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Thermal compact modeling approach of droplet microreactor based Lab-on-a-Chip devices

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ABSTRACT

The paper presents a novel compact model which enables the thermal analysis of microchannels consisting of continuously moving microdroplets with biologically active content inside. The compact model utilizes the switched capacitor approach to describe the convective heat transfer and as a behavioral model, it can be easily integrated into an IC-MEMS design flow. With this novel approach the temperature profile of the channel can be calculated in minutes compared to conventional numerical techniques that requires days or weeks. The model was validated by a standard CFD solver and a good match was achieved.

1. Introduction

The rising complexity of *Lab-on-a-Chip* (LoC) devices for medical diagnostic purposes requires a multi-domain design. Sample handling is usually enabled by microfluidic techniques as the fluids are flowing in micro-sized channels where separation, mixing and bio-reactions may occur. The effects of such reactions can be detected by biosensors which provide electrical signals as output, more often required to be processed on-chip by integrated circuits. The method of co-design of MEMS and integrated circuits shown in Fig. 1 is already utilized in commercial products [1]. A MEMS device is usually modeled by numerical methods (e.g. FEM or CFD simulation) in order to generate a reduced order model (ROM). The ROM is considered as a behavioral description of the MEMS device therefore the electrical and the mechanical functionality can be handled together at a high level of abstraction. Numerical modeling usually provides high accuracy, and requires high computation times, though. In contrast, reduced order models focus on the key behavior of the device and require only moderate computation time. Therefore bypassing the numerical modeling step the design iteration time can be significantly reduced (Fig. 1). This approach can be generalized [2] especially for electro-mechanical microdevices, however the multi-physical nature of LoC devices requires special care as fluid dynamics, electrostatic/magnetic forces, chemical reactions and signal processing need to be handled at the same time. This paper introduces a reduced order thermal model for droplet microreactors which would enhance the design process of LoC devices.

1.1. Droplet microreactors

The motivation for designing and manufacturing microreactors is that further reduction in sample volume can be achieved by using separate compartments e.g. liquid droplets encapsulating individual reactions.

The flow of droplets is a moving series of slugs of two phases which could be gas and liquid or two immiscible liquids. The slugs form monodisperse compartments in which species and reactions can be isolated and provide the ability to perform large numbers of experiments using extremely small sample volumes [3]. This technique enables the construction of a high throughput Lab-on-a-Chip platform. In addition to several other techniques, reaction heat measurement based biodetection seems to be one of the promising concepts in such micro-scale (chip size) laboratory devices [4].

Heat measurements constitute a direct means of determining enthalpy changes, which appear in all cases of protein–protein or protein–ligand interactions. The method referred to as *calorimetry* is capable of detecting antibody–antigen, protein–ligand or enzyme–ligand interactions at the bedside for any biomedically relevant case, such as cancer, neurological disorders, diabetes, and metabolic diseases. Although calorimetry is traditionally a low throughput method, the micro-scale realization enables higher reaction

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Nomenclature

A	area (m^2)
C	heat capacity (J/K)
c_V	volumetric specific heat capacity (J/m^3 K)
d_n	distance between nodes (m)
δ_F	fluid film thickness (m)
E_0 S_0	initial enzyme, substrate conc. (mol/dm^3)
$[P]$ $[S]$	product, substrate conc. (mol/dm^3)
$[E]$ $[ES]$	enzyme, enzyme–substrate conc. (mol/dm^3)
f_s	frequency (Hz)
h	enthalpy-density (J/m^3)
ΔH_r	reaction enthalpy (J/mol)
k_1, k_2, k_3	reaction rate coefficients (mol/s dm^3)
K_m	Michaelis-constant (mol/dm^3)
λ	thermal conductivity (W/m K)
$\vec{n}$	normal vector (to surface)
Q	heat (J)
$\dot{Q}$	heat current (W)
$\dot{q}$	volumetric heat generation (W/m^3)
$\dot{q}''$	heat flux (W/m^2)
R	radius of the gas droplet (m)
Re	Reynolds number
R_{th}	thermal resistance (K/W)
ρ	density (kg/m^3)
T	temperature (K)
t	time (s)
Δt_{iter}	iteration time (s)
τ	characteristic time (s)
$\vec{u}$	vector of velocity (m/s)
$\overrightarrow{u_{avg}}$	average vector of velocity (m/s)
u_{avg}	average scalar of velocity magnitude (m/s)
V	volume (m^3)

speeds and multiple measurements, therefore higher throughput can be achieved [5]. Continuous flow [6] and droplet calorimetry platforms are already reported [7] and demonstrated in various biological applications such as biomolecular characterization [8]. *Thermal design* is considered to be the key factor of sensitivity and resolution of such calorimetry based biosensors [9,10]. The amount of thermal energy to be measured typically falls in the nano-Joule range. Lee et. al. successfully demonstrated the enthalpy measurement of *urease* enzyme activity with a resolution of 10 nJ in a microfluidic calorimeter with a reactor volume of 3.5 nL [10]. Their measurement results fitted very well with the simple theory of Michaelis–Menten kinetics. Droplet size, reaction kinetics, droplet velocity, material of the channel etc. affect the heat transfer from the droplet towards the ambient. These properties should be considered together with the signal processing solutions (e.g. on-chip integrated analog or digital circuits) at behavioral level. Thermal compact models are widely used in design practice, where such reduced order models (in contrast to detailed numerical models) yield results quickly in the early design phase.

2. Modeling

Heat transfer models and investigations are traditionally based on the determination of the Nusselt number, which is obviously practical when the heat transfer properties of the individual droplets are neglected and an overall description of the flow is possible. This is widely used e.g. for modeling fluids in electronic cooling applications such as cooling integrated circuits. In contrast, for bio-analytical investigations the thermal interactions should be analyzed in detail as they happen in the individual droplets, each accommodating an individual bio-chemical reaction. Typical simulation run-times of the droplet-flow problem vary in wide scale from roughly 1.5 days to about 60 days [11,12]. A thermal compact model for integrated circuits with cooling microchannels was presented [13], which consists of thermal resistances and controlled voltage sources. This model can predict the temperature distribution of the channel wall, but it is not suitable for the analysis of individual droplets. We aimed to develop a new compact model of microchannels with segmented flow which

- describes the heat transfer inside the microchannel containing one or more liquid slugs separated by gas bubbles,
- provides direct input for a subsequent transient analysis and handles transient chemical (e.g. enzyme) reactions taking place inside the droplets and results in a temperature field as output,
- has an interface to attach to the representative thermal solid model of the device package,
- has common behavioral level representation like the one used in electrical subsystems (e.g. VHDL-AMS or electronic circuit),
- results in execution time in the order of magnitude of minutes allowing reasonable iteration times in the LoC design flow.

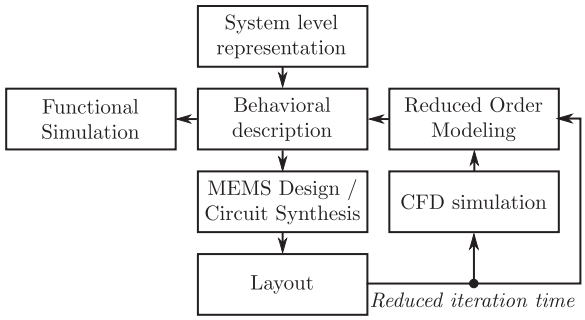

Fig. 1. Simplified IC-MEMS co-design flow.

Our new compact model was validated with the help of detailed CFD simulations. For this purpose we reproduced the work of Gupta et al. [11]. Their CFD simulation results were validated by actual experiments [14]. For our work we used the same multi-physical CFD tool that Gupta et al. have used. Therefore we considered the reproduced detailed CFD model as a reliable benchmark. Using this detailed model the simulation parameters (fluid flow velocity, type of fluids) were changed and the capability of modeling chemical reactions was also added to our baseline detailed model. Preliminary results achieved with this model were presented earlier [15]. With this CFD model we checked our compact model in two relevant cases: for constant heat flux boundary condition and for internal heat generation by an enzyme reaction.

2.1. Governing equations

The modeling approach applied is based on the suggestion of Sridhar et al. [16]. Here we summarize the most essential parts of their work; further details can be found in their paper. The energy conservation equation for heat transfer in a finite control volume