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Calibration Method of Biochip Temperature Sensors

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Abstract. Currently, a microanalysis technology is employed in detection systems in fields such as medical science, food safety, and environmental monitoring, and it is being developed in the form of a lab-on-a-chip. However, the reproducibility and sensitivity of biochips are essential factors for its commercialization. Because this requires accurate temperature control, there should be no errors in the temperature sensor used for the biochip. This paper proposes a method that can calibrate the temperature sensor in an accurate and efficient manner.

Keywords: Biochip, Temperature calibration, Temperature sensor.

1 Introduction

Biochips can obtain information regarding multiple genes within a short period of time, and this enables the analysis of the gene. Further, biochips are used to diagnose various diseases based on reactions with components inside the body of a target person to be examined.

The commercialization of biochips requires them to be reliable in terms of their reproducibility and sensitivity, and therefore, accurate temperature control and calibration of the biochip's temperature sensor are required. To realize temperature control, a heater and a temperature sensor are usually attached to the surface on which the DNA is amplified [1-4]. For this, the biochip is equipped with various temperature sensors such as a metal film, a thermistor, and a thermocouple; however, a calibration method has not yet been reported. An example of a calibration method that can be employed for the biochip temperature sensor involves placing the biochip in a constant-temperature water bath and measuring the resistance and voltage of the temperature sensor against fundamental temperatures in each application. However, in the case involving the constant-temperature water bath, there is a problem with the long calibration time required by the biochip temperature sensor as the temperature of the constant-temperature water bath changes slowly. Therefore, in this paper, we propose a calibration system and a method that calibrates the biochip temperature sensor by measuring the surface temperature of the biochip using a biochip temperature sensor and a precision temperature sensor.

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2 Materials and Methods

Figure. 1 is a block diagram of the biochip calibration system and the quick response (QR) code recognition system. The biochip driving mechanism has a microprocessor (local system processor), and it controls or monitors each component of the biochip via a peripheral interface. For example, the temperature sensor is converted to a digital sensor using the analog-to-digital converter (ADC) of the microprocessor. The electric power for the heater is controlled through a pulse width modulation (PWM) device. The polymerase chain reaction (PCR) chip driving mechanism is connected to the PC using a USB interface. The PCR driving mechanism and the PCR chip interface are driven by distributing the USB power supply through power supply circuits within the driving mechanism.

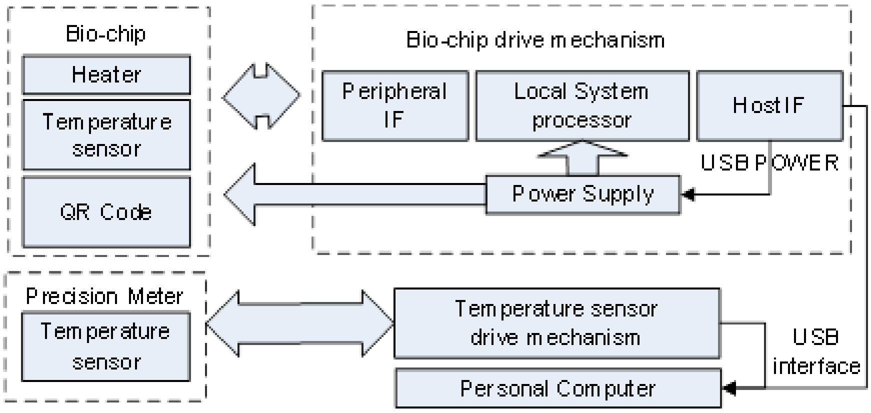

Fig. 1. Block diagram of biochip calibration system and QR code recognition system.

The speed of the biochip used in this paper is measured as 10℃ per second as it reaches 95℃ from the room temperature. The temperature is measured by heating the biochip and shifting to a temperature range that is important for each application. Then, the ADC value is sent to the PC from the thermistor that is attached to the biochip, and in the process passing the biochip driving mechanism. The precision measurement device measures the biochip temperature at an important temperature for each application as it is attached to the surface of the biochip. The measured value is sent to the PC through the precision sensor driving mechanism. The PC compares the biochip temperature sensor value and the temperature value that has been sent from the precision measuring sensor, and it records the value of the calibration factor. The value of the calibration factor can be stored or recorded using various methods, which include saving it as a file or saving it as a QR code. This paper uses the QR code because embedding the calibration value in each biochip significantly increases user convenience. This is because a different calibration value should be applied for each biochip, which contains the corrected information, when a user uses the biochip. To store the calibration value on the biochip, both ROM and flash memory can be used, but they are much more expensive than using the QR code printed on paper. The PC prints out the calibration value on the paper using the QR code, and the printed QR code is attached to the biochip. When the user uses this biochip, a biochip controller uses a webcam (SDC-100) to capture the attached QR code, and the captured images are sent to the PC. Then, the image delivered to the PC is converted to a calibration parameter by the QR code decoder.

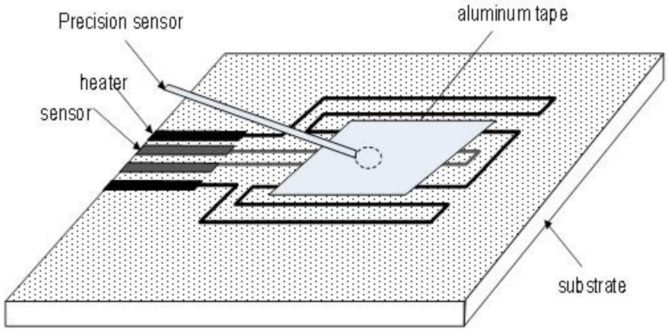

Fig. 2. Precision sensor attached to the biochip surface.

Figure. 2 shows the precision sensor attached to the surface of the biochip using an aluminum tape to calibrate the biochip. Here, the aluminum tape is used because it is easy to transfer the heat. When the ADC value is sent to the PC from the thermistor attached to the biochip, using the biochip driving mechanism, Eq. (1) is used to calculate the temperature value.

$$T^{-1} = A + B \cdot \ln R + C \cdot (\ln R)^3 \qquad (1)$$

In Eq. (1), A, B, and C are Steinhart–Hart coefficients, and R represents the measured resistance value of the thermistor. To solve the Steinhart-hart coefficient (A, B, C), we need the resistance and temperature values of each three section. To set the temperatures for the three sections, we apply the temperature used in the process that amplifies the DNA. A 3-step process and a 2-step process are usually used to amplify the DNA. In the case of the 3-step process, sections of 92–96℃ (denaturing), 50–65℃ (primer annealing), and 72℃ (primer extension) are used, and in the case of the 2-step process, sections of 92–96℃ (denaturing) and 50–65℃ (primer annealing) are used. Here, the Steinhart–Hart coefficient is solved using the temperatures of the three sections (60, 72, 95) to calibrate the temperature sensor. The Steinhart–Hart coefficient can be solved using a cubic equation after substituting the standard temperatures provided in the data sheet (T1, T2, T3) and resistances corresponding to the standard temperatures (R1, R2, R3) in Eq. (1).

$$R = \exp\left(\sqrt[3]{\beta - \alpha} - \sqrt[3]{\beta + \alpha} \right), \quad \text{where } \alpha = \frac{A - \frac{1}{T}}{2C} \text{ and } \beta = \sqrt{\left(\frac{B}{3C}\right)^3 + \alpha^2}. \qquad (2)$$

Upon completion of the calibration, it is finally saved as the Steinhart–Hart coefficient, and it is printed out as the QR code. The QR code output is attached to the biochip surface.

3 Calibration Accuracy Evaluation

To evaluate the precision of the calibration system before the calibration, the same basic Steinhart–Hart coefficient was used. When the basic Steinhart–Hart coefficient is used, there was an error of temperature (±0.4℃), and the average error for the temperature measurement is about 0.161℃. Using for each chip calibrated the Steinhart–Hart coefficient for each chip, there was an error of temperature (±0.1℃), and the average error for the temperature measurement is 0.037℃. Therefore, the proposed calibration system improves the accuracy and reduces the calibration time.

4 Conclusion

We In this paper, we proposed a system that calibrates the temperature sensor of the biochip by directly heating the biochip and using the difference between the measured values of the temperature sensor attached to the biochip and the precision temperature sensor on the biochip surface. In addition, directly heating the biochip was observed to shorten the time taken to reach the target temperature, compared to the chip calibration by placing it in the constant-temperature water bath. The shortened calibration time of the biochip enables us to realize reduced production cost when the chips are manufactured on a large scale.

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