Development of Micro Electrical Impedance Tomography System for Cell Distribution Visualization in Microchannel

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Abstract: Micro Electrical Impedance Tomography (μEIT) system is developed for cell distribution visualization in an electrode-multilayered microchannel. Simulation and experiments were conducted to evaluate the developed μEIT system. In the simulation, 3 phantoms of cell/liquid suspension were established, 3 kinds of image reconstruction algorithms were employed to solve the ill-posed inverse problem, Projected Landweber Iteration (PLW) was found to be the optimum algorithm in the present study. In the experiments, measurements of the cell distribution of two-phase flow which consist of yeast cells and purified water in the microchannel adopted a range of frequencies alternate current (AC) to the electrodes to find the optimum for image reconstruction. Images of cell distribution reconstructed by PLW in three cross-sections showed cells sediment at the bottom of the microchannel. The developed μEIT system can realize the cell distribution visualization successfully and provide a novel μEIT approach for cell sensing in biomedical applications.
Key words: micro electrical impedance tomography, microchannel, Cell/liquid two-phase flow, image reconstruction.

1. Introduction

It is a great significance that visualization measurement of the spatial distribution of cells in microfluidics developed for biomedical applications [1]. The measurements of the distribution of each phase in multiphase flow have the potential to improve the control of cells in the microfluidics even it is useful for validating computational models of microfluidics [2]. Electrical impedance tomography (EIT) is one of the visualization measurement techniques which determine the electrical conductivity or permittivity distribution within a medium using electrical measurement from a series of electrodes on the surface of the object [3]. Since EIT uses a non-invasive data acquisition method, low frequencies (0–10MHz), low voltage (0–5V) and low current (0–4mA) [4], it has advantages such as no radioactive source, non-invasive, fast and low cost over other measurement techniques like X-ray, computed tomography (CT) imaging, magnetic resonance imaging (MRI) and ultrasound imaging [5]. Benefiting for these advantages, EIT has been widely applied to biological applications. Bera [6] designed a multi-frequency EIT system for biomedical imaging. Sun [5] developed a miniaturized electrical impedance tomography system with a chip containing a circular 16-electrode array to image the process of cell culture.

For image resolution, due to the nonlinear ill-posed inverse problem of the soft field technique which the conductivity at each pixel affected by measured value, different image reconstruction algorithm has been employed to improve the image resolution. Various algorithms are existing for finding the distribution of materials from the boundary measurements [7], which are mostly based on the determination of a ‘sensitivity matrix’ that relates changes in the computed value of permittivity for each pixel to changes in each boundary measurement.

As biological applications with various image reconstruction algorithms, the diameter of an EIT sensor is usually between 2.5 cm and 10 cm [8], although smaller and larger sensors were attempted by some researchers [5][9], however, few EIT methods were reported in image visualization of micro systems due to the difficult fabrication of microchannel surrounded by embedded electrodes in a microchannel. Our research team has developed a novel electrode-multilayered microchannel which with square cross-section and successfully applied it to cell sensing and manipulation [10].

In the present study, a μEIT system is developed for 3D cell distribution visualization in the microchannel. To evaluate the developed μEIT system, simulation and experiments was conducted. In the simulation, to find the optimum image reconstruction algorithms for the μEIT system, three algorithms which are Tikhonov Regularization, Landweber Iteration (LW) and Projected Landweber Iteration (PLW) were compared. In the experiment, to realize the 3D cell distribution visualization with the developed μEIT system at an optimum frequency, the optimum algorithm (i.e. PLW) was employed to reconstruct the image in 3 cross-sections of the microchannel at a range of frequencies.

2. Materials and Methods

Electrical Impedance Tomography (EIT) is conducted via an array of electrodes placed around the region of interest. For cell distribution visualization, the image reconstruction by EIT was conducted in 3 steps:

- Measurement of voltages among electrode-pairs after AC current applied to other electrode-pairs;
- Sensitivity matrix calculation by solving forward problem;
- Image reconstruction of cell distribution by solving inverse problem.

2.1. Fabrication of Electrode Array

The electrodes are integrated into the microchannel using MEMS technique and photolithography. The details of the fabrication method have been reported by Yao (2016). [11] The target size of the electrode is selected to satisfy the requirements for the main target application involving cell flow. Figures below show the microchannel chips (Fig 1), dimension of the microchannel with integrated electrodes (Fig 2), and the measurement strategy (Fig 3). During operation, the EIT system injects a controlled current which value is 10mA through one electrode, ‘sinks’ the opposite electrode to ground, and measures voltages at all other pair of electrodes.

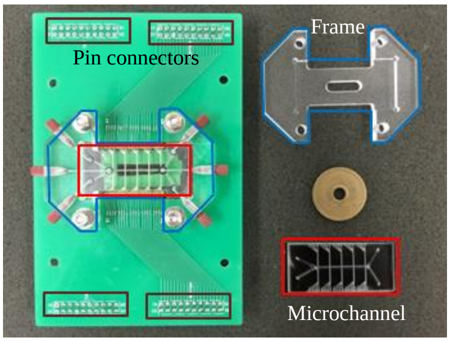


Fig 1 Photo of microchannel and connections

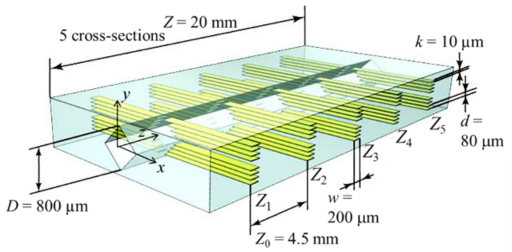


Fig 2 Dimension of the microchannel

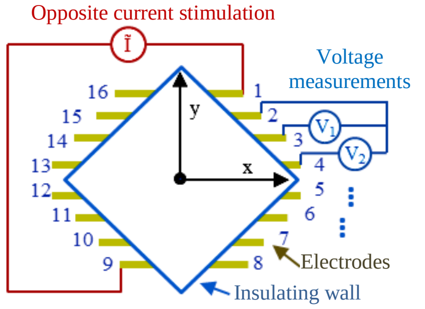


Fig 3 One section of microchannel and measurement strategy

2.2. Sensitivity matrix calculation

The EIT image reconstruction problem is a nonlinear inverse problem. Solution of such a nonlinear inverse problem usually requires a forward solver for Poisson's equation. The forward problem mainly described as the calculation of sensitive matrix from the known conductivity distribution and the measurement voltage in each pairs of electrodes by simulation. In this work, the higher order finite element method (FEM) was adopted to segment the domain of cross-section in the microchannel and calculate the potential field for the forward solver. The task of the image construction for EIT is to determine the change in conductivity distribution $\boldsymbol{\sigma}$ from the change in the measured voltage $\boldsymbol{U}$ as shown in Equation (1):

$$\boldsymbol{U}^{M} = \boldsymbol{J}^{M\times N}\boldsymbol{\sigma}^{N} \quad (1)$$

where $\boldsymbol{J}^{M\times N}$ is the sensitive matrix and $\boldsymbol{\sigma}^{N}$ is the conductivity, M is the number of measurements and N is the number of units segmented.

To solve the equation (1), the sensitive matrix $\boldsymbol{J}^{M\times N}$ can be calculated as equation (2):

$$\boldsymbol{J}^{M\times N} = \begin{bmatrix} \frac{\partial U^1}{\partial \sigma_1} & \frac{\partial U^1}{\partial \sigma_2} & \cdots & \frac{\partial U^1}{\partial \sigma_N} \\ \frac{\partial U^2}{\partial \sigma_1} & \frac{\partial U^2}{\partial \sigma_2} & \cdots & \frac{\partial U^2}{\partial \sigma_N} \\ & \vdots & & \\ \frac{\partial U^M}{\partial \sigma_1} & \frac{\partial U^M}{\partial \sigma_2} & \cdots & \frac{\partial U^M}{\partial \sigma_N} \end{bmatrix} \quad (2)$$

2.3. Image reconstruction algorithms

To solve the EIT inverse problem usually need Image reconstruction algorithms to find the distribution of conductivity changes inside the conductive domain that corresponds to measurements of electrode potentials. The existing image reconstruction algorithms, including non-iterative and iterative algorithms, were exhaustively reviewed by Yang (2002) (12). To obtain a better image quality, three iterative algorithms, Iterative Tikhonov Regularization (TK), Landweber Iteration (LW), and Projected Landweber Iteration (PLW) are employed to solve the ill-posed inverse problems.

Iterative Tikhonov Regularization (TK) is a universal tool for solving ill-posed inverse problems and has been applied to EIT for image reconstruction (13). The solution is expressed as

$$\boldsymbol{\sigma}^{0} = \left(\boldsymbol{J}^{T}\cdot\boldsymbol{J} + \mu\boldsymbol{I}\right)^{-1}\boldsymbol{J}^{T}\cdot\boldsymbol{U} \quad (3)$$

$$\boldsymbol{\sigma}^{k+1} = \boldsymbol{\sigma}^{k} + \left(\boldsymbol{J}^{T}\cdot\boldsymbol{J} + \mu\boldsymbol{I}\right)^{-1}\left(\boldsymbol{J}^{T}\cdot\boldsymbol{U} + \mu\boldsymbol{\sigma}^{k}\right) \quad (4)$$

where μ is the regularization factor as a small positive number, $\boldsymbol{I}$ is a unit matrix.

Landweber Iteration (LW) is the most widely used iterative method for EIT, and also produces the best images (14) in most cases. The process of Landweber Iteration is expressed as:

$$\boldsymbol{\sigma}^{k+1} = \boldsymbol{\sigma}^{k} + \mu\boldsymbol{J}^{T}\left(\boldsymbol{U} - \boldsymbol{J}\cdot\boldsymbol{\sigma}^{k}\right) \quad (5)$$

A problem with Landweber Iteration (LW) method is that its convergence property is poor (12). A simple way to improve the convergence is given in the Projected Landweber Iteration (PLW) method (15). the Projected Landweber (PLW) method is used as the equation (6):

$$\boldsymbol{\sigma}^{k+1} = P\left[\boldsymbol{\sigma}^{k} + \mu\mathbf{J}^{T}\left(\mathbf{U} - \mathbf{J}\cdot\boldsymbol{\sigma}^{k}\right)\right] \quad (6)$$

where P is a projection operator defined by:

$$P(f(x)) = \begin{cases} 0 & \text{if } f(x) < 0 \\ f(x) & \text{if } 0 \le f(x) \le 1 \\ 1 & \text{if } f(x) < 0 \end{cases} \quad (7)$$

The solution is projected to a convex set after each iterating. The implementation details of the Projected Landweber Iteration are described by Zhang and Cheng (2010) (16).

2.4. Simulation conditions and method

The purpose of the simulation is aimed on the optimum image reconstruction algorithm. The method of the simulation is to compare the result of image reconstructed by different algorithm.

With the conductive of the simulations, 3 phantoms have been created, for each simulation, 16 electrodes were equally spaced around the model periphery. A 10 mA current was injected through opposite electrode pairs while recording the voltage differences across the remaining electrode pairs. For each current projection, the resulting voltages were obtained by solving the Poisson equation in a finely meshed finite-element system. Using the conductivity distribution and sensitive matrix from the simulated phantom, the images can be reconstructed by the different algorithms as TK, LW and PLW. We assumed that the cells are temporarily placed in an electrically insulating.

2.5 Experimental setup and method

The developed EIT system consists of a multi-layered microchannel, a multiplexer, an Impedance analyser and a PC for collecting data. A schematic diagram of the system is shown in FIG. 4.

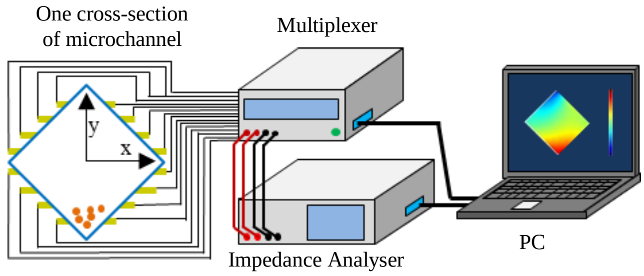


Fig. 4 Experimental setup

When EIT is used in cell distribution visualization, it uses the biophysical properties of tissues and their cellular structure to reconstruct an image which represents human physiology or biological mechanisms associated with cell structures (17).

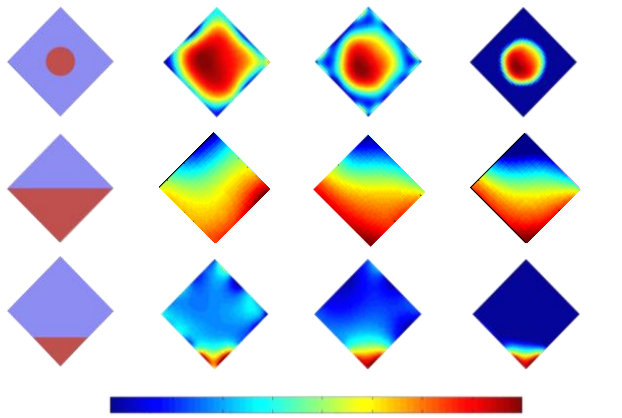
3. Results And Discussion

3.1. Simulation Results

In the simulation analysis, three types of phantoms were built to evaluate the measurement performance of the Micro-EIT system as shown in Table 1. The reconstructed images using different algorithms were compared. The parameters, σ_w, σ_c, ε_w and ε_c are the conductivity of water and cells, relative permittivity of water and cells, respectively, the value of them are shown in Table 1. Blue colour and red colour represent low conductivity and high conductivity of the cells/water two-phase flow. From the simulation results, The PLW algorithm is the optimum one to reconstruct the image for the Micro-EIT system.

Table 1 Phantoms and simulation results with different image reconstruction algorithms.

Phantom	TK (μ=0.03)	LW (μ=0.07)	PLW (μ=0.07)



Low Relative conductivity σ*[-] High

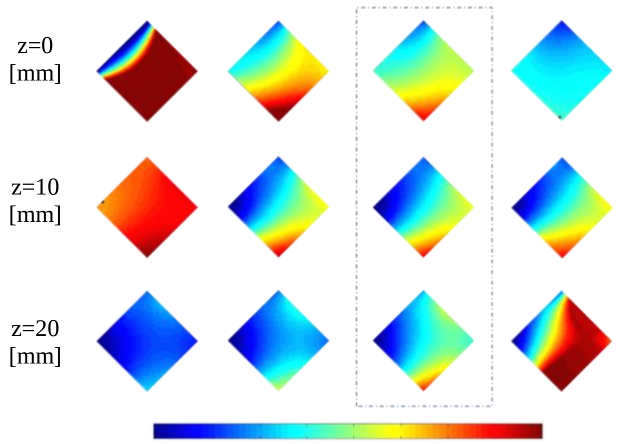
σ_w =5.5×10^{-6}[S/m], σ_c=2.34×10^{-3}[S/m], ε_w'=78.5[-], ε_c'=100[-]

3.2. Experimental results and discussion

The image construction of the cell distribution could be realized as an optimum frequency where the difference of conductivity is larger than at other frequencies. Table 2 shows the image reconstruction of cell distribution with PLW along the microchannel at different frequencies. According to the results, f=1 MHz was selected as an optimum frequency to reconstruct the images for cell visualization measurement.

Table 2 Image reconstruction of cell distribution along the microchannel at different frequencies.

	f=500KHz	f=750KHz	f=1MHz	f=2MHz



Low Relative conductivity σ*[-] High

Furthermore, the reconstructed images of cell distribution in the 3 cross-sections at flowing status were combined with the quantitative measurement results using electrochemical impedance spectroscopy (EIS) method by Yao [18]. The reconstructed images with the Micro-EIT system show that the cell concentration deceases along the microchannel because of the cell sedimentation.

Fig. 5 shows the Images of cell distribution with PLW in three cross-sections of the microchannel. The reconstructed images show that cells sediment at the bottom of the microchannel, which are explained with the quantitative results in the previous study by electrical impedance spectroscopy (EIS) method [18], which demonstrates that the developed µEIT system can realize the cell distribution visualization successfully in the electrode-multilayered microchannel. The present study provides a novel µEIT approach for cell sensing in biomedical applications.

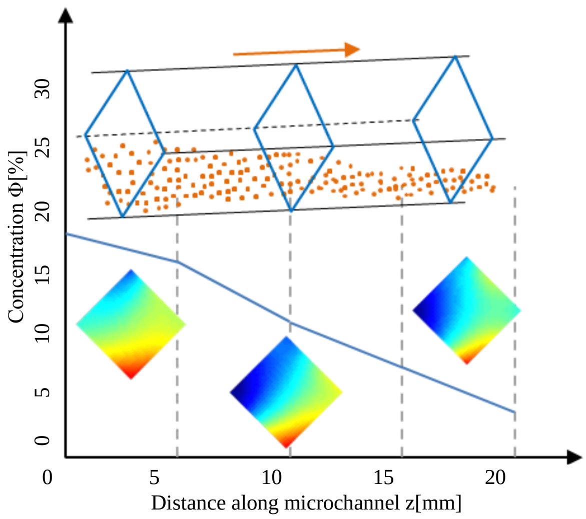


Fig. 5 Application of cell visualisation in the µEIT system

4. CONCLUSIONS

Micro Electrical Impedance Tomography (µEIT) system has been developed for cell distribution visualization in an electrode-multilayered microchannel with diamond cross-section.

- Simulation was conducted to evaluate the developed µEIT system. In the simulation, 3 kinds of phantoms of cell/liquid suspension were established; three image reconstruction algorithms which are Iterative Tikhonov Regularization (TK), Landweber Iteration (LW) and Projected Landweber Iteration (PLW) are employed to solve the ill-posed inverse problem. Projected Landweber Iteration was found to be the optimum for image reconstruction in the present study.
- In the experiment, yeast cells and purified water are employed as two-phase flow to measure the cell distribution in the microchannel. Alternate Current (AC) with a range of frequencies was applied to the electrode in the microchannel to find the optimum frequency for the µEIT system. The optimum frequency for the image reconstruction was found as f = 1MHz.
- Images of cell distribution are reconstructed with PLW in three cross-sections of the multilayered microchannel. The reconstructed images show that cells sediment at the bottom of the microchannel, which were proved with the quantitative results in the previous study.

The present study provides a novel Micro EIT system for cell sensing in biomedical applications. Image quality will be improved with different algorithms and current injection methods in next study.

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