Failure Prediction of Polymerase Chain Reaction Thermal Cycler

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Abstract. In this paper, we predict the aging of the PCR thermocycler by analyzing the heating and cooling rates of the PCR thermocycler. Two kinds of methods were applied to calculate the rise times of the heating and cooling protocol sections that were inversely related to the heating or cooling rates. The temporal changes of the rise times were investigated over several months. For three thermal cyclers with different structures, the increases of the rise times were fairly linear indicating the feasibility of the aging measurement.

Keywords: PCR thermal cycler, maintenance, aging, failure.

1 Introduction

Equipment management is performed by corrective maintenance (CM) and by periodic preventive maintenance (PM) before the failure [1–7]. The development of the internet of things (IoT) technology allows even low-cost equipment to send sensor data to the cloud, changing the paradigm of equipment management [7]. It is possible to perform health monitoring and prognosis of the equipment by gathering and analyzing in the cloud with health information of the equipment such as equipment environment, equipment operation and maintenance data [2]. The development of this technology will enable even the most costly visiting maintenance to be carried out at the manufacturer's office, and the automatic inspection will also be possible through the development of big data analysis technology.

This paper attempts to extract information on aging from sensor data of a typical biochemical polymerase chain reaction (PCR) thermal cycler. PCR is a molecular biological technique that replicates and amplifies a desired portion of DNA. In PCR, two strands of DNA are separated by the application of heat in denaturation and at a low temperature, the primer is annealed to the sequential terminal for amplification, and at slightly higher temperature, the DNA is synthesized—this process is called polymerization or extension. The temperature of the PCR reagent is usually adjusted by adjusting the temperature of the aluminum block where the tube containing the reagent is inserted. Several methods have been developed for controlling the temperature of the aluminum block, but Peltier is the mainstream. The performance of the PCR thermal cycler is almost dependent on the heating and cooling rates of the
aluminum block, so that the aging or failure can be predicted by measuring them [10, 11].

In this paper, the data of the temperature sensor, that is installed to control the temperature of the Peltier, were stored and analyzed for several months. In the temperature profile, the rise and fall intervals are separated and the rise time, which is inversely proportional to the temperature ramping speed, is calculated for each interval. Generally, the rise time is calculate from the difference between 10% and 90% arrival times of the temperature change [12, 13]. However, the measurement time can be jittered for various reasons and the measured temperature is exposed to intrinsic noise. These two factors of variation can make the estimated rise time inaccurate. This can be more accurately estimated by calculating the width of the derivative function of the temperature change [12]. In this paper, we showed that the aging of PCR thermal cycler could be predicted by analyzing the rise time and temperature change rate measured by these two measurement methods.

The second section describes the PCR thermal cycler and the calculation method of the rise time, and the experimental results and the conclusions are presented in the third and fourth sections, respectively.

2. Materials and Methods

In this study, we tested three thermal cyclers with similar structure but different heat dissipation structure and version. They are products of the same company and have proven PCR performances. In this paper, we have analyzed the temperature regulation speed for several months for all three devices.

In order to measure the rate of temperature regulation of the PCR thermal cycle, we used a simplified protocol that modified from the thermal cycling protocol used for PCR. The heating and cooling rates were calculated from the start to the target temperature between 10% and 90% of the temperature difference. In this paper, we analyze only two intervals: one is from 50 to 95 degrees, and the other is from 95 to 50 degrees.

Generally, the rise time of the step response is calculated as difference between the start and end time of each interval. However, since there will be fluctuation due to noise at the measurement temperature and measurement time, it can be estimated by the width of the derivative function of the step response. The width of the function is obtained by the second order moment [3].

$$t_r = \frac{\int (t - m)^2 e'(t) dt}{\int e'(t) dt}, \quad m = \frac{\int te'(t) dt}{\int e'(t) dt}. \quad (1)$$

Where $t_r$ and $e'(t)$ are the rise time and the derivative of the step response $e(t)$, respectively.
The two methods of finding the rise time are named 'direct difference' and 'derivative width', respectively, hereafter. As the equipment ages, it is expected that the rate of heating and cooling will decrease, so the rise time is expected to increase. The change of rise time for each device was investigated by linear regression. If the coefficient of determination of the regression is close to 1, we can predict the aging by the method proposed in this paper.

3 Results

In the all experiments, since the rise time obtained by 'direct difference' was 3.5 times higher than the value obtained by 'derivative width', the latter was 3.5 times. Both methods showed almost the same values, but in the following results, the rise time was obtained by the derivative width method.

In this study, the heating performance decreased more rapidly than the cooling performance. This trend was common to the three devices indicating that the heating performance was degraded faster. The rise time increases for three thermal cyclers showed strong linearity. The slope and the coefficient of determination $R^2$ were compared when fitting the line to the rise time change trend for heating and cooling of each equipment. $R^2$ was more than 0.84 and especially was more than 0.90 for heating interval. The increase rate of rise time was $0.24 \sim 0.31$ for heating and $0.08 \sim 0.09$ for cooling, and the relative deviation was about 11%.

From the above, it could be seen that the increase tendency of the rise time was very linear and the change of rise time about heating was larger. Also, it was found that even if the structures of the equipment were different, the slopes were similar. In reality, the failure of the device was related to the success of the PCR, but the longer the rise time, the longer the PCR execution time. Therefore, the magnitude of the rise time itself was closely related to aging and failure.

A simple method of finding the difference between 10% and 90% arrival time gave almost the same results as using a statistical method to reduce the influence of noise. It was interpreted that the temperature measurement error of the equipment used in the experiment was relatively small.

3 Conclusions

In this paper, we analyzed the heating and cooling time of PCR thermal cycler over time to predict the aging of PCR thermal cycler. In the temperature profile, the heating and cooling sections were separated and the rise time of each section was measured and tracked for several months. Rise time increased linearly regardless of heating and cooling and increased faster for heating. Using this, we could predict the aging and failure of PCR thermal cycler.

When all the devices are connected to the cloud, the sensor data abstraction method proposed in this paper can reduce the amount of data and the cloud will accommodate more equipment and sensors. But this approach should be carefully adopted because of losing the detail.
In this paper, we use the sensor data which is essential for the operation of the equipment to extract the aging information. However, the same data abstraction methodology can be applied to the sensor data added for the purpose of equipment management.

References