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# Non-invasive measurement of normal skin impedance for determining the volume of the transdermally extracted interstitial fluid

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ABSTRACT

Normal skin impedance, which has a good correlation with skin permeability, can be used to calculate the volume of extracted interstitial fluid. However, it is still very difficult to determine non-invasively the normal skin impedance. In this study, a novel non-invasive method based on equipotential theory for real-time, in vivo and accurate measurements of normal skin impedance was proposed. The suggested method was based on the theory of an equipotential between the saliva and interstitial fluid of an organism, and this method was compared with the method based on an implanted electrode. The effects of humidity and pressure on the measurement accuracy of normal skin impedance were also studied. The feasibility of this method was verified by the results of the experiments. The proposed method is expected to enhance the blood glucose prediction accuracy and demonstrates a huge significance for the minimally invasive measurements of blood glucose in clinical application.



## 1. Introduction

Continuous glucose monitoring is highly important because diabetes has become a worldwide problem [1,2]. Additionally, the glucose concentration of interstitial fluid (ISF) is closely related to the blood glucose level. Thus, ISF is used to predict blood glucose levels because it can be transdermally extracted to continuously monitor blood glucose levels in a minimally invasive manner [3]. However, the volume of the ISF transdermally extracted for a patient in a single position fluctuates with time. And it fluctuates more widely for different positions of the same patient or for different patients. These fluctuations seriously affect the measurement accuracy of continuous glucose monitoring. Thus, it is very important to measure the volume in real time. Although the volume of the ISF transdermally extracted can be detected by a microflow meter which is integrated into a microfluidic chip [4], liquid residue remained in the microchannels makes a big influence on the measurement results. In fact, even with ultrasonic skin pretreatment, only a tiny volume of ISF (approximately 1 μL) could be obtained after 15 min vacuum extraction. But clinical application may require shorter extraction time (e.g. 5 min or less), which makes the volume of the extracted ISF much smaller. Additionally, the tiny extracted ISF scatters on the skin surface with an area of 0.785 $cm^2$ similar to micro-dewdrops under a microscope. Therefore, the extracted ISF is difficult to be collected and measured directly. Thus, until now it is still a challenge to accurately measure the volume of the ISF transdermally extracted in vivo.

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Modern medical research indicates that normal skin impedance is an indicator of the skin permeability coefficient [5]. The term "normal impedance" represents the skin impedance containing epidermis, dermis and subcutaneous tissues in the normal direction. The volume of ISF can be determined based on the relationship between the normal skin impedance and the skin permeability coefficient if the normal skin impedance can be accurately measured [6,7]. Therefore, the measurement of normal skin impedance is critical for continuous glucose monitoring based on transdermally extracted ISF. Several methods have been proposed to accomplish the measurement of skin impedance. Kinouchi et al. [8] proposed a fast in vivo method based on two electrodes to measure the local tissue impedance. The most significant drawback of the method is the invasion of a needle implanted subcutaneously. Martinsen et al. [9] put forward a system to detect live finger, which was based on simultaneously measuring the electrical bio-impedance of different skin layers. Ivanic et al. [10] proposed a method using a thin-film non-symmetric microelectrode array for impedance monitoring of human skin. Colbert et al. [11] proposed a single channel skin impedance system to measure the skin impedance of an acupuncture area. All of these methods lost the sight of the aeolotropy of skin, and the skin impedance achieved had no specific direction.

A novel method for measuring the normal skin impedance, in which one electrode is placed on the skin surface and the other one is kept in the mouth for complete contact with saliva, has been investigated in this paper. The proposed method is based on the theory of an equipotential between the saliva and ISF of an organism [12]. Moreover, the method can specifically obtain the normal impedance in real time non-invasively. The value of the obtained normal skin impedance can be used to calculate the volume of the ISF transdermally extracted. Animal experiments were performed to verify the feasibility of the proposed method. The effects of humidity and pressure on the accuracy of measuring the normal skin impedance were also studied in this paper.

## 2. The method of measuring normal skin impedance

### 2.1. The extraction method for interstitial fluid

The extraction method for ISF has been published, the Sonoprep was used to enhance the skin permeability [13]. The ISF was extracted by the vacuum generated from an oil-less vacuum–pressure pump (Tianjin Auto-science Instrument Ltd., China), then the variation of the normal skin impedance caused by the extraction of ISF could be detected by the measuring electrode. Thus, the volume of the extracted ISF could be determined accordingly with the impedance measurement results. In order to effectively collect the tiny volume of the transdermally extracted ISF which scatters on the skin surface, a defined volume of buffer solution was injected into the chamber before extraction. At the end of extraction, the mixture including buffer solution and the extracted ISF were collected to measure the glucose concentration using an enzyme-based biological sensing analyzer (SBA-40C, Key Laboratory of Biosensor in Shandong Province, Jinan, China). Furthermore, to miniaturize the glucose measurement system, other methods may be utilized to extract and collect ISF in the future. For example, the hollow-microneedle array used by Chua et al. [14], the interspace of which can be used as a cavity to hold buffer solution, and the measuring electrode can be coupled with the tip of the microneedle which contacts to the epidermis.

### 2.2. The method for measuring the volume of interstitial fluid

The transdermal permeation rate of glucose molecules is inversely proportional to the skin impedance in the normal direction [10,15]. Additionally, the volume of ISF is determined by the transdermal permeation of the skin and the extraction time. Thus, the volume of ISF can be calculated based on the acquired normal skin impedance [16].

The relationship between the volume of extracted ISF and the skin permeation rate can be expressed as [17]:

$$V = P \cdot t \cdot A \tag{2.1}$$

where $V$ is the volume of the ISF extracted transdermally; $P$ is the permeation rate of ISF through the skin; $t$ is the extraction time; and A is the skin area of the ISF extraction. The following relationship between $P$ and the skin conductivity could be demonstrated as [6]:

$$P = C\frac{\sigma}{\Delta x} \tag{2.2}$$

where $C$ is a constant related to the size of skin pores, the permeating substance, the inherent characteristics of the electrolyte solution, and the charged ions; $\sigma$ is the skin conductivity; and $\Delta x$ is the thickness of the stratum corneum. Considering the following relation:

$$\frac{\sigma}{\Delta x} = \frac{G}{A} = \frac{1}{A \cdot Z} = \frac{1}{A \cdot (R + jX)} \tag{2.3}$$

where $G$, $Z$, $R$ and $X$ are the conductance, normal skin impedance, resistance and reactance, respectively, of the skin with an area $A$ and thickness $\Delta x$ ($A$ is much bigger than $\Delta x$). Additionally, the reactance can be ignored as it is too small compared to the resistance when 10 Hz low-frequency signal is used in the measurement, so we can obtain the following relation from Eqs. (2.2) and (2.3):

$$P = C\frac{1}{A \cdot R} \tag{2.4}$$

Thus, the relationship between the normal skin impedance and ISF volume can be expressed as:

$$V = C \cdot \frac{1}{A \cdot R} \cdot t \cdot A = \frac{C \cdot t}{R} \tag{2.5}$$

where $C$ is a constant related to the skin, $t$ is the extraction time, and $R$ is the normal skin impedance. Thus, we can determine the value of $V$ by measuring the skin impedance as $C$ and $t$ are known.