

[0221] Referring to FIGS. 27A and 27B, an exemplary PCR reaction chamber 1001 in a microfluidic substrate, typically a chamber or channel having a volume $\sim 1.6 \mu\text{l}$, is configured with a long side and a short side, each with an associated heating element. A PCR reaction chamber may also be referred to as a PCR reactor, herein, and the region of a cartridge in which the reaction chamber is situated may be called a zone. The heater substrate therefore includes four heaters disposed along the sides of, and configured to heat, a given PCR reaction chamber, as shown in the exemplary embodiment of FIG. 27A: long top heater 1005, long bottom heater 1003, short left heater 1007, and short right heater 1009. The small gap between long top heater 1005 and long bottom heater 1003 results in a negligible temperature gradient (less than 1°C . difference across the width of the PCR channel at any point along the length of the PCR reaction chamber) and therefore an effectively uniform temperature throughout the PCR reaction chamber. The heaters on the short edges of the PCR reactor provide heat to counteract the gradient created by the two long heaters from the center of the reactor to the edge of the reactor.

[0222] It would be understood by one of ordinary skill in the art that still other configurations of one or more heater(s) situated about a PCR reaction chamber are consistent with the methods and apparatus described herein. For example, a 'long' side of the reaction chamber can be configured to be heated by two or more heaters. Specific orientations and configurations of heaters are used to create uniform zones of heating even on substrates having poor thermal conductivity because the poor thermal conductivity of glass, or quartz, polyimide, FR4, ceramic, or fused silica substrates is utilized to help in the independent operation of various microfluidic components such as valves and independent operation of the various PCR lanes. It would be further understood by one of ordinary skill in the art, that the principles underlying the configuration of heaters around a PCR reaction chamber are similarly applicable to the arrangement of heaters adjacent to other components of the microfluidic cartridge, such as actuators, valves, and gates.

[0223] Generally, the heating of microfluidic components, such as a PCR reaction chamber, is controlled by passing currents through suitably configured microfabricated heaters. Under control of suitable circuitry, the lanes of a multi-lane cartridge can then be controlled independently of one another. This can lead to a greater energy efficiency of the apparatus, because not all heaters are heating at the same time, and a given heater is receiving current for only that fraction of the time when it is required to heat. Control systems and methods of controllably heating various heating elements are further described in U.S. patent application Ser. No. _____, filed Nov. 14, 2007 and entitled "Heater Unit for Microfluidic Diagnostic System".

[0224] In certain embodiments, each heater has an associated temperature sensor. In the embodiment of FIG. 27A, a single temperature sensor 1011 is used for both long heaters. A temperature sensor 1013 for short left heater, and a temperature sensor 1015 for short right heater are also shown. The temperature sensor in the middle of the reactor is used to provide feedback and control the amount of power supplied to the two long heaters, whereas each of the short heaters has a dedicated temperature sensor placed adjacent to it in order to control it. As further described herein, temperature sensors are preferably configured to transmit information about temperature in their vicinity to a processor in the apparatus at

such times as the heaters are not receiving current that causes them to heat. This can be achieved with appropriate control of current cycles.

[0225] In order to reduce the number of sensor or heater elements required to control a PCR heater, the heaters may be used to sense as well as heat, and thereby obviate the need to have a separate dedicated sensor for each heater. In another embodiment, each of the four heaters may be designed to have an appropriate wattage, and connect the four heaters in series or in parallel to reduce the number of electronically-controllable elements from four to just one, thereby reducing the burden on the associated electronic circuitry.

[0226] FIG. 27B shows expanded views of heaters and temperature sensors used in conjunction with a PCR reaction chamber of FIG. 27A. Temperature sensors 1001 and 1013 are designed to have a room temperature resistance of approximately 200-300 ohms. This value of resistance is determined by controlling the thickness of the metal layer deposited (e.g., a sandwich of 400 \AA TiW/ $3,000 \text{ \AA}$ Au/ 400 \AA TiW), and etching the winding metal line to have a width of approximately 10-25 μm and 20-40 mm length. The use of metal in this layer gives it a temperature coefficient of resistivity of the order of $0.5\text{-}20^\circ \text{C}/\text{ohms}$, preferably in the range of $1.5\text{-}3^\circ \text{C}/\text{ohms}$. Measuring the resistance at higher temperatures enables determination of the exact temperature of the location of these sensors.

[0227] The configuration for uniform heating, shown in FIG. 27A for a single PCR reaction chamber, can also be applied to a multi-lane PCR cartridge in which multiple independent PCR reactions occur.

[0228] Each heater can be independently controlled by a processor and/or control circuitry used in conjunction with the apparatus described herein. FIG. 27C shows thermal images, from the top surface of a microfluidic cartridge when heated by heaters configured as in FIGS. 27A and 27B, when each heater in turn is activated, as follows: (A): Long Top only; (B) Long Bottom only; (C). Short Left only; (D) Short Right only; and (E) All Four Heaters on. Panel (F) shows a view of the reaction chamber and heaters on the same scale as the other image panels in FIG. 27C. Also shown in the figure is a temperature bar.

[0229] The configuration for uniform heating, shown in FIG. 27A for a single PCR reaction chamber, can be applied to a multi-lane PCR cartridge in which multiple independent PCR reactions occur. See, e.g., FIG. 28, which shows an array of heater elements suitable to heat a cartridge herein.

Heater Multiplexing (Under Software Control)

[0230] Another aspect of the heater unit described herein, relates to a control of heat within the system and its components. The method leads to a greater energy efficiency of the apparatus described herein, because not all heaters are heating at the same time, and a given heater is receiving current for only part of the time.

[0231] Generally, the heating of microfluidic components, such as a PCR reaction chamber, is controlled by passing currents through suitably configured microfabricated heaters. The heating can be further controlled by periodically turning the current on and off with varying pulse width modulation (PWM), wherein pulse width modulation refers to the on-time/off-time ratio for the current. The current can be supplied by connecting a microfabricated heater to a high voltage source (for example, 30 V), which can be gated by the PWM signal. In some embodiments, the device includes 48 PWM