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Thermal modeling and design analysis of a continuous flow microfluidic chip

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ABSTRACT

Although microfluidics has demonstrated the ability to scale down and automate many laboratory protocols, a fundamental understanding of the underlying device physics is ultimately critical to design robust devices that can be transitioned from the benchtop to commercial products. For example, the miniaturization of many laboratory protocols such as cell culture and thermocycling requires precise thermal management. As device complexity scales up to include integrated electrical components, including heating elements, thermal chip modeling becomes an increasingly important part of the design process. In this paper, a computationally efficient, three-dimensional thermal fluidic modeling approach is presented to study the heat transport characteristics of a continuous flow microfluidic thermocycler for polymerase chain reaction (PCR). A two-step simulation model is developed, consisting of a solid domain modeling of the entire microfluidic chip that examines thermal crosstalk due to lateral diffusion across multiple thermal cycles, and a one pass simulation model to study the thermal profile in the fluidic domain as a function of critical parameters like flow rate and microchannel material. The results of the solid domain model are compared against experimental measurements of the thermal profile in a PDMS-glass microfluidic thermocycler device using a combination of thermocouples and an infrared (IR) camera. The suitability of the device in meeting the ideal thermocycling profile at low flow rates is established and it is further shown that higher flow rates lead to deterioration in thermocycling performance. Thermofluidic modeling tools have the potential to streamline the physical microfluidic device design process, reducing the time required to fabricate functional prototypes while maximizing reliability and robustness.

1. Introduction

Microfluidic systems have gained tremendous attention over the past two decades with regard to their potential to automate chemical and biological assays at a fraction of the cost and time of traditional benchtop research. Microfluidic chips enable the miniaturization of assays and offer the possibility of performing numerous experiments rapidly and in parallel, thus enhancing throughput and reducing the overall cost and consumption of reagents. Microfluidics has made important contributions to many biological and medical fields, including enzymatic analysis [1], DNA analysis [2], proteomics [3,4], nano-particle fabrication [5,6] and drug delivery [7].

Thermal control is a critical element of many biological and chemical assay systems, affecting processes like enzyme catalysis, hybridization between biomolecules (nucleic acids, proteins), and cell culture. Polymerase chain reaction (PCR) is one of the most commonly used biochemical reactions that requires precise thermocycling, making it a good choice for a model system to study spatiotemporal heat transfer in miniaturized diagnostic platforms such as microfluidic chips. Microfluidics and micro electromechanical systems (MEMS) offer several advantages for PCR over conventional thermocyclers, including faster thermal ramping rates [8–10], reduced sample volumes [9,11], disposability [12–14], portability [12,15], functional integration of sample preparation, and post-PCR product detection [8,16].

The history of microfluidic PCR devices dates back to 1993 when Northrup et al. [17] demonstrated the first silicon-based stationary chamber PCR device. Since then, continued efforts have been applied toward developing cheap, portable, reliable and on-field applicable microfluidic systems for PCR. In general, microfluidic thermocycling can be performed in two different ways: 1) stationary; heating and cooling reactants in the same chamber and 2) continuous flow; heating and cooling reactants as they move

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through channels having an imposed temperature distribution. Both types of architectures for microfluidic PCR have been previously developed and characterized by many research groups [18–20]. In the stationary chamber design, a micro or nanoliter chamber containing the PCR solution is cycled between different temperatures. In contrast, continuous flow-type PCR chips follow the 'time-space' conversion principle and typically consist of three independent, fixed temperature zones in space with the PCR sample continually flowing between them via a microchannel. There are several advantages of the continuous flow architecture over thermocycling within stationary chambers. Notably, temperature transition times are minimized as the thermal inertia of the system is minimized (with the only significant contribution due to the thermal mass of the sample), and, adjusting the flow rate of the samples, reaction volume can be scaled up from nanoliter to microliter scale volumes, making the system suitable for downstream diagnostic applications.

As chip device size decreases, thermal crosstalk becomes an important issue due to the temperature sensitivity of the reaction. A central challenge in using microfluidic systems for thermocycling applications is to quantify its thermal performance. Non-specific temperature profiles in the microfluidic chip can lead to inefficient reactions, and in some extreme cases, failed reactions. A comprehensive understanding of the heat transport mechanisms in the microfluidic device is critical for making functional parts [21–27].

Unlike momentum and species transport analysis, which are confined to the fluidic domain, thermal modeling in microfluidics presents some unique challenges [28–32]. The presence of thermal diffusion necessarily extends the modeling domain from the region of interest (*i.e.* the fluid domain) to encompass the material bounding the microchannels. In contrast to a macroscale system, where the fluid domain is often of comparable size to the solid regions, a microchannel system typically encompasses only a very small fraction of the substrate and thus heat transfer is significantly influenced by thermal diffusion process through the solid regions that may lead to thermal crosstalk. Taking the millimeter-scale physical dimensions of microfluidic chips into consideration, with temperature gradients generated by proximal or embedded heating elements, a conjugate, three-dimensional model becomes necessary to completely capture lateral thermal diffusion, which strongly affects the thermal profile in the fluid domain.

Three-dimensional conjugate heat transfer in microchannel flows has been well studied especially in the context of heat sinks. Earlier studies focused primarily on numerical implementation of the three-dimensional conjugate heat transfer equations, typically in a rectangular microchannel geometry extracted from a multichannel heat sink [33–36]. Recently, Nunes et al. [37] extended the understanding of heat sinks by developing a 2D model of parallel-plate microchannel geometry and comparing it with experiments. They showed that conjugate heat transfer and fluid axial diffusion leads to non-uniform local Nusselt number. Koşar [38] studied the effect of substrate thickness in straight microchannel heat sinks by implementing a 3D simulation and developed an empirical Nusselt number correlation. Three-dimensional transient conjugate heat transfer simulations have also been performed to study time-dependent heating of rectangular straight microchannels [39].

In heat sinks, the principal objective is to remove heat from a substrate using convective and conductive heat transport. Such modeling has primarily addressed understanding and optimization of the bulk cooling characteristics of heat sinks and the temperature distribution in the solid domain. For biochemical applications, it is imperative to study the temperature profile in the fluid domain as a function of design and operating parameters. Furthermore, for many continuous flow designs, the serpentine configuration of the microchannels makes it critical to capture the effect of thermal crosstalk. Wang et al. [25] previously presented a two-dimensional thermal fluidic model to predict the performance of a continuous flow microfluidic chip. Though two device performance parameters were defined to describe the uniformity of temperature and deviation from target temperatures, limited studies were carried out to understand variation in temperature profile with respect to design variation and operating parameters. Similarly, Li et al. [40] developed a two-dimensional semi-analytical thermal transport model and carried numerical simulation to predict temperature profile in the continuous flow PCR microchip. Chen et al. [41] considered a three-dimensional model of the chip to first estimate temperature distribution in the solid domain but evaluated the temperature distribution in the fluid domain using a simplified two-dimensional model. Though some work has been done on understanding thermal profiles in continuous flow architectures [21,25,40–42], modeling efforts have been limited to simplified two-dimensional geometry which neglects thermal crosstalk due to lateral diffusion and the effect of convective heat transfer on device performance has not been comprehensively studied.

In this paper, a detailed, three-dimensional thermal modeling of a continuous flow microfluidic thermocycler is performed. Design and fabrication of the microfluidic platform is first presented and the implications of the channel geometry on residence time and hydraulic resistance are discussed. A simplified two-dimensional analytical model is initially developed to identify the critical parameters determining temperature distribution in the microfluidic channel and justify the need for a three-dimensional model for correct design analysis, which was developed in the commercial software package Comsol Multiphysics 4.0. As the first step, a solid domain modeling of the entire microfluidic chip with embedded heaters is performed neglecting the presence of the fluid layer. The model is used to estimate the effect of Joule heating, thermal crosstalk in the multi-pass thermocycler chip, and quantify the applicability of a one pass model for understanding temperature profile in the fluid domain. The results of the solid domain simulations are compared with experimental measurements of the thermal profile in a PDMS-glass microfluidic thermocycler obtained using a combination of thermocouples and an infrared (IR) camera. Subsequently, the one pass numerical model examines the quality of thermal profile in the fluid domain as a function of critical parameters like flow rate and microchannel material. Two device performance parameters, ramp rate, Γ, and maximum temperature difference between different zones, $\max(\Delta T)$, are defined and evaluated with respect to variations in sample flow rate through the device. Additionally, mesh sensitivity analysis of the simulation models is performed to establish the numerical accuracy of the simulations results.

2. Methods and materials

2.1. Design of the microfluidic platform

Fig. 1 defines the microfluidic continuous flow thermocycler platform configuration used for modeling. Design of the test bed microfluidic platform can be conceptually divided into two parts: (1) a monolithic microfluidic chip, through which all of the biological reagents are flowed (Fig. 1a) and 2) a thin film patterned glass wafer used to create fixed temperature distribution in space (Fig. 1b). A glass wafer (50 mm (w) $\times$ 75 mm (l)) patterned with thin film of platinum/titanium functions as a resistive heating unit, with thermal energy dissipated from powering the heating elements used to create the desired spatial temperature distribution. Design of the microfluidic channels follows the basic serpentine design proposed by Kopp et al. [18] with some modifications, discussed in Section 2.2. PCR reagents are designed to flow through three zones,