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Visualization of electrical field of electrode using voltage-controlled fluorescence release

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ABSTRACT

In this study we propose an approach to directly visualize electrical current distribution at the electrode–electrolyte interface of a biopotential electrode. High-speed fluorescent microscopic images are acquired when an electric potential is applied across the interface to trigger the release of fluorescent material from the surface of the electrode. These images are analyzed computationally to obtain the distribution of the electric field from the fluorescent intensity of each pixel. Our approach allows direct observation of microscopic electrical current distribution around the electrode. Experiments are conducted to validate the feasibility of the fluorescent imaging method.

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1. Introduction

Understanding the interface between biosensors and living systems has been one of the greatest challenges in the field of biomedical engineering. It requires a confluence of studies in not only engineering, life science, but chemistry, physics, mathematics, and other fields [1]. Biopotential electrodes, which are used to record electric activities of living cells or deliver electric currents, allow current flow across the interface between electronic measurement circuit and biological tissue [2]. To evaluate the performance of electrode, impedance of the electrode–electrolyte/tissue interface is always an important variable because it facilitates charge transfer between electrolyte and electrode. With a low impedance electrode, high-quality signal can be obtained during recording (e.g., electroencephalography) and the voltage applied to the tissue can be reduced during stimulation (e.g., deep brain stimulation) [3]. Traditionally the impedance is measured using electrochemical impedance spectroscopy (EIS) [4], which is a popular method to study the electrode–electrolyte interface using a small-amplitude signal in varying frequencies. The interface is usually simplified as a combination of electronic circuit elements, and these elements are parameterized and identified through measurements by the EIS. Although different equivalent models (e.g., Warburg model and Randles model [2,5]) have been proposed to study the electrochemical reaction occurred at the interface, the impedance has been considered a global property of the electrode, ignoring the structure of the electrode and the inhomogeneous nature of the electrolyte and the tissue.

Because current density distribution in local regions of an electrode is important in understanding electrode–tissue interaction, it is desirable to know how the current flows from the electrode to tissue and vice versa. Due to the inability of directly observing charge transfer at the interface, finite element model (FEM) has become a commonly used tool to visualize the electric field in the electrolyte [6–19]. If the FEM model is accurate in geometrical, electrical and material properties, the current/voltage can be calculated and visualized at each element (e.g., tetrahedra in 3D space). As a result, electrode geometry, material, and surface properties with respect to the surroundings of the electrode can be studied, and the results can be used to evaluate the performance of biopotential recording and the efficiency of electrical stimulation. McIntyre and his colleagues studied a conical metal microelectrode and found that the surface area, roughness, resistive coating of the electrode surface, and the radius of curvature of its tip affected the spatial distribution of the current over the surface of the electrode [8]. It has been shown that the activation of axons depends on the second-order spatial derivative of the extracellular potential [20,21]. Based on this result, high-perimeter planar electrodes have been developed to improve the efficiency of neural response to deep brain stimulation (DBS) by increasing the spatial non-uniformity of the current density around the electrode [13–15]. Kuncel and Grill provided a way to choose stimulation parameters for DBS by investigating the effects of electrode contact

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location and geometry on the electric field using FEM [17]. Yousif et al. constructed a FEM model of the electrode-brain interface with graded complexity in structure. This model was used to study the mechanism of DBS during the acute and post-implantation stages [18,19]. To model the electrical potentials recorded in microelectrode arrays, Ness et al. established a biophysical forward model based on the FEM to link the neural activity in the brain tissue slice and the potentials recorded by microelectrode arrays [16]. Howell et al., studied the influences of electrode geometry, and the electrode–tissue interface on models of electric fields produced by DBS [6]. However, the FEM-based analysis has two major limitations: (1) the knowledge of the geometry and electrical property (i.e., conductivity) of each element of FEM is required which are difficult to measure for a living system, and (2) validating the modeled voltage/current distribution is difficult.

In order to image the current density directly at the electrolyte–electrode interface, the electrical current density vectors in electrolyte is measured using the current density imaging (CDI) [22–26]. The CDI, a type of magnetic resonance imaging method, was used to observe the current density distributions on the DBS electrode surface as well as in the electrolyte within several millimeters beneath the electrode on a homogenous gel phantom [26,27]. However, this method can only visualize the pathway of the controlled alternating electric currents and the spatial resolution of this method is low, in the order of millimeters. As a result, the CDI has mainly been used to solve the inverse problems of the current field in conductivity imaging [26,28]. As an imaging mode for the atom force microscope, electric force microscopy measures the electric field gradient distribution above a sample surface by applying a voltage between the conductive tip of an electrode and the sample [29–31]. However, the measurement has to be conducted in an ultra-high vacuum environment and no conductive material is permitted between the tip and the electric field. This approach is suitable for applications such as distinguishing conductive and insulating regions in the printed circuit board rather than detecting current flowing in conductive electrolyte. In 1999, Maus and co-workers utilized electrically generated chemiluminescence to image the nonuniform current density in the vicinity of an electrode [32]. When excited by an alternative current, the chemiluminescence arising from reaction of radical cations of 9,10-diphenylanthracene (DPA) and benzonitrile (solvent) radical anions in the electrolyte were captured by fluorescent microscopy as an indicator of the current density. Although the spatial resolution could be as high as one micrometer, the electrolyte concentration (containing DPA) and the excitation frequency had to be optimized to achieve a high luminescent intensity. An experimental approach has also been undertaken to characterize the spatial distribution around an active stimulating electrode [33]. In this work, implanted microelectrodes were used to record the voltages generated by the active electrode in a monkey animal model. The measurement results are compared with the voltages calculated from a finite element model. Although this approach is feasible, it is invasive and expensive.

Till now, visualization of electric field at the electrode–electrolyte interface remains an unsolved problem although fluorescent tracers have been available for the study of the interaction between the electrode and tissue. Fluorescent staining of neural tissue was used to study the inflammatory response by imaging the electrode–tissue interface with implanted electrodes [34]. Fluorescein derivatives have also been used for imaging of pH gradients in biological system [35–37]. Voltage-sensitive dye was applied to visualize the voltage change across the membrane of cell attached on a silicon chip [38].

In this work, we proposed to image the current distribution at the interface using voltage-controlled fluorescence release, inspired by the mechanism of electrically-controlled drug release [39,40]. Different from those previous studies, we coat the electrode with a solution containing fluorescent tracer using electrochemical deposition, and then release the tracer by applying an electric potential across the interface. A high-speed fluorescent microscopy is used to capture the distribution of the tracer at different time points. By analyzing these images, the electric current distribution at the interface is calculated. Our method is easy to perform and no specific instrumentation is required except a use of fluorescent microscopy.

The rest of the paper is organized as follows. Section 2 describes the fluorescent tracer, a method to release the tracer, and a derivation of the current distribution in the fluorescent images. Sections 3 and 4 present experimental design and results, respectively. Conclusion and discussion are provided in Section 5.

2. Materials and methods

2.1. Fluorescent tracer

In order to image the electrode–electrolyte interface, fluorescein sodium salt (Sigma-Aldrich Corporation, St. Louis, MO) was used as a fluorescent tracer. The molecular radius of this salt is small and each molecule has two negative charges. Fluorescein is among the most common fluorescent dyes for many applications. Fluorescein sodium (see Fig. 1) is a disodium salt of fluorescein that possesses a high solubility in water, equal to 500 mg mL^{-1}. These properties make fluorescein sodium a good fluorescent tracer to investigate the working of electrodes.

2.2. Electrically controlled release of fluorescent tracer

The Polypyrrole (PPy) film was deposited on the electrode by one-step electropolymerization [38]. Negatively charged fluorescein as a dopant was incorporated into the PPy thin film to maintain charge neutrality during electrochemical oxidation. The doped PPy film can be reversibly switched between an oxidized state and a reduced state accompanied by the movement of dopant ions in and out of the polymer film for charge compensation. Therefore, upon the application of a negative electrical potential, PPy was reduced, expelling fluorescein anions from the PPy film. After the fluorescein anions were released from the PPy film, electric-field-driven migration played an important role in the movement of negatively charged fluorescein in the electrolyte toward the opposite charged electrode. This procedure is illustrated in Fig. 2.

2.3. Electric field imaging

Because the process of the fluorescence release can be captured by high-speed fluorescent microscopy and the fluorescent intensity of each pixel in the mages can be assumed to be proportional to the concentration of the fluorescent tracer at the location, we propose a computational method to calculate the distribution of the electric field from the captured images.

Let V represent a given volume in the electrolyte between the active electrode and the ground electrode in 3D space. Eq. (1) holds in regions where no fluorescent tracer is injected, i.e., the inflow flux of the tracer equals the outflow flux in volume V

$$\frac{\partial}{\partial t}\iiint_V C_d dV = -\oint_S (\boldsymbol{J}_d - \mu \boldsymbol{E} C_d)\boldsymbol{n} dS \tag{1}$$

where the left side is a volume integral over volume V, and the right side is a surface integral over its boundary S, C_d is the concentration of the tracer, $\boldsymbol{J}_d$ is the diffusion flux of the tracer, μ is the

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