for 2 hours. Then the solution was centrifuged and washed by water for three times. The obtained SiO_2 loaded with DA was used as the hydrogel precursor to prepare the PVA/SiO_2/DA hydrogel via the freeze-thaw process. The PVA/SiO_2/DA hydrogel with customized shape was placed on the heater to achieve the heat-triggered DA-releasing function (Supplementary Fig. 1 v).

The microfluidic part consisted of a bottom PET layer and PDMS-based microfluidic films (microchannel width of 220 μm, a square hole of 4 mm × 3 mm as the hydrogel reservoir and a circle hole with diameter of 1.5 mm as the solution outlet) (details given in the Supplementary Text 5). When buffer solution was dropped onto the hydrogel, the solution containing substance released from the hydrogel would flow through the hydrophilic channels to the circle area due to the capillary force.

Characterization and testing methods.

The morphological characterization of materials and devices was acquired with a field emission scanning electron microscopy (JSM-7600F). All electrochemical experiments were performed on a CHI 660C electrochemical workstation (Shanghai Chenhua Equipment, China). The electrochemical impedance spectroscopy measurements were carried out at the open circuit potential in the frequency range of 10 mHz to 10^6 Hz with an amplitude of 10 mV AC potential. 5 mM of $K_3Fe(CN)_6$ and 5 mM of $K_4Fe(CN)_6$ mixture in 0.1 M PBS solution (pH 7.0) was used as a redox probe. The electrical measurement of individual device and integrated system were conducted by Keithley 4200 semiconductor device parameter analysis. The viscoelastic properties of hydrogels were measured by Discovery hybrid rheometer (DHR-3, TA Instruments, USA) under temperature sweep mode (30~80 ^oC, heating rate of 5 ^oC/min, parallel plate with diameter of 25 mm, 1% plate-to-plate strain, frequency of 1 Hz). Nitrogen sorption isotherms were obtained on a Tristar ASAP 2020 pore analyzer at 77 K under continuous adsorption conditions (surface area, pore size and pore volume are calculated based on Brunauer-Emmett-Teller (BET) and Barrett-Joyner-Halenda (BJH) methods). Cells images were taken by laser scanning confocal microscope (LSM710, Zeiss, German). The patch clamp experiment was taken on a HEKA amplifier equipped with a Nanion port-on-a chip system. Animal experiments were approved by the Institutional Animal Care and Use Committee of Nanjing Medical University (No. IACUC-2110033).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgements

We thank the financial support from the National Key Research and Development Program of China (2017YFA0205302, Wang), Natural Science Foundation of Jiangsu Province-Major Project (BK20212012, Wang), National Key R&D Program of China under Grant (2021YFB3601200, Wang), National Natural Science Foundation of China (81971701, Hu), the Natural Science Foundation for Young Scholars of Jiangsu Province (BK20210596, Wang), the Natural Science Foundation of Jiangsu Province (BK20201352, Hu), the Program of Jiangsu Specially-Appointed Professor (Hu, Wang), Science Foundation of Nanjing University of Post and Telecommunications (NUPTSF, NY221004, Wang), the Agency for Science, Technology and Research (A*STAR) under its AME Programmatic Funding Scheme (Project #A18A1b0045, Chen), the National Research Foundation (NRF), Prime Minister's office, Singapore, under its NRF Investigatorship (NRF-NRFI2017-07, Chen), and Singapore Ministry of Education (MOE2017-T2-2-107, Chen).

Author contributions

T.W., M.W. and X.C. designed the study. T.W., J.W., Z.L., H.Z, and J. N. designed and characterized the DA sensor and hydrogel. T.W., X.Y., R.L., T.Y., Y.C., B.Y., S.L. and

B.H characterized the artificial neuron/PC12 cells biointerface. S.G., and F.L conducted the patch clamping test. S.C, Y.Y., B.H, G.X. and X.F. characterized artificial neuron/sciatic biointerface. T.W. and M.W. designed and characterized the memristor. T.W., Y.L., S.J. and Z.C. fabricate the hydrogel and microfluidics. T.W. and M.W. fabricated and characterized the system. T.W., M.W. L.W. and X.C. wrote the paper and all authors provided feedback.

Additional information

Supplementary information is available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints.

Competing interests

The authors declare no competing interests.

Fig. 1 | Conceptual scheme of the neurotransmitter-mediated artificial neuron. a, Scheme of biohybrid neuro-interface where artificial neurons chemically communicate with biological neurons, forming a complete neuromorphic communication loop. A biological neuron comprising neurotransmitter receptors on the dendrite to specifically recognize neurotransmitters, followed by the spiking of action potential based on ions fluctuation-induced membrane potential changes, and the triggering of neurotransmitter release in the vesicle at the terminal of axon. **b,** An artificial neuron comprising neurotransmitter detection via an electrochemical sensor, sensory signal processing with synaptic plasticity using a resistive switch memristor device, and signal-triggered neurotransmitter release based on a hydrogel component.

Fig. 2 | Characterization of the individual building blocks for artificial neuron. a, Scheme of DA sensing by carbon nanotube/graphene oxide (CNT/GO) nanocomposite-modified gold electrode. **b,** Sensing performance of CNT/GO nanocomposites with different CNT-to-GO ratios. **c,** Linear detection of DA based on CNT/GO/Au electrodes. **d,** Scheme of Ag/Ag NPs-silk fibroin/Au memristor device. **e,** Typical *I–V* characteristics of the Ag/Ag NPs-silk fibroin/Au device with current limitation of 1 mA and 10 μA. **f,** Modulation of the resistance state of memristor device with synaptic plasticity. The device shows the short-term plasticity (STP), long-term plasticity (LTP) (1.2 and 2 V with pulse of 100 μs in the upper panel), and paired pulse facilitation (PPF) behaviors (0.7 V with pulse of 2 ms in the lower panel). **g,** Scheme of DA release based on a temperature sensitive PVA/SiO_2/DA hydrogel. **h,** Tuning the modulus and transition temperature by controlling the mass ratio of PVA with high molecular weight (PVA_{HW}) to PVA with low molecular weight (PVA_{LW}). **i,** Heat-induced release of DA by using a PVA/SiO_2/DA hydrogel. The data are presented as mean values (SD) (n = 3 different hydrogels examined in independent measurements).

Fig. 3 | Chemical-mediated artificial synapse with in-sensing memory and memristor-mediated DA-releasing behaviors. a, In-sensing memory based on the combination scheme of the DA sensor with the memristor. **b,** The response of DA electrochemical sensor and the corresponding response of memristor following DA period. **c, d,** The response of DA sensor and the synchronous response of memristor with a steady stepwise increase of DA concentration when the memristor is in high resistance state (HRS) (c) and low resistance state (LRS) (d). **e,** The integration scheme of memristor with a heat-responsive hydrogel in series. **f, g,** Increasing the input voltage steadily from 0 to 2 V leads to hydrogel deformation (microscope images) and heater temperature increase. For memristor in initial HRS state, higher voltage is needed to trigger hydrogel deformation and heater temperature increase compared with that when memristor is in initial LRS.

Fig. 4 | System demonstration of an interneuron. a, An interneuron in central neuron system where neuron connection relies on DA as the chemical messengers. **b,** Scheme of an artificial neuron that simulates the function of an interneuron including pre-neurotransmitter recognition, synaptic plasticity, and post-neurotransmitter release. **c,** Dynamic releasing of DA from the hydrogel induced by DA stimuli when memristor is in initial HRS and LRS. The inset shows the digital image of a flexible artificial neuron that contains a CNT/GO-based DA sensor, a Ag/Ag NPs-silk fibroin/Au memristor, a heater and a PDMS-based microfluidic film. The data are presented as mean value (SD). The error bars are obtained from n = 3 different artificial neurons examined in independent measurements. **d,** Visualization of DA-triggered releasing behavior using methylene blue (MB) as the indicator.

Fig. 5 | Artificial neuron for neuro-interfaces. a, Connection of the artificial neuron with PC12 cells which are characterized by Ca^{2+} image mapping and patch clamping (K^+ current). **b**, Fluorescence Ca^{2+} imaging to indicate the activation of neuron cells by released DA stimuli. Ca^{2+} imaging results were repeated and reproduced six times. **c**, The relative fluorescence intensity of a neuron cell when exposed to DA stimulus with different concentration. The neuron cell is marked in b. **d**, Patch clamping characterization of the K^+ current of neuron cells when exposed to DA stimulus with different concentration. **e**, Connection of the artificial neuron to mouse sciatic nerve where DA-dependent potential of the resistance is applied on the sciatic nerve. **f, g**, Monitoring the movement of mouse leg when the artificial nerve is exposed to DA stimulus with different concentrations. **h**, The response angle of mouse leg under DA stimulus with different concentration. The data are presented as mean values (SD). Error bars are obtained from n = 4 mouse legs.

References

1 U. Chaudhary, N. Birbaumer, A. Ramos-Murguialday, Brain–computer interfaces for communication and rehabilitation, *Nat. Rev. Neurol.* **12**, 513 (2016).

2 Y. Lee, T.-W. Lee, Organic synapses for neuromorphic electronics: from brain-inspired computing to sensorimotor nervetronics, *Acc. Chem. Res.* **52**, 964 (2019).

3 D. T. Simon, E. O. Gabrielsson, K. Tybrandt, M. Berggren, Organic bioelectronics: bridging the signaling gap between biology and technology, *Chem. Rev.* **116**, 13009 (2016).

4 M. Zhang, Z. Tang, X. Liu, J. Van der Spiegel, Electronic neural interfaces, *Nat. Electron.* **3**, 191 (2020).

5 S. R. Patel, C. M. Lieber, Precision electronic medicine in the brain, *Nat. Biotechnol.* **37**, 1007 (2019).

6 T. Araki, et al., Flexible neural interfaces for brain implants—the pursuit of thinness and high density, *Flex. Print. Electron.* **5**, 043002 (2020).

7 Y. Liu, et al., Soft conductive micropillar electrode arrays for biologically relevant electrophysiological recording, *Proc. Natl. Acad. Sci.* **115**, 11718 (2018).

8 G. Schiavone, et al., Bioelectronic interfaces: soft, implantable bioelectronic interfaces for translational research, *Adv. Mater.* **32**, 2070133 (2020).

9 S.-H. Sunwoo, et al., Advances in soft bioelectronics for brain research and

clinical neuroengineering, *Matter* **3**, 1923 (2020).

10 J. M. Sabandal, J. A. Berry, R. L. Davis, Dopamine-based mechanism for transient forgetting, *Nature* **591**, 426 (2021).

11 J. D. Berke, What does dopamine mean?, *Nat. Neurosci.* **21**, 787 (2018).

12 A. Pristerà, et al., Dopamine neuron-derived IGF-1 controls dopamine neuron firing, skill learning, and exploration, *Proc. Natl. Acad. Sci.* **116**, 3817 (2019).

13 T. Wang, et al., Cyber–physiochemical interfaces, *Adv. Mater.* **32**, 1905522 (2020).

14 T. Patriarchi, et al., Ultrafast neuronal imaging of dopamine dynamics with designed genetically encoded sensors, *Science* **360**, eaat4422 (2018).

15 J. A. da Silva, F. Tecuapetla, V. Paixão, R. M. Costa, Dopamine neuron activity before action initiation gates and invigorates future movements, *Nature* **554**, 244 (2018).

16 A. A. Grace, Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression, *Nat. Rev. Neurosci.* **17**, 524 (2016).

17 K. M. Song, et al., Skyrmion-based artificial synapses for neuromorphic computing, *Nat. Electron.* **3**, 148 (2020).

18 X. Zhang, et al., An artificial spiking afferent nerve based on Mott memristors for neurorobotics, *Nat. Commun.* **11**, 51 (2020).

19 Z. Wu, et al., A habituation sensory nervous system with memristors, *Adv. Mater.* **32**, 2004398 (2020).

20 C. Choi, et al., Curved neuromorphic image sensor array using a MoS_2-organic

heterostructure inspired by the human visual recognition system, *Nat. Commun.* **11**, 5934 (2020).

21 C. Wan, et al., Artificial sensory memory, *Adv. Mater.* **32**, 1902434 (2020).

22 S. Zhang, et al., Selective release of different neurotransmitters emulated by a p–i–n junction synaptic transistor for environment-responsive action control, *Adv. Mater.* **33**, 2007350 (2021).

23 M. D. Pickett, G. Medeiros-Ribeiro, R. S. Williams, A scalable neuristor built with Mott memristors, *Nat. Mater.* **12**, 114 (2013).

24 C. Wan, et al., An artificial sensory neuron with visual-haptic fusion, *Nat. Commun.* **11**, 4602 (2020).

25 H. Tan, et al., Tactile sensory coding and learning with bio-inspired optoelectronic spiking afferent nerves, *Nat. Commun.* **11**, 1369 (2020).

26 T. Tuma, et al., Stochastic phase-change neurons, *Nat. Nanotechnol.* **11**, 693 (2016).

27 Y. Kim, et al., A bioinspired flexible organic artificial afferent nerve, *Science* **360**, 998 (2018).

28 J. H. Yoon, et al., An artificial nociceptor based on a diffusive memristor, *Nat. Commun.* **9**, 417 (2018).

29 Y. Lee, et al., Stretchable organic optoelectronic sensorimotor synapse, *Sci. Adv.* **4**, eaat7387 (2018).

30 S. T. Keene, et al., A biohybrid synapse with neurotransmitter-mediated plasticity, *Nat. Mater.* **19**, 969 (2020).

31 A. Mohebi, et al., Dissociable dopamine dynamics for learning and motivation, *Nature* **570**, 65 (2019).

32 R. Lin, et al., The raphe dopamine system controls the expression of incentive memory, *Neuron* **106**, 498 (2020).

33 J. W. Squair, et al., Neuroprosthetic baroreflex controls haemodynamics after spinal cord injury, *Nature* **590**, 308 (2021).

34 M. Wang, et al., Gesture recognition using a bioinspired learning architecture that integrates visual data with somatosensory data from stretchable sensors, *Nat. Electron.* **3**, 563 (2020).

35 J.-M. Moon, et al., Conducting polymer-based electrochemical biosensors for neurotransmitters: A review, *Biosens. Bioelectron.* **102**, 540 (2018).

36 X. Liu, J. Liu, Biosensors and sensors for dopamine detection, *VIEW* **2**, 20200102 (2021).

37 Z. Wang, et al., Resistive switching materials for information processing, *Nat. Rev. Mater.* **5**, 173 (2020).

38 M. A. Zidan, J. P. Strachan, W. D. Lu, The future of electronics based on memristive systems, *Nat. Electron.* **1**, 22 (2018).

39 Y. Oh, et al., Tracking tonic dopamine levels in vivo using multiple cyclic square wave voltammetry, *Biosens. Bioelectron.* **121**, 174 (2018).

40 J. A. Ribeiro, P. M. V. Fernandes, C. M. Pereira, F. Silva, Electrochemical sensors and biosensors for determination of catecholamine neurotransmitters: A review, *Talanta* **160**, 653 (2016).

41 G. Chen, et al., Plasticizing silk protein for on-skin stretchable electrodes, *Adv. Mater.* **30**, 1800129 (2018).

42 W. Wang, et al., Surface diffusion-limited lifetime of silver and copper nanofilaments in resistive switching devices, *Nat. Commun.* **10**, 81 (2019).

43 B.-G. Chae, et al., Nanometer-scale phase transformation determines threshold and memory switching mechanism, *Adv. Mater.* **29**, 1701752 (2017).

44 F. L. Marten, *Vinyl alcohol polymers*, in *Encyclopedia of Polymer Science and Technology*.

45 C. M. Hassan, N. A. Peppas, Structure and morphology of freeze/thawed PVA hydrogels, *Macromolecules* **33**, 2472 (2000).

46 Z. Lian, L. Ye, Effect of PEO on the network structure of PVA hydrogels prepared by freezing/thawing method, *J. Appl. Polym. Sci.* **128**, 3325 (2013).

47 J. Lisman, K. Cooper, M. Sehgal, A. J. Silva, Memory formation depends on both synapse-specific modifications of synaptic strength and cell-specific increases in excitability, *Nat. Neurosci.* **21**, 309 (2018).

48 A. J. Rashid, et al., D1–D2 dopamine receptor heterooligomers with unique pharmacology are coupled to rapid activation of Gq/11 in the striatum, *Proc. Natl. Acad. Sci.* **104**, 654 (2007).

49 C. Liu, P. Goel, P. S. Kaeser, Spatial and temporal scales of dopamine transmission, *Nat. Rev. Neurosci.* **22**, 345 (2021).

50 J. Li, et al., Construction of dopamine-releasing gold surfaces mimicking presynaptic membrane by on-chip electrochemistry, *J. Am. Chem. Soc.* **141**,

8816 (2019).

51 J. Wang, et al., Artificial sense technology: emulating and extending biological senses, *ACS Nano* **15**, 18671 (2021).

52 M. Shin, Y. Wang, J. R. Borgus, B. J. Venton, Electrochemistry at the Synapse, *Annu. Rev. Anal. Chem.* **12**, 297 (2019).

53 M.-J. Lee, et al., A fast, high-endurance and scalable non-volatile memory device made from asymmetric Ta_2O_{5-x}/TaO_{2-x} bilayer structures, *Nat. Mater.* **10**, 625 (2011).

54 C. Li, et al., Ultralow power switching of Ta_2O_5/AlO_x bilayer synergistic resistive random access memory, *J. Phys. D: Appl. Phys.* **53**, 335104 (2020).

55 C. Zhao, et al., Implantable aptamer field-effect transistor neuroprobes for in vivo neurotransmitter monitoring, *Sci. Adv.* **7**, eabj7422 (2021).

56 S. E. Skrabalak, L. Au, X. Li, Y. Xia, Facile synthesis of Ag nanocubes and Au nanocages, *Nat. Protoc.* **2**, 2182 (2007).

57 T. Wang, et al., Mechanical tolerance of cascade bioreactions via adaptive curvature engineering for epidermal bioelectronics, *Adv. Mater.* **32**, 2000991 (2020).