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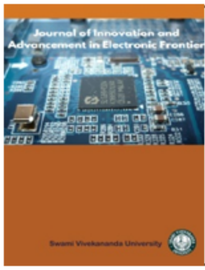

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Real-Time Monitoring of Electrical Wound Healing Using Impedance Sensing: Techniques, Challenges, and Future Directions

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Abstract

Wound healing is a complex physiological process that involves multiple stages, including hemostasis, inflammation, proliferation, and remodeling. Monitoring the progress of wound healing is crucial to optimize treatment strategies and prevent complications such as infection or chronic wounds. Recent advancements in electrical impedance sensing have shown promise for real-time, non-invasive wound monitoring. This paper provides an overview of the techniques used for electrical impedance-based wound healing monitoring, outlines the challenges associated with these methods, and explores potential future directions in this field. The integration of impedance sensing with emerging technologies, such as wireless systems and machine learning algorithms, is also discussed

Keywords: *Wound healing, Real-time monitoring, ECIS, Impedance monitoring, plethysmography*

1. Introduction

Wound healing is a dynamic process that involves several physiological and biochemical events, with the ultimate goal of restoring tissue integrity and function. Timely assessment of wound healing is critical in clinical settings, especially for chronic wounds, which may take a prolonged period to heal or may not heal adequately. Traditional methods of wound monitoring involve visual inspection and periodic biopsies, both of which are invasive and subjective. Various studies have explored the use of electrical impedance spectroscopy (EIS) and related techniques for non-invasive, real-time monitoring of wound healing [1, 2]. Impedance sensing measures the electrical properties of the tissue, such as resistance, capacitance, and inductance, which can be indicative of changes in the tissue's hydration, cellular activity, and overall health. A review of recent progress in flexible wearable sensors for wound monitoring utilizing optical and electrical sensing techniques has been carried out. They provided an overview of key biochemical markers and physical parameters in wounds along with their physiological significance. It reviews recent progress over the past years in flexible wearable sensors for wound detection based on optical and electrical sensing principles and explores the challenges and future directions in this field [3].

This paper discusses about continuous monitoring of wound healing using impedance measurement techniques along with existing challenges and futuristic applications.

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2. Impedance Sensing Techniques for Wound Healing

2.1 Electrical Impedance Spectroscopy (EIS)

EIS is a technique that involves the application of an alternating current (AC) signal to the tissue and the measurement of the resulting voltage drop across the tissue [4]. The electrical impedance is frequency-dependent and provides information about the tissue's properties at different depths and scales. Changes in impedance values can reflect the physiological alterations occurring during wound healing, such as inflammation, tissue proliferation, and collagen deposition [5].

EIS can be applied to monitor wound healing by using electrodes placed on the surface of the wound or around its perimeter. These electrodes measure the impedance of the tissue at various frequencies, and changes in the impedance spectra are analyzed to evaluate the stages of healing [2]. EIS has been shown to be effective for tracking the progression of wound healing in both animal models and human patients [6]. Electrical pulses are used to create precise wounds, and the healing process is continuously tracked in real time by measuring impedance variations over time with the Electric Cell-Substrate Impedance Sensing (ECIS) platform [7-9].

Mondal et al. presented continuous monitoring of wound healing processes using PS substrates with two distinct pore morphologies through impedance measurements. A distributed electrical model has been developed for the PS substrates to quantify the cell migration rate, proliferation rate, and the time-dependent coverage of the cell-free area. Impedance measurements and model analysis indicate that wound closure occurs most rapidly on 50 nm pores, followed by 500 nm pores, and then planar ECIS substrates. This observation has been qualitatively explained using a well-established mechanical model of wound healing, based on the extracted time-dependent cell-cell and cell-substrate interaction parameters. Figures 1 and 2 show the typical time course of normalized resistance and capacitance respectively at 4 kHz frequency when confluent HaCaT cells are wounded using an elevated electric pulse of 4V, at 40 kHz for 10 sec and also show the optical micrographs of substrates, depicting the cell recovery at approximately 9 hrs after wounding [10]. Keese et al. presented an electrical method for conducting wound-healing assays in tissue culture, which is applicable to some and potentially most cell lines. This approach provides highly quantitative data on cell migration within a relatively short time, requiring minimal labor and cell culture manipulation. Further research is needed to determine the nature of cellular injury caused by the elevated electrical fields and currents, as well as to compare the results of this assay with traditional mechanical wounding techniques. To investigate the fate of wounded cells, they conducted microscopic observations of cells on the active electrode both before and immediately after wounding. Additionally, we examined the cells several hours later, once impedance measurements indicated that the healing process was complete. Phase contrast micrographs of the MDCK Type II cell line are presented in Figure 3 [11]. A real-time, label-free clinical monitoring of skin wound healing have been carried out for regenerative medicine applications [12]. A nano-groove based impedance measuring device has been developed to mimic the internal extracellular matrix (ECM). Human Fibroblasts (HFF) and Human Keratinocytes (HaCaT) cells were cultured on these nano-grooves, with only HFF cells showing alignment along the grooves. During wound healing, both cell types exhibited increased normalized impedance (NI) values at characteristic frequencies of 977 Hz (HFF) and 1465 Hz (HaCaT). Compared to flat electrodes, nano-groove electrodes generated weaker impedance signals for HFF cell migration and proliferation, as well as for HaCaT cell migration, but stronger signals for HaCaT cell proliferation.

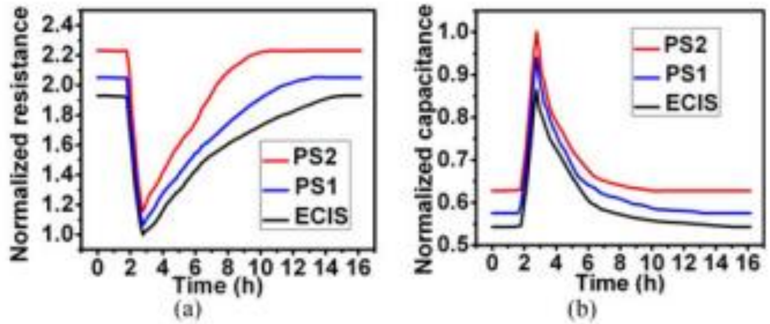

Figure 1 HaCat cells are wounded using an elevated electric pulse of 4V, at 40 kHz for 10 sec after confluence on different substrates (a) variation of normalized resistance with time at 4 kHz frequency (b) variation of normalized capacitance with time at 4 kHz frequency (Adapted from ref. [10]).

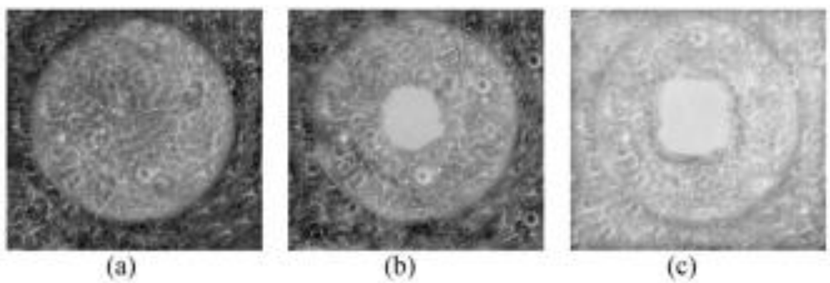

Figure 2 Optical microscopic image of cells on different substrates after 9 h of wounding (a) PS2, (b) PS1, (c) ECIS substrate (adapted from ref. [10]).

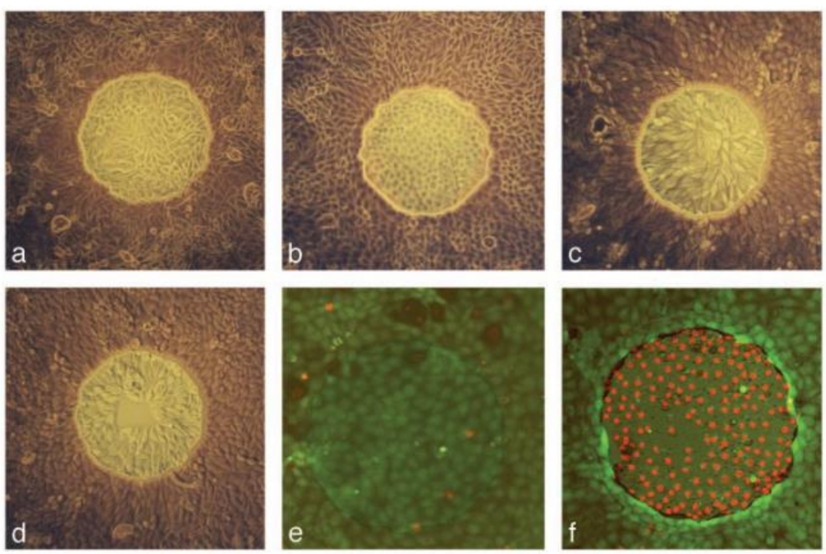

Figure 3 Photomicrographs of cells before and after wounding. (a–d) Phase contrast views of the ECIS electrode (250-µm diameter) with MDCK cells before wounding (a), immediately after wounding pulse (b), and 20 h after wounding (c and d). The wounding pulse was 2.5 V at 40 kHz applied for 30 sec (e and f) Vital staining of NRK cells on the ECIS electrode (250-µm diameter) before and after the elevated field pulse, respectively. The wounding pulse was 3 V at 40 kHz applied for 10 sec (Adapted from ref. [11]).

2.2 Impedance Plethysmography

Impedance plethysmography involves the measurement of changes in electrical impedance in response to changes in tissue volume or blood flow [13]. This technique can be used to monitor the vascularization and perfusion of the wound site, which are crucial factors in wound healing. As the wound heals, increased blood flow and the formation of new blood vessels lead to changes in the impedance of the area, which can be detected by impedance plethysmography sensors

3. Challenges in Electrical Impedance Monitoring

While impedance sensing holds significant promise for wound healing monitoring, several challenges remain in implementing this technology in clinical practice.

3.1 Tissue Heterogeneity

One of the primary challenges in using impedance sensing for wound healing is the heterogeneous nature of biological tissues. Variations in tissue composition, including the proportion of extracellular matrix, water content, and cell type, can affect the impedance measurements [4]. These variations complicate the interpretation of impedance data, as different tissue types may exhibit similar impedance profiles despite having different healing conditions.

3.2 Signal Interference

Electrical impedance measurements can be susceptible to interference from external factors such as motion artifacts, electromagnetic interference, and changes in temperature [5]. These sources of noise can lead to inaccurate readings and affect the reliability of impedance-based monitoring systems. Proper calibration and filtering techniques are necessary to minimize these effects.

3.3 Standardization and Calibration

Another challenge is the lack of standardized protocols for impedance measurement in wound healing. Variations in electrode placement, frequency range, and measurement conditions can lead to inconsistent results across different studies and clinical applications [13]. A unified approach to impedance measurement and data interpretation is needed to ensure the reproducibility and reliability of results.

4. Future Directions

The integration of electrical impedance sensing with other emerging technologies offers exciting opportunities for advancing wound healing monitoring.

4.1 Wireless Impedance Sensing Systems

Wireless systems allow for continuous monitoring of wound healing without the need for direct physical contact. These systems can transmit impedance data to remote healthcare providers, enabling real-time assessment and early intervention if complications arise [6]. Pei et al. created a flexible, wireless electronic system for real-time, in-situ monitoring of the bio-impedance in wounded skin [14]. Wireless impedance sensors that are flexible and biocompatible are being developed for use in clinical settings.

4.2 Machine Learning and Artificial Intelligence

Machine learning algorithms can be used to analyze the large amounts of data generated by impedance sensing systems. By identifying patterns and correlating impedance measurements with clinical outcomes, these algorithms can improve the accuracy of wound healing assessments and provide personalized treatment recommendations [1]. Furthermore, artificial intelligence can help in the development of predictive models for chronic wounds, facilitating proactive management and reducing the risk of complications.

4.3 Multimodal Monitoring

Combining impedance sensing with other monitoring techniques, such as optical coherence tomography (OCT), infrared thermography, and ultrasound, could provide a more comprehensive view of the wound healing process [5]. Multimodal systems could offer complementary insights into different aspects of wound healing, such as tissue oxygenation, blood flow, and cellular activity.

5. Conclusion

Electrical impedance sensing has shown great potential as a non-invasive and real-time method for monitoring wound healing. While significant progress has been made in developing impedance-based monitoring techniques, several challenges remain, including tissue heterogeneity, signal interference, and the need for standardization. Future advancements in wireless sensing, machine learning, and multimodal monitoring systems are expected to overcome many of these challenges, making impedance sensing a valuable tool for clinical wound management. Continued research and development in this field will help improve patient outcomes by enabling more accurate and timely assessments of wound healing.

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