

Robotic Cell Contents Extraction in Biological Tissues Based on Cell Membrane Capacitance Variation

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I. INTRODUCTION

Abstract—We present a robotic quantitative cell content extraction method for cells in biological tissues based on membrane capacitance variation. This method provides quantitative electrical feedback for robotic cell content extraction when microscopic visual feedback is limited or not available. First, an electric aspiration model was developed to establish the relationship between cell volume and membrane capacitance. Then, a real-time cell membrane capacitance measurement was realized based on a time-domain method. Further, a deep learning-based rotation detection of a bending micropipette was achieved to calibrate the actual volume of extracted cytoplasm and rectify the above obtained relationship for quantitative cell content extraction. Based on the above work, a robotic quantitative cell content extraction process was realized without microscopic view feedback. The experimental results on neurons in mouse brain slices indicate that the average control error of cytoplasmic extraction amount is $0.69\% \pm 0.37\%$ of the total cell volume, with an overall success rate of 65%. Besides, a dynamic variation of neuron surface area during cell content extraction was detected for the first time, which may spike the study of morphological regulation of cells in dynamic environments.

Index Terms—Biological cell manipulation, automation at micro-nano scales, robotics and automation in life sciences.

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CELL content extraction technique, using a micropipette to enter intracellular space and extract part of cytoplasm out of cell, is a key technique in many cell engineering applications. For example, extraction of cell contents containing genetic materials has been applied in genetic materials sequencing [1]. Through analysis of the composition of extracted contents, the transcriptome information can be obtained to correlate gene expression and phenotype at the single-cell level. Furthermore, micropipette aspiration of cytoplasm containing the nucleus has been applied in oocyte enucleation operation of nuclear transplantation technique [2], [3]. In genetic materials sequencing, the amount of extracted cytoplasm should be quantitatively controlled to guarantee detection accuracy of transcriptome information. Further, the removed cytoplasm in oocyte enucleation should be limited to guarantee the developmental competence of the oocyte. In summary, quantitative removal of cytoplasm is desired in cell content extraction operation.

At present, the removed cytoplasm amount in cell content extraction is mainly estimated through the observation results under microscopic view. Through the observed length of the aspirated cytoplasm section inside micropipette, the volume of the removed cytoplasm can be estimated online through inner diameters of the micropipette according to geometrical relationship [4], [5]. When the removed cytoplasm amount reaches the set values, the operator cuts off aspiration pressure inside the micropipette and moves the micropipette tip out of cell immediately. However, the above removed cytoplasm volume control methods are only applicable for suspended cells or cultured adherent cells in vitro. For these cells, they usually have clear and apparent extracellular environment facilitating the observation of the removed cytoplasm length under microscopic view. In comparison to suspended cells and cultured adherent cells, the cells in biological tissues such as the neurons in brain slices are closer to its normal physiological state in vivo, and thereby have more research value. However, for these cells, the poor transparency of tissue environment, occlusion of other cells and vessels, and the tilt angle of the micropipette make the aspirated cytoplasm inside the micropipette hard to be observed, making quantitative cell content extraction and calibration a challenging task for cells in biological tissues.

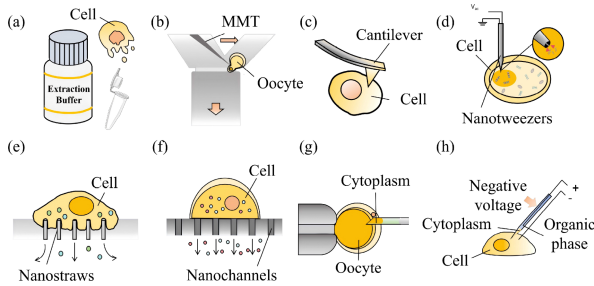


Fig. 1. Schematic review of the presenting robotic cell content extraction methods. (a) Cell lysis and centrifugation. (b) Magnetic driven microtooling. (c) Fluidic force microscopy. (d) Dielectrophoretic nanotweezers. (e) Alumina nanostraws. (f) Microwell array format live-cell analysis device. (g) Control of cytoplasmic extraction volume during oocyte enucleation. (h) Electrowetting method.

In recent years, new robotic systems have been reported to extract cell content according to references, as schematically shown in Fig. 1. The cell lysis and centrifugation in Fig. 1(a) have been utilized to separate the cell contents for cell content extraction [6], [7]. Magnetic-driven microtools (MMT) method [8] uses magnetically controlled microtubes to mechanically cut cells in microfluidic channels, and control the resection amount through visual feedback, which can also obtain cytoplasm, as shown in Fig. 1(b). The above two methods break the cellular structure and the cell lysis method have difficulty in quantitatively obtaining a portion of the cytoplasm. Fluidic force microscopy (FluidFM) [9], [10] shown in Fig. 1(c), combined atomic force microscope with microfluidic channel, has been used to puncture cells and extract a small amount of cell content. Dielectrophoretic systems [11] were also utilized to capture polar molecules in cells using non-uniform electric fields [12], as shown in Fig. 1(d). Alumina nanostraws [13], [14] utilizing electroporation to actively diffuse intracellular substances into the straws in Fig. 1(e) have been utilized to extract cytoplasm accounting approximately 7% of the cell volume. An automated high-throughput microwell array format live-cell analysis device (LCAD) has been utilized to perform localized-electroporation induced membrane permeabilization for intracellular sampling [15], and control the amount of contents by optimization of electroporation parameters (Fig. 1(f)). Although these techniques have demonstrated excellent performance in their respective applications, they generally rely on dedicated equipment, specialized probes, or visual guidance. Therefore, their application scenarios are different from the brain slice tissue, where visual feedback of aspirated cell content is limited.

Recently, robotic cell content extraction methods using traditional micropipettes [16], [17] have also been reported to achieve in-situ cell content extraction. For example, in robotic enucleation systems with microscopic imaging processing algorithms have been utilized to calculate the aspiration length of cytoplasm inside a horizontal micropipette for closed-loop control of extracted cytoplasm amount through aspiration pressure adjustment [5], as shown in Fig. 1(g). To exclude the influences of cytoplasm expansion inside micropipette resulting from aspiration pressure, our group measured the volume of aspirated cytoplasm sphere formed after it is injected out of

micropipette in previous research [18]. However, that method cannot provide a real-time estimation of removed cytoplasm amount during extraction process, making closed-loop control of removed cytoplasm amount impossible. Besides, Fig. 1(h) shows works combining micro-manipulators with electrowetting method [4], [19], using nanopipettes to achieve automated quantitative extraction of adherent cell contents through voltage, electrolyte concentration control and visual feedback. Although these methods achieved quantitative in situ cell content extraction, microscopic view feedback is still required to regulate the removed cytoplasm volume inside micropipette, limiting their applications for cells in biological tissues. In summary, a new quantitative cytoplasm extraction method without relying on microscopic view is still desired for quantitative cellular content extraction in biological tissues.

In this work, we propose a robotic quantitative cell content extraction method based on membrane capacitance variation for cells in biological tissues. This study investigates the feasibility of using membrane capacitance as a quantitative electrical feedback signal for robotic cell extraction when visual feedback is limited. Instead of replacing existing methods, it offers a new approach for tissue manipulation in visually constrained environments. First, an electric model of cell content extraction was developed to establish the relationship between cell volume and cell membrane capacitance. Then, a real-time capacitance measurement method was implemented based on time-domain method. Finally, a calibration method of cell content extraction volume was conducted through deep learning-based rotation detection of a bending micropipette to rectify the above obtained relationship for quantitative cell content extraction. Based on the above work, a robotic quantitative cell content extraction process was realized. The experimental results on neurons in visual cortex of mouse brain demonstrate that the average control error of cytoplasmic extraction amount by detecting membrane capacitance variation is $0.69\% \pm 0.37\%$ of the total cell volume, with a success rate of 65%. Besides, a dynamic variation of neuron surface area during cell content extraction was detected for the first time, which may spike the study of morphological regulation of cells in dynamic environments.

II. SYSTEM SETUP

The robotic cell content extraction system was self-developed by our laboratory, as shown in Fig. 2. It is built around a standard upright microscope (Eclipse FN1, Nikon). This microscope offers a $20 \text{ mm} \times 20 \text{ mm}$ movement range in the X - Y plane and maintains a repeatability of $\pm 1 \text{ } \mu\text{m}$. A motorized focusing device (ES10ZE, Prior, Cambridge, U.K.) is used to adjust the objective lens along the Z -axis with $\pm 1 \text{ } \mu\text{m}$ repeatability. A charge-coupled device (CCD) camera (IR-2000, DAGE-MTI) mounted on the microscope captures microscopic images at 60 fps to provide microscopic visual feedback. An X - Y - Z micro-manipulator (S-PS-7000C, Scientifica, Uckfield, U.K.) is used to position the micropipette, with a $20 \text{ mm} \times 20 \text{ mm} \times 20 \text{ mm}$ travel space and $\pm 20 \text{ nm}$ repeatability. A self-made micropipette rotation module was utilized to rotate the micropipette after cell content extraction to observe and calibrate the actual removed

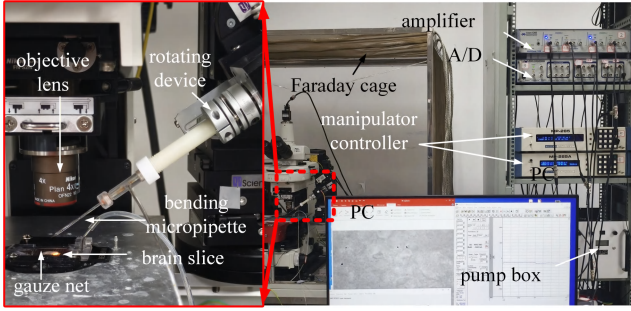


Fig. 2. Robotic quantitative cell contents extraction system based on membrane capacitance variation.

amount of cytoplasm inside micropipette for calibration. A fixed platform installed on an anti-vibration desk is utilized to place the target biological tissues.

A self-designed pump [20], supplies the pressure (-5 psi $\sim$ 15 psi) inside the micropipette for cell content extraction operations. The electrical signals detected during cell content extraction are first amplified via an amplifier (MultiClamp 700B, Molecular Devices), then converted into digital signals through an A/D converter (Digidata 1550B1, Molecular Devices), and finally transmitted to the host computer to estimate the cell membrane capacitance. To isolate environmental electrical noise, the entire robotic system is covered by a Faraday cage. A host computer is responsible for electrical signal acquisition, aspiration pressure control, and motion control of both the microscope and manipulator. The micropipette utilized to extract cell content was fabricated from a borosilicate glass tube (Sutter, BF150-86-10) with an outer diameter of 1.5 mm and inner diameter of 0.86 mm. The glass tube was first pulled using a micropuller (Sutter, P97) to generate a micropipette with an opening diameter of about 1 μ m. Then, the micropipette was bent by 30° using microforge (MF-900, NARISHIGE, Tokyo, Japan), which can increase the tilt angle for operating the cells in biological tissues after amounting on micromanipulator. The micropipette tip is in a horizontal state after rotation by about 180° , facilitating the observation of aspirated cytoplasm inside micropipette after cell content extraction. After bending, a silver electrode (Sheng Shi Jing Xin New Materials Co., Ltd) with a diameter of 0.3 mm was inserted into the micropipette from behind to form a micropipette electrode. Before being mounted on the manipulator, the micropipette is filled with intracellular liquid (IL) [21] to immerse the silver electrode tip, forming a closed circuit.

III. KEY TECHNOLOGIES AND METHODOLOGIES

A. Electric Model of Cell Content Extraction

The existence of ion transporters in cell membrane leads to a difference in ion concentration between the inside and outside of the membrane. The opening of ion channels leads to ion diffusion, resulting in a voltage difference between two sides of cell membrane. The formed voltage difference hinders the ion diffusion in return. Finally, the ion concentration difference reaches an equilibrium state, forming a stable membrane potential. Since

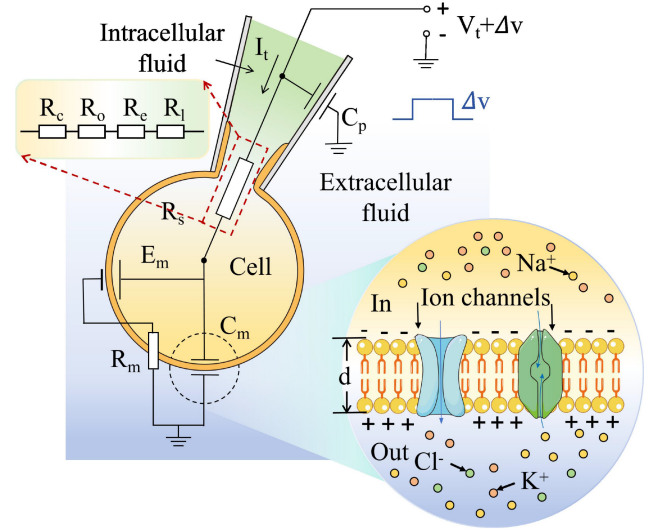


Fig. 3. Electrical model of cell membrane capacitance during extraction process.

the ions diffusing across the cell membrane are primarily potassium, sodium, calcium, and chloride ions [22], the inside of the cell membrane is usually negatively charged [23], with negative charges mainly distributed inside the cell membrane and positive charges mainly distributed outside the membrane.

Except for a few opening ion channels, the phospholipid bilayer of cell membrane can be considered non-conductive, resulting in a capacitive effect. The outer and inner layers correspond to the two plates of the capacitor, and the effective facing area of the two plates is equal to the surface area of the cell membrane. Fig. 3 shows the Hodgkin-Huxley model of cell membrane capacitance during extraction process [24], where C_m represents the membrane capacitance, R_m and E_m are the resistance of channel proteins and the potential difference across the membrane affected by ion channels, respectively. The cell membrane capacitance C_m can be estimated by the following formula [25]

$$C_m = \epsilon A / d \quad (1)$$

where ϵ is the dielectric constant of the cell membrane, A is the surface area of the cell membrane, and d is the distance between the two phospholipid bilayers of cell membrane. From (1), it can be seen that, besides membrane surface area A , the cell membrane capacitance may also be affected by the cell membrane dielectric constant ϵ and the distance d between the two phospholipid bilayers. Fortunately, the ratio of the above two parameters, also known as the specific membrane capacitance, is often assumed to be approximately constant in practical research [26], with an estimated value of 0.01 pF/ μ m². In summary, the membrane capacitance is mainly affected by the membrane surface area during the cell content extraction process.

Due to the continuous decrease in the volume of the contents within the cell during the extraction process, the cell shrinks as the cell extraction goes, resulting in a decrease in the surface area of the cell membrane since the rate of endocytosis is higher

than that of exocytosis [27]. According to (1), the value of the membrane capacitance also decreases. Thus, the changes in membrane capacitance can be treated as an indicator reflecting the removed volume of cell contents, making it possible for quantitative control of cell content extraction amount based on detected membrane capacitance value.

To estimate the amount of extracted cellular contents more accurately, a model of the relationship between cell volume and cell membrane surface area is established. Considering the cells are not standard spheres, the shape related coefficients k_1 and k_2 are used to represent the deviations of the actual cell surface area and volume from the ideal spherical cell area and volume, respectively. The surface area of the cell membrane and cell volume can be calculated as

$$A = 4k_1\pi R^2 \quad (2)$$

$$V = 4k_2\pi R^3/3 \quad (3)$$

respectively, where V is the cell volume, and R is the cell radius. As these two effects are coupled in the capacitance-to-volume conversion and cannot be independently identified from capacitance measurements, their combined effect is represented by an equivalent geometric calibration coefficient k . The relationship between cell membrane surface area and cell volume can be derived from the above two formulas as follows

$$A = k(36\pi)^{\frac{1}{3}}V^{\frac{2}{3}} \quad (4)$$

Integrating (2), (3) and (4), the relationship between cell membrane capacitance and cell volume is as follows

$$C_m = [k(36\pi)^{\frac{1}{3}}\varepsilon V^{\frac{2}{3}}]/d \quad (5)$$

According to (5), the change in cell volume can be obtained from the change in cell membrane capacitance.

B. Online Membrane Capacitance Measurement Based on Time-Domain Method

A time-domain method is used to detect membrane capacitance online [28] in the cell content extraction process. Specifically, apply a square wave voltage signal with an amplitude of Δv , which causes current response of the cell membrane. After applying the square-wave voltage, the transient current response contains the charging current of the membrane capacitance and the steady-state current through the resistance pathway. By subtracting the steady-state current I_{ss} and integrating the remaining transient current, the total charge variation Q_t stored in the membrane capacitance can be obtained. Therefore, the membrane capacitance can be calculated as follows:

$$C_m = Q_t/V_{ss} \quad (6)$$

where V_{ss} represents the membrane potential change, which can be calculated by Δv , membrane resistance R_m and the total resistance R_t of the cell membrane equivalent circuit in the whole-cell configuration. The formula of V_{ss} is calculated as follows:

$$V_{ss} = \Delta v \times R_m/R_t \quad (7)$$

When analyzing the charge-discharge effect of cell membrane capacitance, the circuit is in a transient state, so R_t is equivalent to the parallel connection of R_m and series resistance R_s . As shown in Fig. 3, R_s is mainly composed of electrode resistance R_e , liquid resistance R_l , residual resistance of the ruptured cell membrane R_o , and internal resistance of cells R_c . Therefore, the membrane capacitance can be expressed as

$$C_m = Q_t \times R_t/(\Delta v \times R_m) \quad (8)$$

By using the patch clamp technique, the time constant τ , total amount of charge change Q_t during measurement, and steady-state current I_{ss} responding to a square wave voltage input are measured to calculate the equivalent circuit total resistance R_t , series resistance R_s and membrane resistance R_m , further calculate the membrane capacitance value. Generally, when analyzing the charging and discharging effects, the system is in a transient state, R_m and R_s are in parallel, and R_m is much larger than R_s , so the time constant τ is represented as

$$\tau = (R_m//R_s)C_m \approx R_sC_m \quad (9)$$

Since the cell is in a steady state after complete charging and discharging, R_t is a series connection of R_m and R_s when reaching steady state, that is

$$R_t = \Delta v/I_{ss} = R_s + R_m \quad (10)$$

so R_t is approximately equal to R_m , then the time constant τ is also represented as

$$\tau = R_s(Q_t \times R_t)/(\Delta v \times R_m) = Q_t \times R_s/\Delta v \quad (11)$$

Hence, R_s is calculated as

$$R_s = \tau \times \Delta v/Q_t \quad (12)$$

According to (10), calculate R_m by the following formula

$$R_m = R_t - R_s \quad (13)$$

Combining (8) and (13), the membrane capacitance C_m can be obtained.

C. Cell Content Amount Calibration Through Deep Learning-Based Rotation Detection of Bending Micropipette

Before extraction, the micropipette was manually rotated around its axis to make its bent tip basically downward to increase the tilt angle which facilitates the penetration of tissues and target cell. After the cell content extraction is completed, the micropipette tip is rotated by about 180° around its central axis, so that the bent tip is basically parallel to the horizontal plane, making the contents inside the micropipette tip clearly visible. Here, a deep learning method is introduced to more accurately judge the rotation state of the micropipette tip.

Under the microscope's field of view, the central axis of the micropipette tip that has been rotated in place is approximately parallel to the X -axis. The tip that has not been rotated in place bends in the Y -axis direction in the field of view and the boundary of micropipette can be easily distinguished from the background. Deep neural network is used to learn micropipette tip features and achieve real-time detection of tip rotation. Using

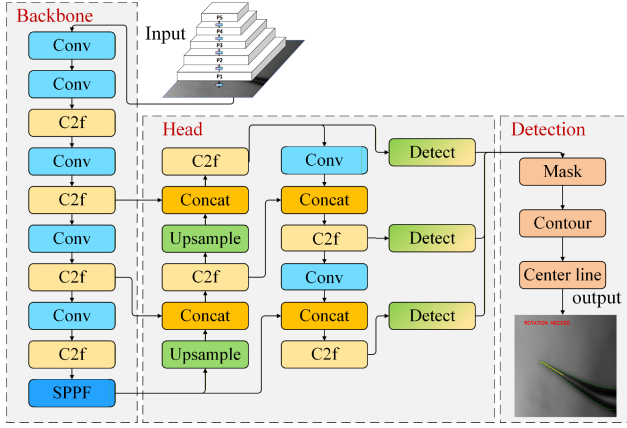


Fig. 4. Model structure of bent micropipette rotation detection.

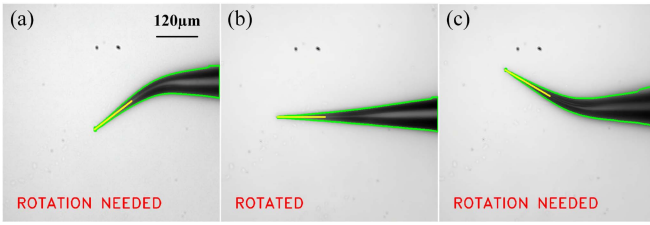


Fig. 5. Detection results of the bending micropipette (a) Downward (b) Rotated into place (c) Upward.

YOLOv8 [29] for segmentation, the contour of micropipette can be obtained. Therefore, it is possible to perform linear fitting on the midline of the upper and lower halves of the micropipette. By detecting whether the angle between the fitted line and the horizontal direction is less than the threshold, it can be determined whether the micropipette has been rotated properly. The threshold was determined based on experimental observations and practical requirements of calibration. Specifically, experienced operators check the shape of the micropipette at different rotation angles and determine the angle range it maintains parallel to the X -axis. When the rotation angle exceeded this range, an obvious deviation in the micropipette morphology could be observed, which may affect subsequent calibration process. Fig. 4 shows the model structure for segmenting contours of micropipette and rotation detection based on the YOLOv8 model. Actual tests have shown that this rotation detection method can be well applied to different micropipettes. The result of rotation detection on different states of the bending micropipette is shown in Fig. 5, including bending upward, bending downward and rotated in place. The contour of micropipette is drawn using green lines, and the yellow lines represent the fitted lines used to determine the degree of rotation.

Since the micropipette tip is almost parallel to the X - Y plane, the shape of the contents appear trapezoidal in the microscope field of view. The inner diameter $R_{in}(x)$ of the micropipette at a distance x from the tip can be calculated by fitting the calibrated inner diameter function at different positions using the liquid interface displacement method reported in previous work [30], and the volume of the extracted content can be obtained from

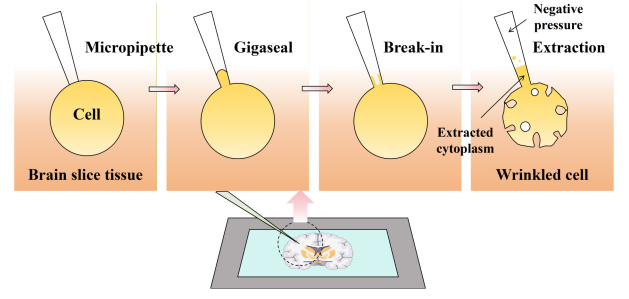


Fig. 6. Schematic: robotic cell content extraction process.

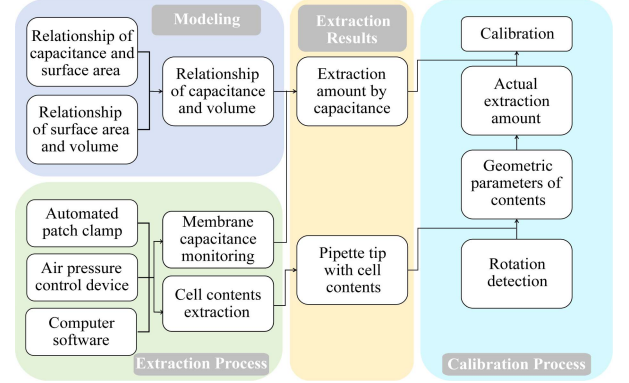


Fig. 7. Robotic quantitative cell content extraction flow.

the formula

$$V = \pi \int_0^h (R_{in}(x))^2 dx \quad (14)$$

where h represents the height of the extracted contents. Therefore, by clicking the mouse to determine the positions of two points on the upper and lower bases respectively, the volume of the contents is calculated according to these geometrical parameters.

Besides, the cell volume is estimated to calculate the relative amount of extracted cytoplasm to total cell content. Again, the target cell is simplified as a sphere. We measure the long and short axes of the X - Y plane of the target cells through mouse click. The average of the two values is set as the diameter of the spherical cell to estimate cell volume. With the calculated extracted cytoplasm volume, the relative amount of extracted cellular content is calibrated through the ratio between the cytoplasm volume inside micropipette and the whole cell volume.

Finally, the obtained volume of extracted cytoplasm is compared to the calculated results through membrane capacitance variation to rectify the obtained relationship in Section III-B. The reader may find more details in Section IV-B.

D. Robotic Cell Content Extraction Process Based on Cell Membrane Capacitance Variation

Based on the above work, we propose robotic cell content extraction process based on cell membrane capacitance as shown in Fig. 6 and Fig. 7. Firstly, the operator finds and locates the target cell with mouse click, usually selecting cells with a droplet

shape and clear contours. Before extraction, an automated patch clamp operation including approaching the target cell, aspirating part of cell membrane into micropipette opening to form a giga ohm-scale seal (gigaseal) and then breaking the aspirated cell membrane with negative pulses (break in) is conducted as shown in Fig. 6. For detailed operational procedures, please refer to the previous publication [31]. After breaking the aspirated cell membrane, the system waits for a period of time until the cell state stabilizes, and then continues to apply negative pressure to extract the cell contents. Meanwhile, the change in membrane capacitance is obtained online according to Section III-B. If the removed cytoplasm amount has not reached the set value, the extraction process continues. Otherwise, the aspiration pressure stops and the micropipette tip moves out of cell immediately to stop the cytoplasm extraction. The reader can find more details of the above operation process in uploaded supplementary file “Robotic cell content extraction process.mp4”.

Based on the calculation formula of membrane capacitance, we can obtain the relationship between cell membrane surface area and membrane capacitance. Then, the extraction amount reflected by membrane capacitance can be calculated by the following formula

$$V_i/V_0 = [1 - (C_i/C_0)^{3/2}]/k \quad (15)$$

V_0 and C_0 represent the cell volume and membrane capacitance values before extraction, V_i and C_i represent the extracted cell volume and membrane capacitance values during extraction, respectively. The calibration coefficient k is obtained from calibration process, with a value of 1.15, details can be found in Section IV-B.

IV. EXPERIMENTS AND RESULTS

To verify the effectiveness of our method, we extract cell contents from neurons in the visual cortex of acute brain slices. These brain slices are prepared from four to six weeks old female mice (C57BL/6J) according to the protocols in reference [32]. All animal experiments were approved by the Committee for Animal Experimentation of the College of Life Sciences at Nankai University (No. 2008) and were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals (No. 8023, revised in 1996).

A. Robotic Cell Content Extraction Experiments

A bending micropipette electrode with a tip bent by about 30° is used to perform cell content extraction operation under a constant aspiration pressure. The aspiration pressure is set as a constant value from 5 to 25 hPa, which was determined through preliminary experiments. This range provided a suitable balance between aspiration efficiency and success rate, avoiding insufficient extraction at low pressures and potential cell breakage caused by excessive pressure. A successful cell content extraction operation is defined as the detected membrane capacitance exhibits a significant change (larger than 1% of its initial value) after 10 minutes of aspiration. The failure of cell content is defined as the cell detachment during extraction process with no significant decrease in detected capacitance (with variation less than 1%), which can be detected through a significant

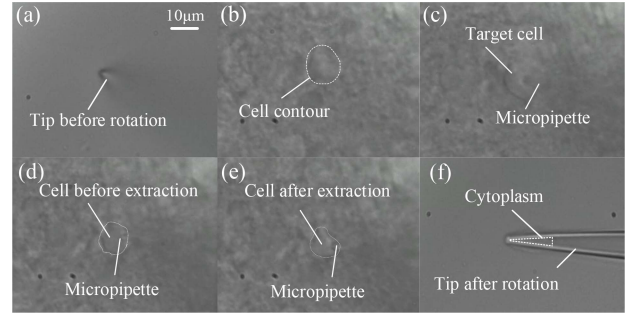


Fig. 8. Cell and micropipette in robotic extraction and calibration process. (a) The morphology of bending micropipette before extraction process under a 40x magnification. (b) The position and contour of target cell. (c) Micropipette tip in contact with cell before extraction. (d) Cell contour when starting extraction. (e) Cell contour after extraction process. (f) After extraction process and rotating the micropipette, the contour of contents in micropipette tip.

decrease of the micropipette resistance. When encountering some abnormal situations, such as micropipette damage, cell detachment, and cell breakage, it is necessary to immediately stop negative pressure and lift the micropipette away from the brain tissue to prevent further contamination, and then replace a new micropipette. Fig. 8 shows the microscopic images of cellular content extraction for neurons in brain slice of mouse. The figure illustrates the morphology of the bent micropipette, the contour of the target neuron before extraction, the interaction between the micropipette and the cell during extraction, and the extracted cytoplasm inside the rotated micropipette used for volume calibration. There were 24 out of 37 cell content extraction operation succeed, with a success rate of 65%, and the average operation time is 16.38 ± 9.90 min. Apparently, the above success rate is lower and operation speed is slower than those in most of the visual-guided cell content extraction methods for oocytes/embryos reported in references [5], [8]. This is mainly because the diameter of target neuron is much smaller than oocytes and embryos (about $15 \mu\text{m}$ [33] versus over more than $100 \mu\text{m}$ [34]). The opening diameter of the extraction micropipette used in this paper (about $1 \mu\text{m}$) is much smaller in comparison to those used for extraction of oocytes/embryos (about $20 \mu\text{m}$ [18]). In comparison to those thick micropipettes, the $1 \mu\text{m}$ -sized micropipette opening is easily blocked or detach with cell during gigaseal, break-in or extraction process. Further, the relatively long operation time is also because of the small opening limiting the extraction speed of cytoplasm entering the micropipette. Increasing the micropipette opening size may reduce the above blockage detachment incidences. However, it will increase the mechanical harm to neurons and also increase the difficulties to form a seal between micropipette opening and aspirated cell membrane which is required for measuring cell membrane capacitance.

B. Extracted Cell Content Volume Calibration Results

To calibrate the equivalent coefficient k , 15 successful results were randomly selected with set extraction amounts varying from about 10%–40%. Fig. 9 shows the comparison results through membrane capacitance variation and visual feedback calibration after extraction. Before applying the coefficient k ,

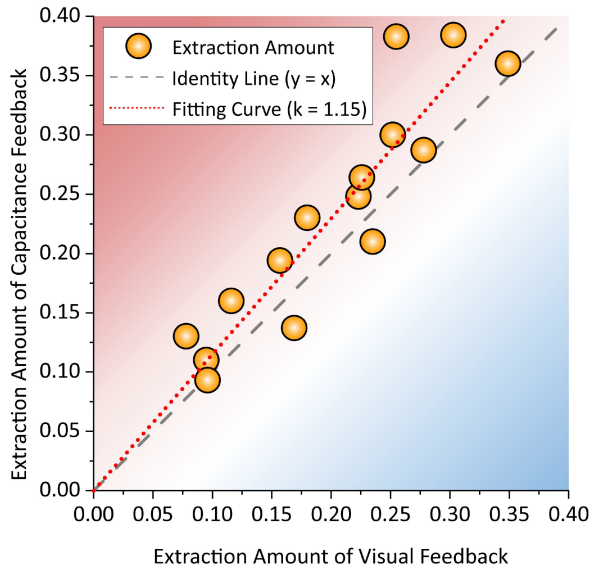


Fig. 9. Relationship between the extraction amount obtained from membrane capacitance feedback and visual feedback.

TABLE I
CELL CONTENT EXTRACTION ERROR CALIBRATION EXPERIMENTS AFTER
CALIBRATION OF k

Number	Calibrated Capacitance Amount	Visual Feedback Amount
1	8.70%	7.67%
2	14.61%	15.36%
3	19.48%	19.19%

the average control error between visually estimated amount and set value using this method is $2.87\% \pm 1.91\%$. It can be found that extraction amounts reflected by the membrane capacitance are generally larger than those obtained by visual feedback calibration (the dashed line represents the equation between them). The linear relationship between them is fitted as shown by the red dotted line in Fig. 9. The relationship between them is fitted as $y = 1.15x$, with $R^2 = 0.98$, where the coefficient $k = 1.15$ compensates for systematic deviations from ideal spherical modeling, calibrating theory and experimental measurements.

In order to verify the validity of the calibration relationship between the capacitance and the actual extraction amount and equivalent coefficients proposed earlier, we conducted cell content extraction experiments again, which were independent of the 15 previous experiments with results shown in Table I. When k is set as 1.15, the average error between visual feedback extraction amount and set value is $0.69\% \pm 0.37\%$, which is significantly reduced compared with the error before calibration ($2.87\% \pm 1.91\%$).

C. Dynamic Cell Surface Area Variation During Extraction Process

The dynamic membrane capacitance were recorded to estimate the dynamic cell surface variation during whole cell content

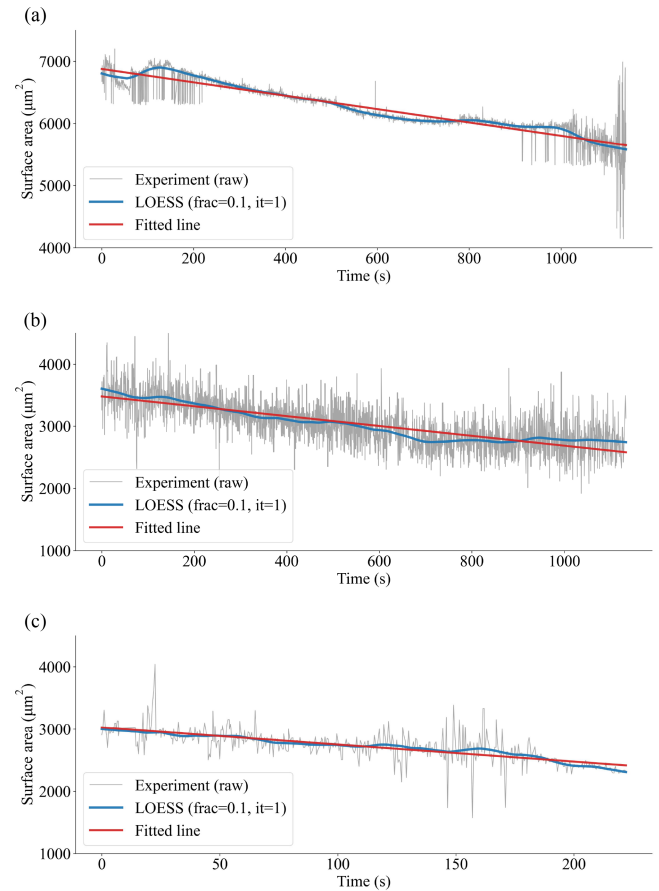


Fig. 10. Dynamic cell surface area trend during cell content extraction process with constant aspiration pressure. The aspiration pressures are 2500 Pa for (a), and 500 Pa for (b) and (c), respectively.

extraction process. Fig. 10 summarizes the dynamic cell surface area variation trends in three extraction processes using constant aspiration pressure. Results of LOESS smoothing ($\text{frac} = 0.10$) of the experimental trace indicate that the surface area of the cell membrane shows a decreasing trend with extraction time. Linear fitting was performed on the raw experimental data. It can be found that an approximately linear decreasing trend of cell surface occurs during extraction process, as shown in Fig. 10. In the experiment, there are some fluctuations in the surface area of the cell membrane, which may be related to membrane trafficking events (e.g., endocytosis) or morphology changes beside the membrane capacitance calculation errors. With the ability to measure the dynamic variations of cell surface area, our method is expected to be applied to study the morphological regulation of cells in dynamic environments in the future.

V. CONCLUSION

This letter presents a quantitative extraction method of cellular contents based on changes in cell membrane capacitance for cells in biological tissues where removed cell content is difficult to observe. This method utilizes automated patch clamp and air pressure control device to extract cell contents automatically, while determining the extraction amount based on

the relationship between the change of cell volume and membrane capacitance. Quantitative calibration based on rotation detection of bending micropipette is performed to calibrate key parameters of the cell membrane capacitance model and further verify the effectiveness of this method using image processing. After calibration, independent validation experiments further indicated that the average cell content extraction error was $0.69\% \pm 0.37\%$ of the total cell volume. This study demonstrates the feasibility of using membrane capacitance as a quantitative electrical feedback signal for robotic cell content extraction in cells embedded in tissues where direct visualization of intracellular extraction is limited. Future work will include comprehensive comparisons with other quantitative cell manipulation techniques and further investigation of the applicability of the proposed method to different cell types. Subsequent research will also focus on improving system automation and closed-loop control.

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