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Reliability analysis of a mini-instrument for simultaneous monitoring water content, deep tissue temperature, and hemodynamic parameters

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ABSTRACT

Autoimmune diseases, congenital genetic diseases, cancer and other diseases originated by immune or genetic problems threaten public health. Gene/cell therapy is a highlighted potential method for the treatment of these diseases. But it causes cytokine storm, which probably triggers multiple organ failure, acute respiratory distress syndrome and so on. In this work, a novel device for monitoring multiple physiological parameters response to cytokine storm is designed. Some measures are taken to make custom device have better sensitivity, specificity and robustness, including utilization of twisted-pair line, design of 50 Hz trap filter, and utilization of voltage follower. Several reliability tests of this device are conducted, which includes sensitivity test, stability test and pre-clinical experiments. The results of these reliability tests demonstrate that custom device has good sensitivity, stability and reliability and potential for measuring human physiological parameters.

1. Introduction

Autoimmune diseases, congenital genetic diseases, cancer and other diseases originated by immune or genetic problems threaten public health. Nowadays, these diseases have become main causes of death, and both of their morbidity and mortality are still rising [1].

Gene/cell therapy is a highlighted potential method for the treatment of these diseases [2–4]. Immune cell can kill pathological cell and release a lot of cytokines and different kinds of antigen proteins, at the same time. Soon, more immune cells will be activated by the particular substance to attack these pathogens together. An excessively large amount of cytokines are produced in an instant. This is a positive feedback to ensure us an efficient immune system. But the strong immune response may cause adverse consequence, the so-called cytokine storm, because the process is too sensitive and fast. Cytokine storm probably trigger multiple organ failure, acute respiratory distress syndrome and so on [5]. Absence of effective monitor and early warning can usually lead to rescue failure. Therefore, monitor and early warning is an indispensable part of the gene/cell therapy.

The current method for cytokine storm monitoring is to measure a patient's heart rate, respiration, and pulse oximetry by a multi-physiological parameter monitor. However, these parameters cannot effectively assess the intensity of cytokine storm. Under the current conditions, fever, edema and shock, these main symptoms are difficult to be measured, which happen when a cytokine storm occurs [6]. In addition, patient who is in the gene/cell therapy is usually in bad health, especially poor cardiopulmonary function. In such critical condition, patient cannot afford uncomfortable especially invasive monitoring in a long time. The current detection of shock mainly relies on invasive and complicated operation (central venous catheterization), which cannot real-timely monitor central venous oxygen saturation in real time. For the judgment of fever, doctor is required to operate the thermometer, but only the temperature of surface body can be measured. Recently, researchers used near infrared spectroscopy to study the physiological and pathological parameters associated with cytokine storm, including edema [7], tissue temperature [8–10] and so on [11–14], and achieved some results [15–20].

In this study, we develop a system to monitor important physiological parameters related to cytokine storms [21–24]. Its advantages include noninvasion, real time, continuity and simplicity of operation, and the monitor can work not only at conventional intensive care unit, but also at conventional ward or home. Custom device adopts near-infrared spectroscopy to monitor cytokine storm in real time. Measured physiological parameters include tissue oxygenation, shock status,

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degree of edema/water content, and temperature of lesion.

In this study, we discussed the reasons that may cause the reliability of custom device decline, and measures we took to reduce the adverse effects. Also, we implemented a sequence of performance experiments to examine the reliabilities, including sensitivity test, stability test and pre-clinical trial.

2. Method and experimental design

A. Device design

Custom device consists of five parts, including control module, detection module, signal preprocessing module, memory module and power module. Control module is used for controlling of each modules and processing data. Its function mainly includes: generating sampling control signals, which are used for enabling detectors for different tissue areas and light sources with different wavelengths, analyzing and processing data, data transmission controlling. Detection module can be divided into two parts, probe and probe drive circuit. The probe mainly consists of photo-detector array for detecting the attenuation of reflected light from body tissues, and multiple wavelength integrated near-infrared light sources. The wavelength of the light source is in the range of 650–1000 nm. The distance between light source and detector is 20 mm to 40 mm. Modified Beer-Lambert's law and mixed Monte Carlo method are used to convert electronic signal of detector into physiological signals related to the cytokine storm, such as blood oxygen content, concentration and temperature of tissue water. The function of Probe drive circuit is driving light source and enabling photo detector. The signal preprocessing module can change the analog signal from detectors into digital signal, transfers the signal in each module (Fig. 1).

B. Measures to improve the stability of custom device

Some measures are taken to make custom device have better sensitivity, specificity and robustness. As the detection signal is very weak, it is susceptible to external electromagnetic interference. In addition, custom device needs to measure multiple physiological parameters simultaneously, that is, multiple measurement channels need to work at the same time. Crosstalk between channels reduces the performance of custom device. Moreover, the power supply lines and analog-digital converter will bring greater electromagnetic interference to custom device.

Crosstalk is caused by the close and parallel transmission wires. False triggering of the circuit may be caused by excessive crosstalk. It easily occurs in bundled connector, PCB parallel wires and multi-core cable. The voltage change of aggressor will produce induced current in victim in spite of electromagnetic interaction. Generally, circuit capacitance, mutual inductance and circuit impedance decide the intensity of crosstalk, which are affected by the distance between single lines, the length of wire, the structure of signal lines and so on. The longer distance between signal wires, and the shorter wire length will effectively reduce crosstalk. Therefore, we use a twisted-pair line to reduce the noise due to crosstalk. One of the twisted pairs is the signal line, and the other is grounded. Coupling capacitance and coupling inductance can be greatly reduced by this means.

50 Hz AC for supplying power will also produce electromagnetic interference to the signal. Therefore, we filter the signal before it is analog-to-digital converted. As the frequency of current in power line is fixed, 50 Hz. The noise can be effectively reduced by 50 Hz trap filter. In addition, we designed a voltage follower between analog-to-digital converter and signals. Because the analog-to-digital converter samples the analog signal by scanning voltage, and custom device works at a high scanning frequency, ground capacitor of analog-to-digital converter cannot fully discharge. It makes electromagnetic interference to the signal. The voltage follower can reduce the equivalent resistance to reduce noise.

C. Reliability experiment design

Several experiments are designed to evaluate the reliability of custom device. Sensitivity and stability of the device are analyzed. Especially, pre-clinical experiment is designed to verify the potential and benefits of this device in clinical applications.

1) Sensitivity test

Returned light signal of the highly scattering solution that is gradually added to the light-absorbing solute is detected to verify the response of custom device to different absorption rate of the solution. In the experiment, a fixed proportion of fat emulsion and phosphate buffer solution are added to simulate the human tissue environment, and to provide a higher degree of scattering environment, in order to facilitate the system to detect the return light signal. We increase the light absorption rate of the solution gradually, and use the probe of custom device to collect return light signal. Then we observe and calculate the response time, sensitivity, linearity of the system to external changes, and the consistency of each wavelength response to the same change (Fig. 2).

2) Stability test

Custom device is designed as a monitoring equipment, which should work continuously in a long time during practical applications.

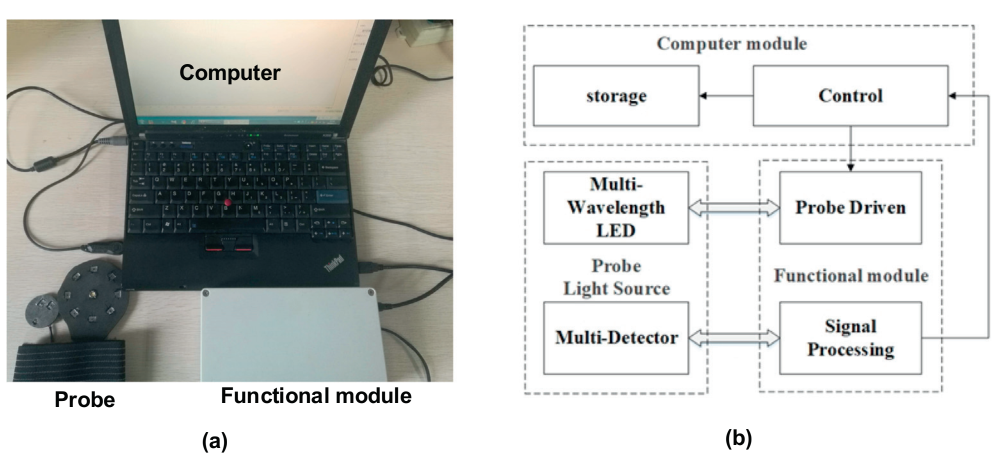

Fig. 1. Device design. (a) Real products; (b) Structure chart.