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Enhancement of Thermal Uniformity for a Microthermal Cycler and Its Application for Polymerase Chain Reaction

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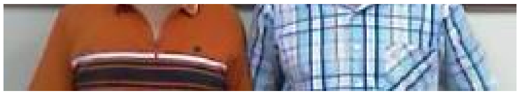
The trend of miniaturization of biomedical instruments began in the last century, and is crucial for furthering progress in medical technology. In this study, an integrated chip–PCR/RT-PCR system is implemented successfully, meeting the requirements for use in miniature thermocyclers – small in size, low power consumption, high heating and cooling rates, and even portability, with resistance temperature detectors and thin-film micro-heaters. Furthermore, due to the modifications made to the micro thermocycler, the thermal uniformity of a specific region has been greatly enhanced, improving the performance of the micro device.

The initial approach of this study was to develop a block-type thin-film micro-heater and resistance temperature detectors on a glass substrate to form a micro thermocycler. Based on the techniques of feedback control and pulse width modulation, PCR thermal cycling was achieved. A new approach was then implemented and applied to increase DNA amplification efficiency and reduce non-specific PCR products. In order to achieve these aims, first, a novel kind of micro thin-film heater, an array-type micro-heater, was designed and developed. The main advantages of array-type micro-heaters are their lower resistance as compared with block-type heaters and their provision of greater thermal uniformity with a uniform heating density. Active compensating (AC) units were also added and applied in order to reduce the edge-effect, i.e., thermal loss from the edges. From these array-type micro-heaters and active compensating units, a miniature thermocycler with enhanced thermal uniformity was developed and the success of its performance verified with S. *pneumoniae*.

The SEM image of the array-type micro-heater with active-compensating units is shown in figure 1. This new approach using on micro thermocycler is based on technique of micro-lithography with two thin-film metals, including of gold and platinum. According to the difference of conductivity, the array-type micro-heater was formed by these two metals. For reducing the thermal loss from the edges, active –compensating units are added, shown in figure 1. Figure 2



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shows the block-diagram of the AC-PCR system, consisted of a thermocycle controller and a PCR chip. This PCR thermocycle controller manages the functions on the PCR chip and forming two feedback loops to precisely control the temperature.

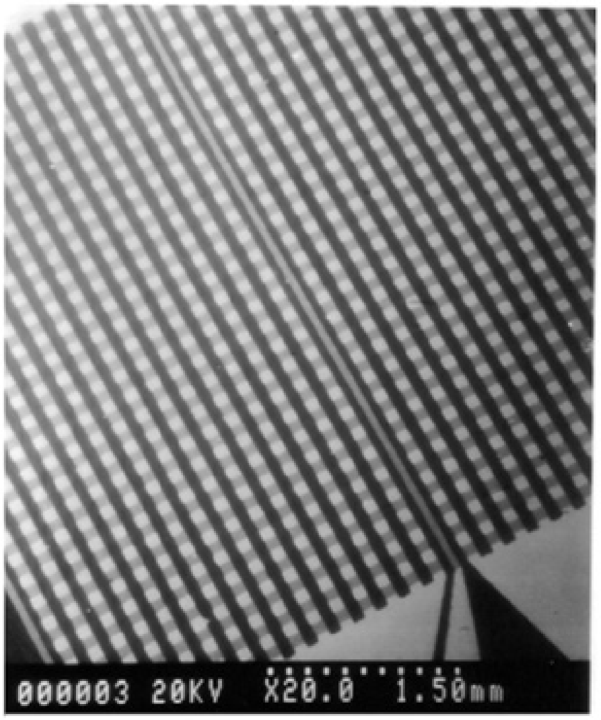

Figure 1 SEM image of active-compensating PCR device.

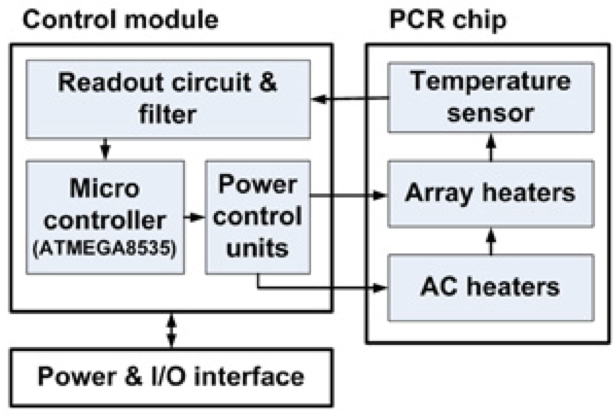

Figure 2 The block-diagram of AC-PCR system

In practical applications, PCR thermocyclers that provide a high cooling rate can significantly reduce the total reaction time; therefore, fans or heat sinks are commonly used for the enhancement of thermal convection or conduction. Figure 3 shows the performance of this new micro-thermocycler with infrared imaging and compared with a common designs on micro-heaters- block-type micro-heater. Besides, the thermal uniformity of block-type micro-heaters with AC units is compared at the same time. This figure presents the 2-D and 3-D temperature profiles for each micro thermocycler equipped with a heat sink operating at a denaturing temperature (94℃). The array-type micro-heater with AC units provided a better thermal uniformity than the block-type micro-heaters. Table 1 lists the percentages of the total area at a uniform set point temperature for three types of micro-heater with heat sinks. Experimental results from infrared images showed that the percentage of the uniformity area with a thermal variation of less than 2℃ was 66.9%, 92.3% and 74.0% at PCR thermocycling temperatures of 94℃, 57℃ and 72℃, respectively, which represents a significant improvement over conventional block-type micro-heaters.

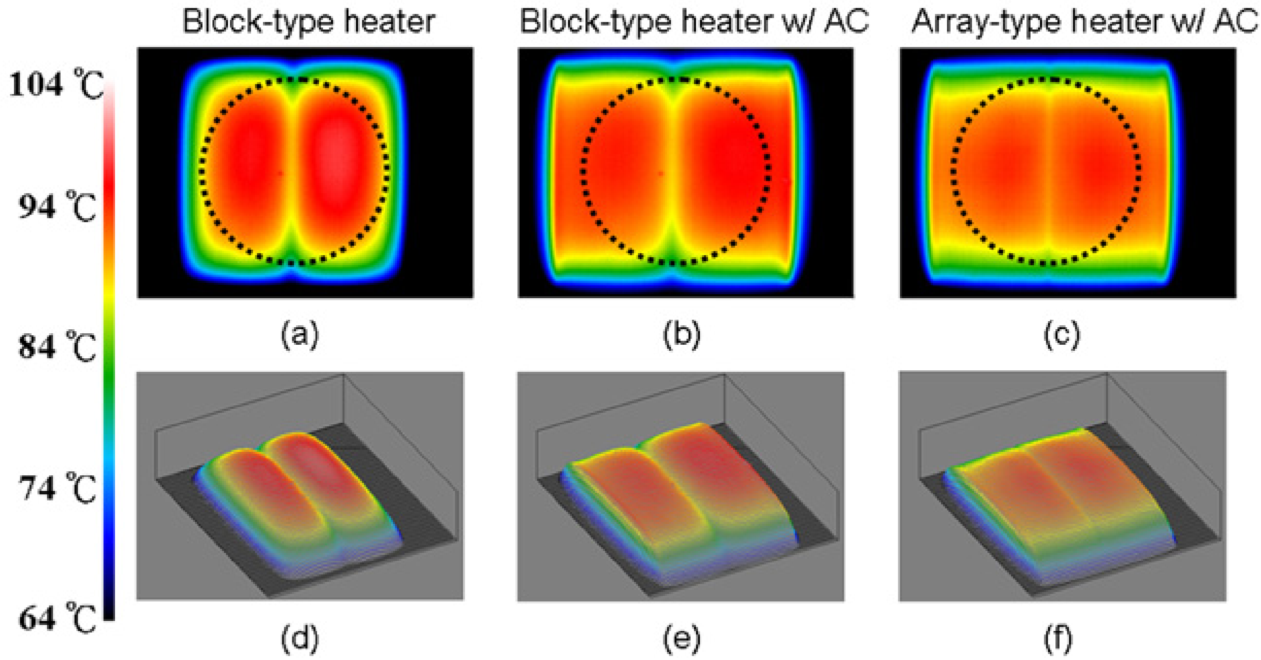

Figure 3 IR images of each microthermal cycler equipped with heat sinks at a denaturing temperture.(a) 2-D temperature profile of the block-type microheaters.(b)2-D temperature profle of the block-type microheaters with AC units. (c)2-D temperature profile of the array-type microheaters with AC units. (d) 3-D temperature profile of the block-type microheaters. (e)3-D temperature profile of the block-type microheaters with AC units. (f)3-D temperature profile of the array-type microheaters with AC units. (The IR image has 320*240 pixels and the resolution of each pixel is 29 μ m. The dotted line shows the location of the PCR reaction chamber.)

Conclusion

This study reported the development of an array-type micro thermocycler with active compensation to enhance the thermal uniformity inside the chemical reaction chamber, which is crucial for micro reactors that require precise control of a critical reaction temperature. Due to this new design, the thermal uniformity inside the reaction chamber was significantly improved without the need for a complicated fabrication process and delicate controllers. The performance of the new chip–PCR system was verified by amplifying a detection gene associated with the detection of S. *pneumoniae* using a PCR process.

Table a. Comparison of the themal uniformity when using a heat sink to improve the cooling rate.

	Uniform area (%)	
94°C	±1°C	±2°C
block w/o AC	20.8	41.1
block w/ AC	34.1	53.8
array w/ AC	41.9	66.9
72°C		
block w/o AC	41.0	60.7
block w/ AC	47.4	68.9
array w/ AC	59.4	74.0
57°C		
block w/o AC	58.7	81.6
block w/ AC	67.2	86.1
array w/ AC	77.8	92.3