Supplementary Figures

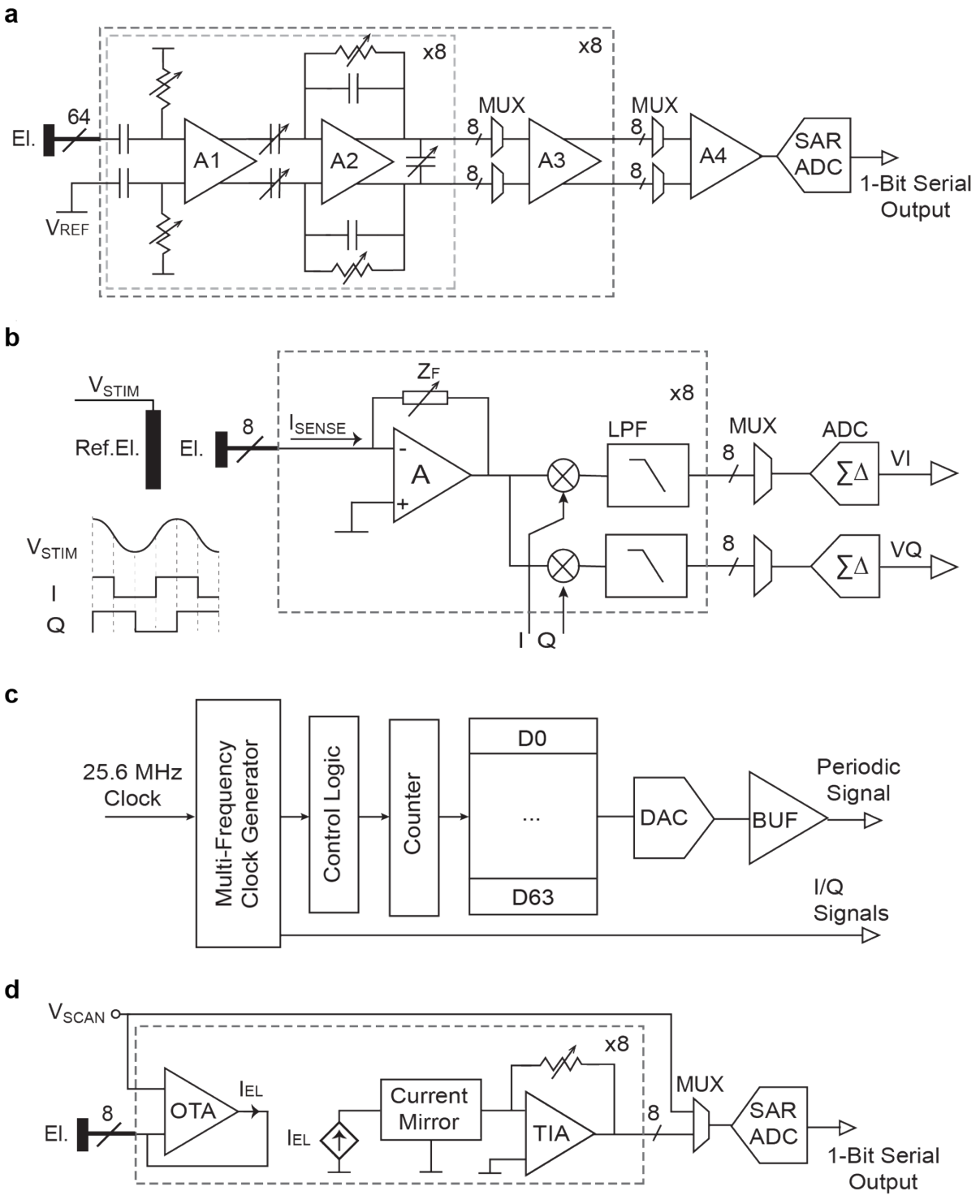

Figure S1. (a) Schematic block diagram of the electrophysiology module. The amplification chain consists of four stages with a programmable total gain ranging from ~29 dB to ~76 dB. The high-pass corner frequency can be tuned from ~0.3 Hz to ~84 Hz. Each channel features individual continuous-time first- and second-stage amplifiers. Every eight channels share eight switched-capacitor (SC) third-stage amplifiers, and all 64 channels share one SC fourth-stage amplifier. All four amplification stages have a fully differential structure to suppress common-mode noise. After filtering and amplification,

signals are digitized using a 10-bit successive-approximation-register (SAR) analog-to-digital converter (ADC) with serial output. The ADC operates at 1.28 MS/s, sampling each of the 64 channels at 20 kS/s. (b) Schematic block diagram of the impedance spectroscopy module. A sinusoidal stimulus voltage, generated by the on-chip waveform generator, is applied between the reference electrode and the target sensing electrodes. The resulting currents are sensed through eight low-noise transimpedance amplifiers (TIAs) and then mixed with the on-chip-generated synchronous in-phase (I) and quadrature (Q) square signals to obtain I/Q demodulated impedance signals. Output signals from the mixers are low-pass filtered to remove high-frequency harmonics. The I and Q demodulated impedance signals are then multiplexed and digitized by delta-sigma ADCs operating at a sampling frequency of 1.28 MHz. (c) Schematic block diagram of the electrochemical sensing module. A triangular voltage scan applied between the sensing electrodes and the reference electrode by changing the sensing electrode potential, while the reference electrode potential is set to the common-mode DC voltage. At each channel, the scan voltage is buffered by an operational transconductance amplifier (OTA) configured in a unity-gain feedback loop, and the resulting current is sensed by a resistively loaded TIA. Outputs of the eight channels, along with the applied scan voltage, are sampled and multiplexed at a rate of 20 kS/s and digitized by a 10-bit SAR ADC with serial output, operating at a frequency of 2.56 MHz. (d) Schematic block diagram of the waveform generator. To achieve different frequencies, the 25.6 MHz system frequency is divided by a digital frequency divider. The programmable sampled values of the desired waveform are stored as 10-bit data in a look-up table containing 64 samples. The samples represent a full period of the signal, enabling the generation of any arbitrary periodic (including asymmetric) waveform. The look-up table values are selected based on the address pointed to by a counter operating at a frequency defined by the frequency divider. These values are then converted to analog signals by the DAC and buffered with an on-chip voltage buffer. Digital logic is also included to generate the I and Q signals of the impedance spectroscopy module, phase-locked to the stimulus sine-wave signal based on the counter values.

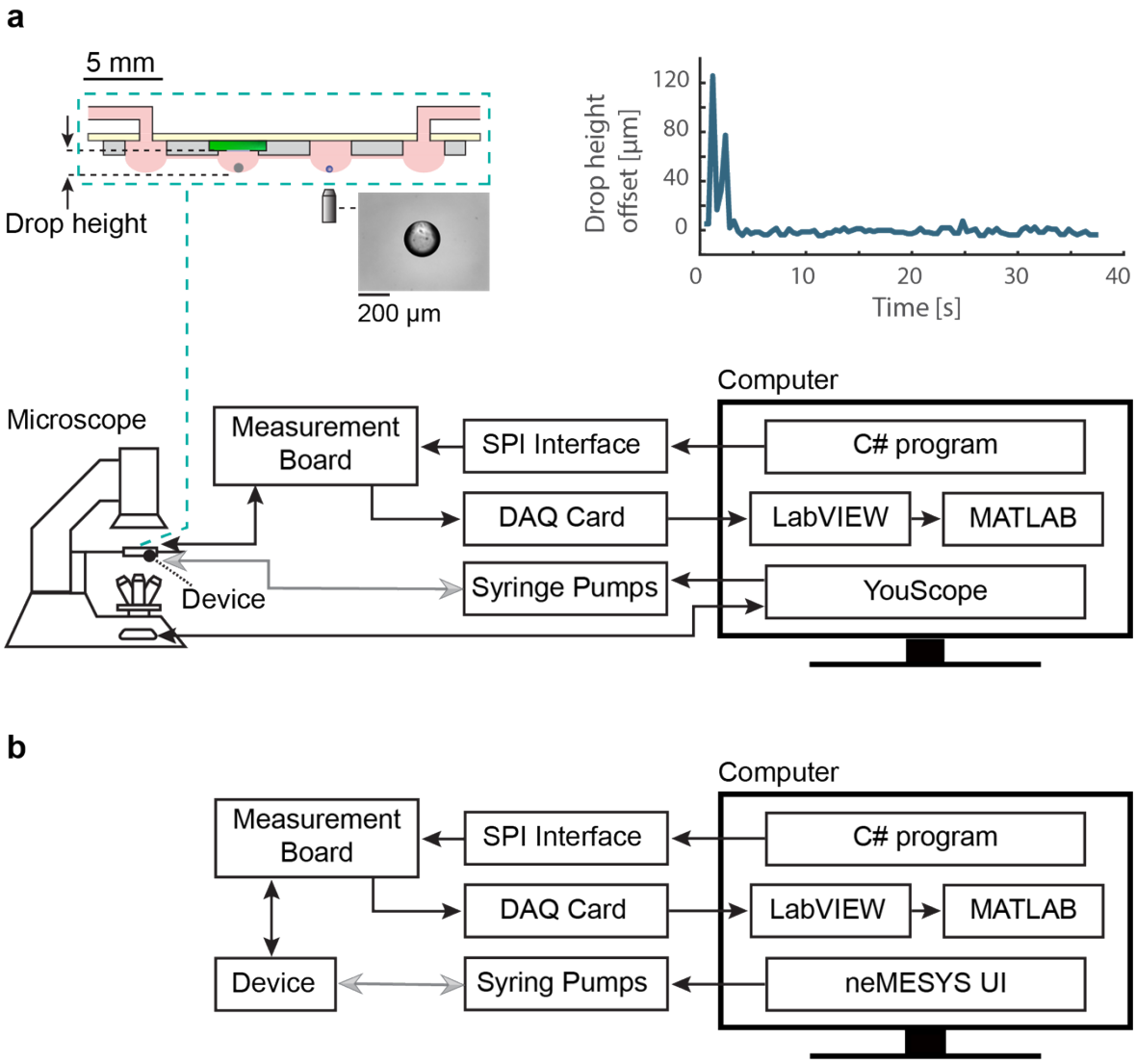

Figure S2. Block diagram of the measurement setup. (a) In the hanging drop mode, the overall system is clamped in a custom-made holder frame, placed in an OmniTray single-well plate on the stage of an inverted microscope. Precision syringe pumps control the fluidic flow. The droplet size is managed using the open-source software YouScope with a fluid-control feedback loop focused on a 200-µm-diameter glass bead. The feedback loop utilizes a PI controller with proportional and integral time constants, set to 2 min and 2 h, respectively. Control commands for the CMOS-MEA chip are sent through the SPI interface using a C# program, while output data is acquired with a DAQ card and analyzed in MATLAB. (b) In the standing-drop mode, syringes are manually controlled via the neMESYS User Interface software.

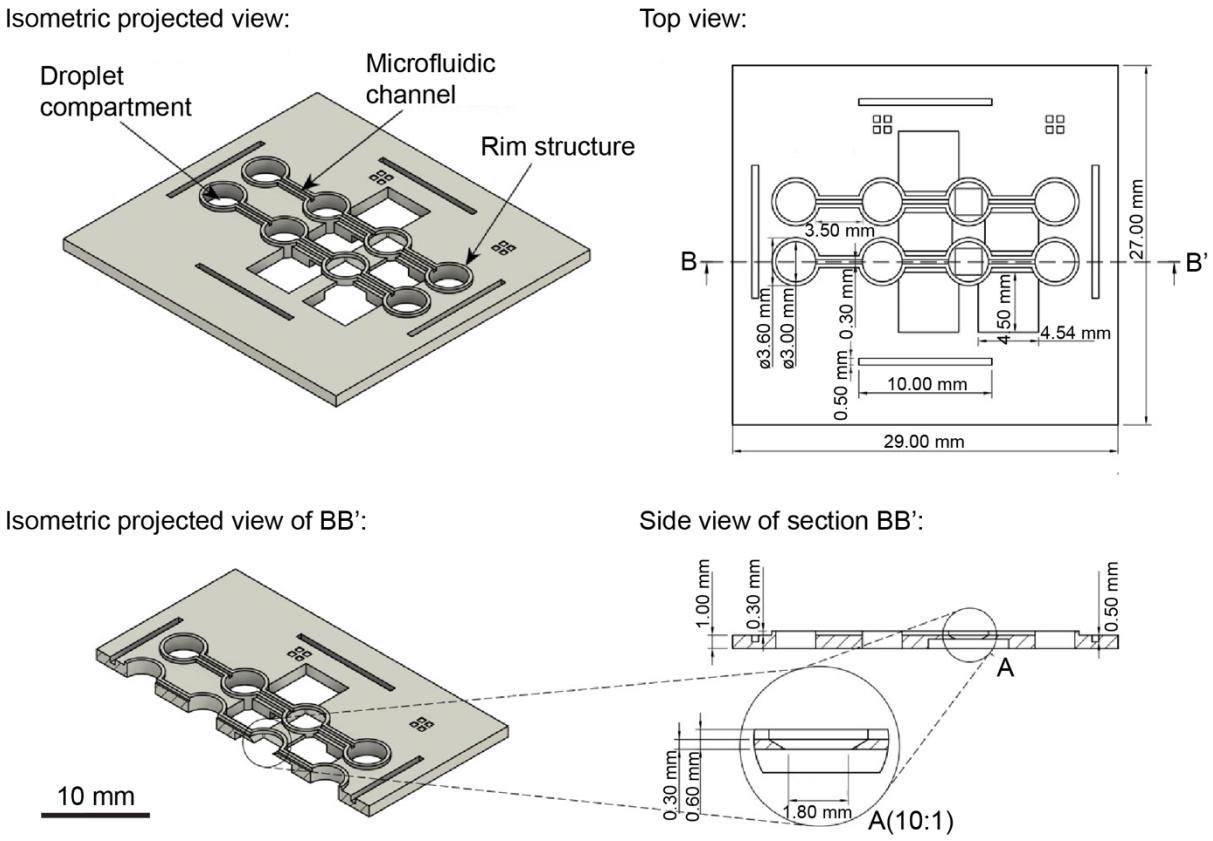

Figure S3. Design details of the PDMS microfluidic system. The top side features two parallel hanging-drop networks, grooves for a potential lid to reduce evaporation, and rectangular openings for bond wires. The bottom side is patterned to accommodate the CMOS-MEA chip. Each system includes two parallel hanging-drop networks, each consisting of four circular compartments with an inner diameter of 3 mm for stable hanging/standing drops. These compartments are interconnected by channels with a 0.3 × 0.3 mm² cross section, forming the fluidic network. The droplets at the ends of the network provide additional medium volume for samples in the incubator or for connection to fluidic inlets and outlets. The central droplets are designed to host tissue samples on the CMOS-MEA chip and features to control the drop height in hanging-drop mode.

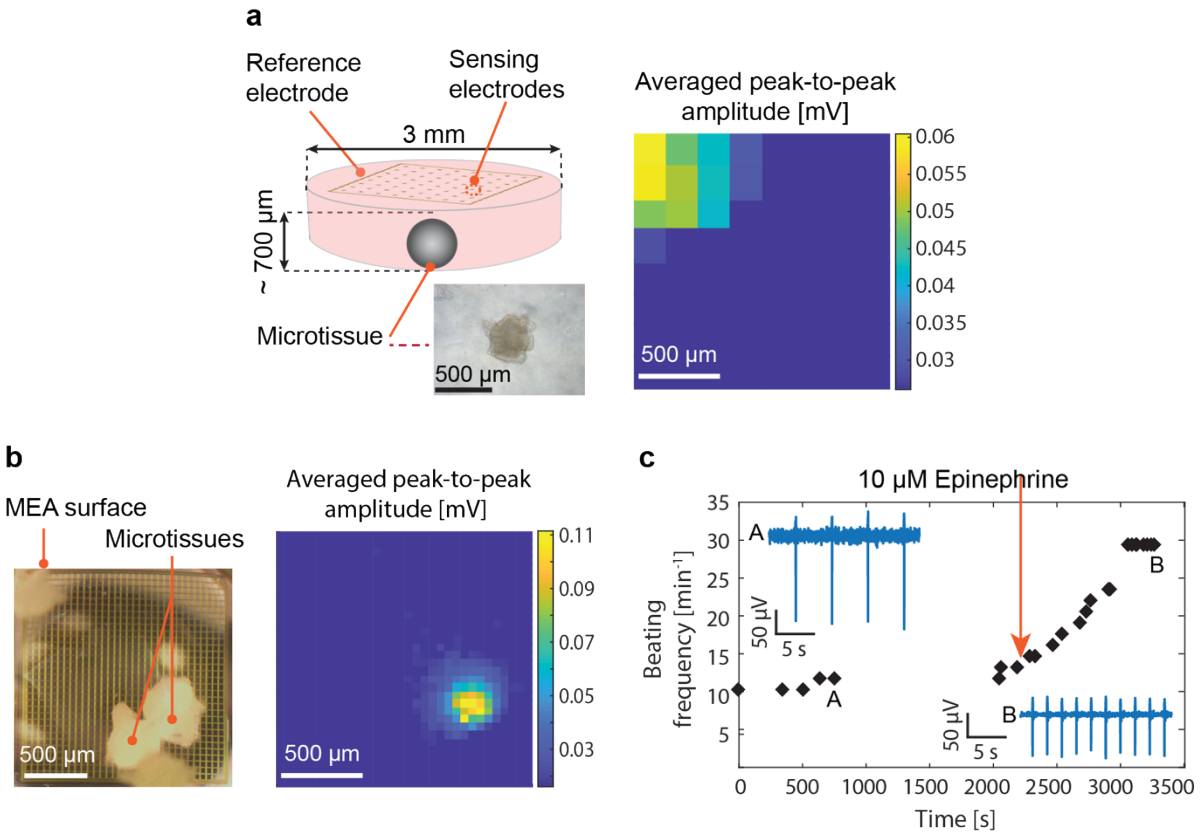

Figure S4. (a) Average peak-to-peak amplitude map of a hiPSC-derived cardiac microtissue in hanging-drop mode. This map was acquired through electrophysiology recordings using 64 uniformly distributed pseudo-large electrodes formed by interconnecting 2 × 2 electrodes. Each pixel represents one pseudo-large electrode. (b) Image of two hiPSC-derived cardiac microtissues on an electrode array in standing-drop mode under flow conditions (right), and average peak-to-peak amplitude map obtained through high-resolution electrophysiology recordings from all 1024 electrodes (left). (d) Beating frequency of the microtissue in (c) recorded from a 64-electrode block underneath the microtissue at different time points before and after the introduction of epinephrine through the integrated microfluidics. Signals A and B show the electrophysiological signal after band-pass filtering, before the administration of epinephrine and after stabilization of the beating frequency, demonstrating the effect of epinephrine in increasing the beating frequency.

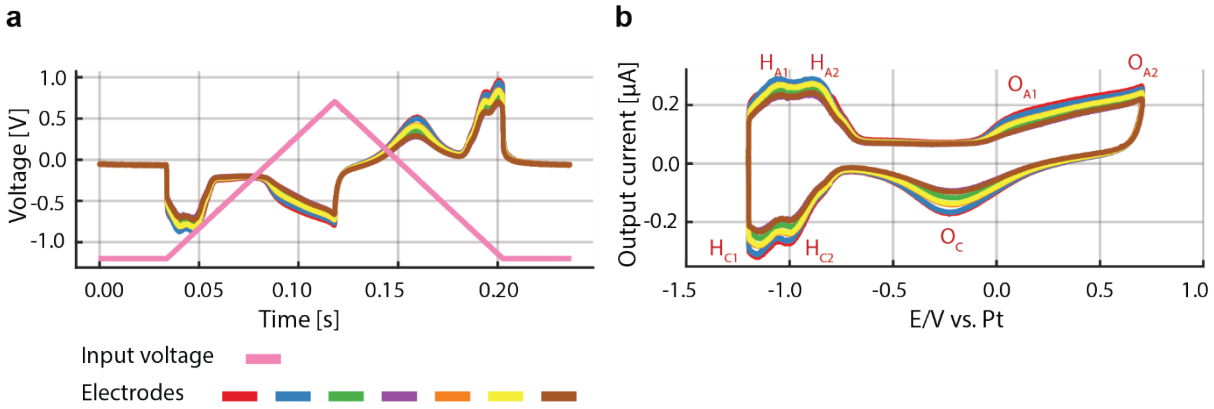

Figure S5: Cyclic voltammetry of sulfuric acid (0.5 M) using a cathodic peak potential of -1.2 V, an anodic peak potential of 0.7 V and a scan rate of 5 V/s. Recordings from several electrodes were normalized against each other and plotted in different colors. (A) Measured potentials against the reference electrode (in colors) versus the applied triangular excitation waveform (in pink). (B) Cyclic voltammogram: output current plotted versus input voltage signal. The redox reactions of sulfuric acid at the surface of the platinum electrodes are indicated.

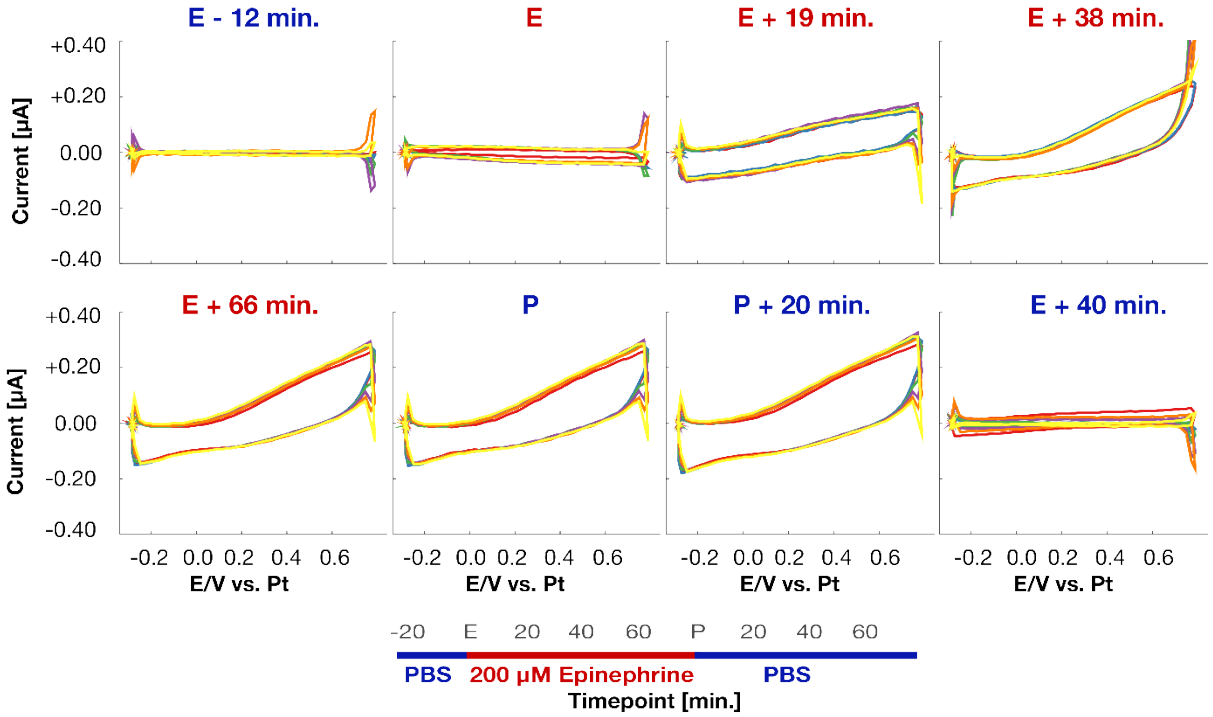

Figure S6. FSCV measurement of epinephrine under flow in a wash-out experiment, following the same methodology as in Figure 6. For the first 30 minutes, PBS was perfused through the device, with data from the initial 15 minutes used to establish the background current, which was subtracted from subsequent measurements. At time point E, perfusion with 100 µM epinephrine began. After 70 minutes, epinephrine administration was stopped, and the medium was switched back to PBS (time point P).

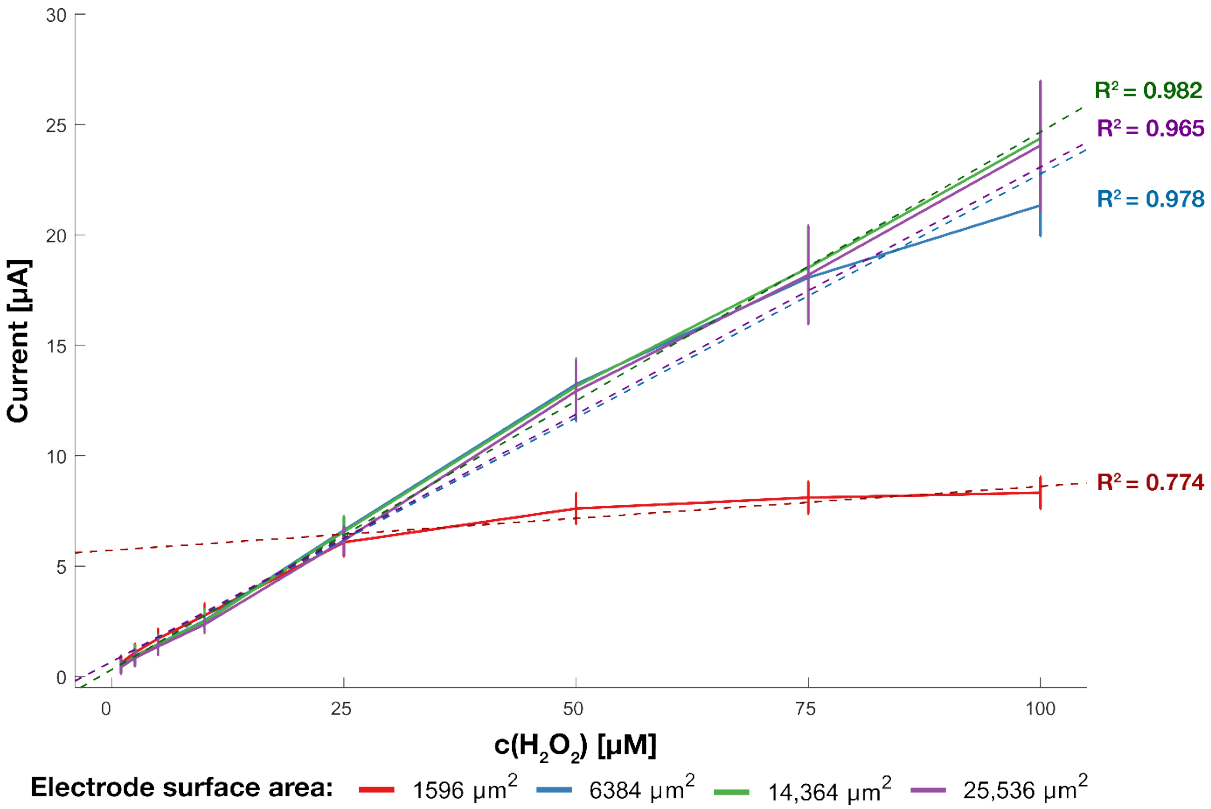

Figure S7. Magnified view of Figure 6C, focusing on the linear range and displaying data separately for the four different pseudo-large electrode configurations. Dashed trend lines were obtained via linear regression analysis, with R² values indicating the goodness of fit. Each data point represents the mean of 64 independent electrodes, and error bars denote the standard deviation across these electrodes within a single experiment.