MODELING AND DESIGN OF A MICROSCALE MULTIPLEXED TEMPERATURE CONTROL SYSTEM

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INTRODUCTION

Controlling the temperature of microfluidic sample volumes is essential for a wide domain of applications, including genetic sample preparation using the polymerase chain reaction (PCR) [1-3], cell lysis [4,5], protein denaturation [6], heat shock DNA transformation [7], enzyme reaction control [8], and numerous other chemical and biological procedures with temperature-dependent behavior. Inaccurate temperature control during thermocycling for PCR can diminish efficiency, yield non-specific products, and, in some cases, completely inhibit the reaction. Conventional methods based on thermoelectric devices are typically slow to transition between temperature setpoints, imprecise (e.g. +/- 1°C), and limited to a single temperature for all samples at a given time. Micro-fabricated integrated resistive heaters and temperature sensors [1,9] can achieve improved precision and ramping rates but at the cost of device complexity and surface fouling. A direct, non-contact approach to heating liquid samples with radiation has been demonstrated with simple fabrication requirements and fast ramping rates but performs at low throughput and limited control due to the nature of the broadband, incoherent source [2]. Others have implemented coherent radiation for temperature control of droplets via lasers and fluorescence-based temperature monitoring [10,11] but inconsistent sample size and position limit the system to serial processing of multiple samples.

The aim of this work is to develop a methodology and instrument for controlling the temperature of an array of microfluidic reaction chambers with independent, simultaneous control of individual samples. Optical and heat transfer modeling, precision positioning and fabrication, and an open loop control scheme are applied to produce compact instrumentation that will set new benchmarks for the performance and throughput of microfluidic genetic sample preparation. Here we present a proof-of-concept for this multiplexed temperature control system.

MODELING

To exploit the advantages of non-contact radiative heating using a laser source and any combination of sample medium and device substrate materials, we have developed a generalized modeling approach [12]. The method begins with determining the absolute radiation absorbed by the sample and surrounding substrate using spectral irradiance data for the laser source, device geometry, and material properties of the target sample. This calculation is then used as a heat generation input for a finite element model of the transient and steady state thermal response, as shown in Fig. 1a.

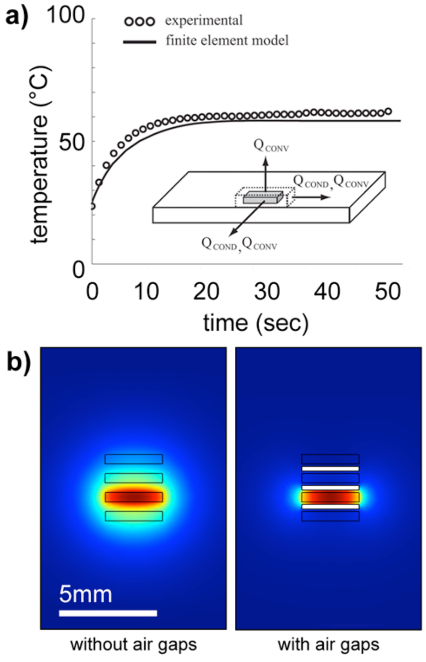

FIGURE 1. Optical and thermal modeling results for heating aqueous samples in microscale chambers. a.) Transient temperature profiles and b.) thermal crosstalk performance can be quickly and accurately assessed.

In addition to using the model for anticipating ramping rates and steady state temperatures, the simulation of thermal crosstalk is essential for confirming the viability of independent control of closely spaced samples. This motivated the addition of air gaps for better thermal isolation, shown in Fig. 1b.

INSTRUMENT DESIGN

Insights gained from the modeling informed the design of prototypes to validate the predicted heating performance and demonstrate a method of multiplexed temperature control. Since scalability is important for the utility of biological instrumentation, an open loop control scheme was devised to obviate the expense and tedium of embedded sensors.

To demonstrate open loop temperature control, a single-chamber prototype was built with an optical system consisting of a 1450nm laser diode, selected for the corresponding peak in absorption by water, coupled to a x-y adjustable collimating lens and aligned using a 30mm cage system. This translates vertically along cage rods and is aligned with a polymer microchip holder. A polymethyl methacrylate (PMMA) microchip was fabricated by micromilling and thermal bonding and is used to contain 1μL aqueous samples. An exploded diagram and photo of the prototype assembly can be seen in Figure 2.

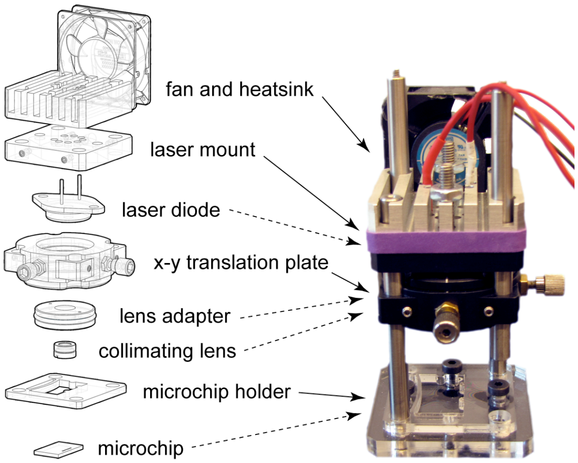

FIGURE 2. Diagram of the first prototype temperature control instrument (left) with the aligned set of optical and microfluidic components. The actual system (right) can be seen in its open configuration for removing or inserting the microchip.

The system was designed for precise and highly repeatable microchip positioning and laser heating as required by open loop operation. Microchip substrates were first lasercut to exact dimensions and fabrication is performed using a custom fixture aligned to a CNC machine with tools zeroed using electrical conductivity. The microchip holder features an integrated leaf spring and three contact points for full kinematic constraint. Tests performed with a microscope over five trials revealed a standard deviation of microchip position of 5.3μm, which results in no measurable difference in thermal response. The laser is equipped with a custom heat sink and fan for stable optical power output.

For calibration, a miniature thermocouple was inserted into the microchip to monitor sample temperature. The thermal response for a range of laser power inputs was then recorded. Using the laser driver's transfer function for converting control voltages to power output, a control sequence is written for the desired temperature setpoints of the experiment and parsed into a LabView program that executes the experiment.

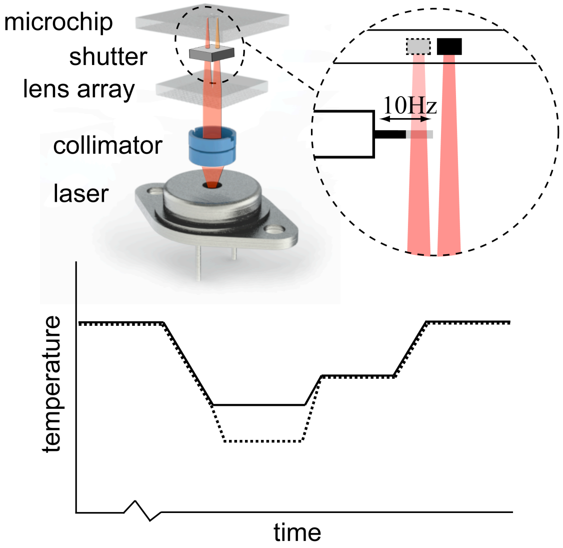

FIGURE 3. Diagram of the second prototype instrument (top) for dual chamber temperature multiplexing. A mechanical shutter operated at 10Hz is used to attenuate the radiation incident on one of the chambers (inset) to achieve independent temperatures, as shown in the representative temperature profile illustrating multiple steps in a thermocycling routine.

To demonstrate multiplexed temperature control, a second prototype was built to integrate a solenoid-driven mechanical shutter (Fig. 3). For this dual-chamber system, in addition to the software-driven modulation of the laser source, secondary modulation via the shutter attenuates the radiation incident on a sample that requires a temperature lower than the setpoint. For reliable optical modulation, the attenuation at a series of duty cycles will be characterized for each point in the calibration for a comprehensive mapping of desired temperatures and corresponding control voltages and duty cycles.

Preliminary results (Fig. 4) show that temperature differences beyond 15°C can be maintained between adjacent microscale sample chambers, with limited thermal crosstalk as predicted by the modeling.

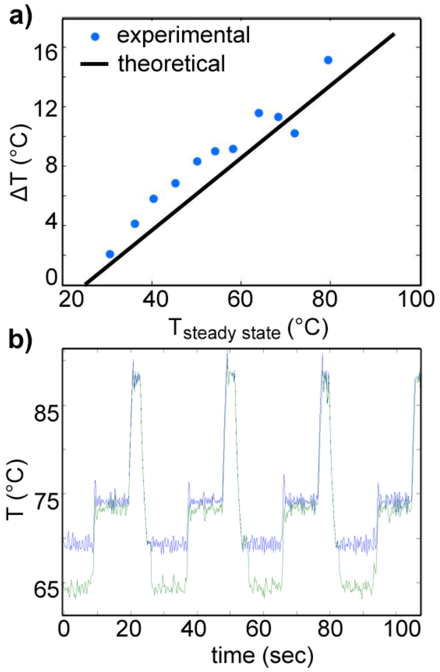

FIGURE 4. Experimental characterization of a dual-chamber temperature control system demonstrates the use of a microshutter to modulate laser radiation and achieve thermal multiplexing. (a) Temperature difference, or thermal crosstalk, ΔT, achievable between adjacent chambers vs. steady state temperature in one chamber, Tss. (b) Thermally-independent cycling measured in our prototype.

CONCLUSION

Combining optical and heat transfer modeling to simulate thermal response of any device with known material properties and a layout amenable to laser irradiation can guide the design and component selection for myriad applications that rely on temperature control, both existing and enabled by this technology. The simple fabrication requirements for the target device minimize cost while the coherent radiation with optical modulation maximizes the potential for thermal multiplexing to achieve higher throughputs and diversity of simultaneous conditions.

REFERENCES

[1] C.N. Liu, N.M. Toriello, R.A. Mathies, Multichannel PCR-CE microdevice for genetic analysis, Analytical Chemistry 78(15) (2006) 5474–5479.

[2] A.F.R. Huhmer, J.P. Landers, Noncontact infrared-mediated thermocycling for effective polymerase chain reaction amplification of dna in nanoliter volumes, Analytical Chemistry 72(21) (2000) 5507–5512.

[3] C.-S.J. Hou, M. Godin, K. Payer, R. Chakrabarti, S.R. Manalis, Integrated micro-electronic device for label-free nucleic acid amplification and detection, Lab on a Chip 7(3) (2007) 347–354.

[4] R.H. Liu, J. Yang, R. Lenigk, J. Bonanno, P. Grodzinski, Self-contained, fully integrated biochip for sample preparation, polymerase chain reaction amplification, and DNA microarray detection, Analytical Chemistry 76(7) (2004) 1824–1831.

[5] S.-W. Yeung, T.M.-H. Lee, H. Cai, I.-M. Hsing, A dna biochip for on-the-spot multiplexed pathogen identification, Nuclear Acids Research 34(18) (2006).

[6] A.W. Chow, Protein separations, in: Microchip Capillary Electrophoresis, (2006) 145–158.

[7] S. Li, L.M. Anderson, J.-M. Yang, L. Lin, H. Yang, DNA transformation via local heat shock, Applied Physics Letters 91(1) (2007) 013902–13903.

[8] Y. Tanaka, M.N. Slyadnev, A. Hibara, M. Tokeshi, T. Kitamori, Non-contact photothermal control of enzyme reactions on a microchip by using a compact diode laser, Journal of Chromatography A 894(1–2) (2000) 45–51.

[9] A. I. K. Lao, T. M. H. Lee, I. Hsing, N. Y. Ip, Precise temperature control of microfluidic chamber for gas and liquid phase reactions, Sensors and Actuators A: Physical, 84(1-2) (2000) 11-17.

[10] H. Terazono, A. Hattori, H. Takei, K. Takeda, and K. Yasuda, Development of 1480nm photothermal high-speed real-time polymerase chain reaction system for rapid nucleotide recognition, Japanese Journal of Applied Physics, 47(6) (2008) 5212.

[11] H. Kim, S. Vishniakou, and G. W. Faris, Petri dish pcr: laser-heated reactions in nanoliter droplet arrays, Lab on a Chip, 9(9) (2009) 1230–1235.

[12] C. R. Phaneuf, N. Pak, C. R. Forest, Modeling radiative heating of liquids in microchip reaction chambers, Sensors and Actuators A: Physical, In Press, Accepted Manuscript.