Temperature Simulation and Control of a Biochip for DNA Analysis

B. A. Costa, J. M. Lemos, M. S. Piedade, L. Sousa, P. Freitas, F. Cardoso and D. Vidal

Abstract—This paper presents the preliminary work on the analysis of the thermal behavior of a biochip for DNA detection. The aim is to have a chip with different zones, allowing the possibility to perform experiments at the same time but with independent temperature profiles. Due to the complexity of the biochip’s structure, a lumped model was build based on the control volume methods (CVM). The volume elements were selected to capture the main path of heat inside the chip. The paper contribution consists thus in evaluating modelling and temperature control strategies that are suitable to the class of BIOMEMS considered. Keywords: Biochip, Temperature, Modelling, Control Distributed System

I. INTRODUCTION

The progress made by the miniaturization engineering [1] [2] applied to electronics led to the integration of complex electronic devices and functions in small die chips. Several benefits were obtained with this trend: energy and size savings and an increase of performance of chips.

The microfabrication/miniaturization have been applied to other fields such as, electromechanical systems (MEMS), chemical-biomedical and biological systems (BIOMEMS). In the case of BIOMEMS, biological processes are used in conjunction with micromachining to develop several types of devices [1]:

- Polymerase Chain Reaction (PCR) - are used to amplify DNA. The amplification is obtained by a sequence of heating and cooling cycles. A typical cycle consists of: a) Denature at 93°C for 15 to 30s; b) Anneal primer at 55°C for 15 to 30s; c) Extend primer at 72°C for 30 to 60s;
- DNA chips (microarrays) - are used for genetic testing. Two techniques can be used, sequencing (breaking of DNA in its compounds) or hybridization (binding of segments of DNA in other segments which have complementary sequences).
- Immunosensors - are used in clinical analysis, diagnostic tests. The principle is based on the chemical reactions (binding) between antibodies and antigens.

The ultimate aim in this trend is to build the Lab-on-a-chip devices, in which all steps, to do a diagnostic, are automated: sample handling and preparation, chemical reaction, separation and purification, detection and data analysis. These systems are described as micro total analysis systems (µTAS).

The biochip that is in the development stage at INESC-MN, is a DNA chip with several functionalized areas (sites) for hybridization using magnetic labelled biomolecules (micromospheres with 2µm diameter having small number of biomolecules immobilized on their surface) [5]. The detection method uses magnetoresistive sensors which are under the functionalized areas. Several chips were build to test the detection principle, where 2 × 6µm² spin valves sensors from magnetic recording technology were used [6] [7]. Each magnetoresistive sensor has two current lines, near of it. The current lines are used to create an oscillating magnetic field to concentrate the magnetic labelled biomolecules near the sensor. Using this approach the time required to start the hybridization process is decreased.

In the biochip operation, temperature control must be done in order that DNA hybridization develops under desired conditions and the results are reliable measured. Several factors have a contribution to the temperature distribution and evolution in the chip, such as, chip size, structure of layers and type of material used, nature of heat transfer, conduction and/or convection.

In [8] a thermal management of BioMEMS is presented. Two systems were developed and integrated, a continuous flow polymerase chain reaction (CPCR) device for DNA amplification, and an electronic DNA detection chip. The detection chip contains gold electrodes spotted with DNA capture probes. The reaction requires hybridization at 35°C ± 5°C with a temperature control ±1°C across the chamber to insure similar kinetics at all pads in the sensor array. Typical hybridization parameters are 1h at 35°C. PI controllers where used to control temperature.

Other techniques having been used to control distributed thermal systems [9] [10]. In [9] a LQG controller is used in a semiconductor wafer processing system. In [10] principal orthogonal decomposition techniques and $H_2/H_\infty$ methods are employed to control temperature in rapid thermal processing (RTP) systems.

The final aim of the project from which the current paper is issued is to develop a lab-on-a-chip that can be used to perform simultaneous biological experiments, where temperature in each site must be controlled to follow specific independent profiles. An important aspect of the control design is that the controller must be easy implemented in a low cost microcontroller.

This paper describes the first steps to model temperature

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in the chip, to evaluated the temperature "cross talk" and to control the temperature at two sites of the hybridization. As a starting point, a simplified model of the chip is developed using a CVM (control volume method). This model is also used to understand the main heat paths in the chip, and to select materials of the layers that improve the temperature control. The paper contribution consists thus in evaluating modelling and temperature control strategies that are suitable to the class of BIOMEMS considered.

This paper is organized as follows. In Section 2, a simplified structure of the biochip is presented, the modelling methodology of the biochip temperature is also discussed. In Section 3 an analysis of the process and simulation results with a simple controller are shown. In Section 4 contains conclusions and a description of the future work.

II. BIOCHIP DESCRIPTION

The structure of the biochip for temperature modelling is based on the biochips that were made by INESC Nanotechnologies and Microsystems, used on tests and evaluation of the detection principle with magnetic labelled biomolecules.

The biochip without the packing case has a square shape of $8mm \times 8mm$. The physical model of the biochip is shown in fig.1.

![Biochip representation](image)

Fig. 1. Biochip representation. Top view of the chip on the left. Cut view along axis A on the right, showing the main layers of the chip and type of materials.

The chip has several layers. At the bottom, the substrate of the chip was assumed to be silicon $Si$ of 200$µm$ thick. The next layer is made of $Al_2O_3$ 0.05$µm$ thick. The heating zone where the heater, temperature sensor and magnetoresistive sensor are placed ($Si$) has an area of 250$µm$ by 250$µm$ and 0.3$µm$ thick. A layer of $SiO_2$ is used to passivate the sensors and current lines, to isolate them from the functionalized area and the solution with magnetic labelled biomolecules. The thermal properties of the solution (containing the magnetic labelled biomolecules) are assumed to be identical to the thermal properties of water $H_2O$. The current lines used for the local magnetic field generation are simulated by a volume of 250$µm$ width and 1.0$µm$ thick and length of 3.875$mm$.

In this work, the thermal properties of materials are assumed to be constant for the temperature interval $[25^\circ C; 60^\circ C]$. Their values are shown in table I.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>$\rho$ [Kg/(m)$^3$]</th>
<th>$C_p$ [J/(Kg K)]</th>
<th>$k$ [W/(m $K$)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Si$</td>
<td>2330</td>
<td>712</td>
<td>148</td>
</tr>
<tr>
<td>$Al_2O_3$</td>
<td>3970</td>
<td>765</td>
<td>36</td>
</tr>
<tr>
<td>$Al$</td>
<td>2770</td>
<td>875</td>
<td>177</td>
</tr>
<tr>
<td>$SiO_2$</td>
<td>2220</td>
<td>745</td>
<td>1.38</td>
</tr>
<tr>
<td>$H_2O$</td>
<td>997</td>
<td>4180</td>
<td>0.607</td>
</tr>
<tr>
<td>$Air$</td>
<td>1.184</td>
<td>1007</td>
<td>0.02551</td>
</tr>
</tbody>
</table>

III. TEMPERATURE MODELING

The operation of the biochip have the following phases: a)-The solution is dropped at the site on the chip. b)-The adjacent current lines are used to create a local magnetic field to attract the magnetic labels to the site. c) - Hybridization starts; d) - After some time, washing cycles are used to remove label that are not bound to the site. e)- Measurements of magnetoresistance are used to detected the presence biomolecules (hybridization).

During this process temperature must be controlled. For this sake heat can be injected in the chip using electric resistances which were build in the chip.

Modelling all elements of the chip is a complex task involving the solution of the heat conduction equation,

$$C_p\rho \frac{dT}{dt} = \nabla \cdot (k\nabla T) + \dot{Q} \tag{1}$$

with appropriate boundary conditions. In (1) where $T$ represents temperature, $C_p$ is the heat capacity, $\rho$ represents density of the material, $k$ is the thermal conductivity, and $\dot{Q}$ represents the heat generation density per volume. As an additional difficulty, the chip has several layers with different thermal properties, and heat convection can occur at the top interface of the chip, towards the air and the solution.

An approach to the modelling problem consists of performing energy balances using control volumes in the zones of interest. According to this approach, a set volume elements were defined (fig. 2) to capture the main heat paths. The description of each volume is shown in the table II.

For each control volume element an equation with the form

$$C_i \frac{dT_i(t)}{dt} = \sum_{j \in N_i} \frac{T_j(t) - T_i(t)}{R_{ij}} + P_i(t) \tag{2}$$

is used, where $P_i(t)$ represents the power (heat generation) that is injected in the volume element $i$, $C_i \triangleq C_{ip}\Delta V$ represents the capacity of the element $i$ with volume $\Delta V$ to store thermal energy, and $R_{ij} = R_{ji}$ represents the thermal resistance between two elements ($i$ and $j$) that are in contact by a surface of area $\Delta A$. The set of elements that have a surface contact with the element $i$ is represented by $N_i$. The thermal resistance is defined as

$$R_{ij} \triangleq \frac{0.5 \times L_{ij}}{k_i \Delta A_{ij}} + \frac{0.5 \times L_{ji}}{k_j \Delta A_{ji}} \tag{3}$$
The resistance model is based on the physical law of heat conduction $Q_{\text{cond}} = -k A_s \frac{dT}{dx}$, where $k$ is the thermal conductivity and $A_s$ is the surface area normal to the heat flux.

It is assumed that no heat flux cross the bottom and lateral surfaces of the chip. Heat could only leave the chip at the top surface. The transfer of heat at the top was modelled assuming a layer of still air 1 mm thick, and its upper surface (air) is assumed to be at 25 °C. This assumption must be validated.

Using the above modelling method a continuous time linear state space model $(dx(t)/dt = Ax(t) + Bu(t))$ with 30 state variables and with 3 inputs was build. The inputs are the power (up to 1.2 W) to each volume element $V_{23}$ and $V_{26}$ and the temperature of the environment ($T_{\text{env}} = 25^\circ\text{C}$).

### A. Analysis of the temperature model

The state vector of the model was defined as $x(t) = [T_1(t) T_2(t) \cdots T_{30}(t)]^T$ where $T_k$ represents the temperature in volume element number $k$. The diagonal values of matrix $A$ are shown in the table III. The eigenvalues of the system

<table>
<thead>
<tr>
<th>Elem.</th>
<th>Value</th>
<th>Elem.</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(1,1)</td>
<td>$-4.4 \times 10^{-3}$</td>
<td>A(10,10)</td>
<td>$-3.9 \times 10^{-7}$</td>
</tr>
<tr>
<td>A(2,2)</td>
<td>$-4.4 \times 10^{-3}$</td>
<td>A(17,17)</td>
<td>$-7.0 \times 10^{-6}$</td>
</tr>
<tr>
<td>A(3,3)</td>
<td>$-4.4 \times 10^{-3}$</td>
<td>A(18,18)</td>
<td>$-4.0 \times 10^{-7}$</td>
</tr>
<tr>
<td>A(4,4)</td>
<td>$-2.5 \times 10^{-8}$</td>
<td>A(19,19)</td>
<td>$-3.9 \times 10^{-7}$</td>
</tr>
<tr>
<td>A(4,5)</td>
<td>$-2.7 \times 10^{-7}$</td>
<td>A(20,20)</td>
<td>$-7.0 \times 10^{-6}$</td>
</tr>
<tr>
<td>A(4,6)</td>
<td>$-2.5 \times 10^{-8}$</td>
<td>A(21,21)</td>
<td>$-1.6 \times 10^{-2}$</td>
</tr>
<tr>
<td>A(7,7)</td>
<td>$-3.0 \times 10^{-6}$</td>
<td>A(22,22)</td>
<td>$-1.7 \times 10^{-2}$</td>
</tr>
<tr>
<td>A(8,8)</td>
<td>$-2.3 \times 10^{-8}$</td>
<td>A(23,23)</td>
<td>$-3.2 \times 10^{-4}$</td>
</tr>
<tr>
<td>A(9,9)</td>
<td>$-1.5 \times 10^{-8}$</td>
<td>A(24,24)</td>
<td>$-1.6 \times 10^{-4}$</td>
</tr>
<tr>
<td>A(10,10)</td>
<td>$-3.0 \times 10^{-6}$</td>
<td>A(25,25)</td>
<td>$-1.7 \times 10^{-2}$</td>
</tr>
<tr>
<td>A(11,11)</td>
<td>$-1.2 \times 10^{-8}$</td>
<td>A(26,26)</td>
<td>$-3.2 \times 10^{-4}$</td>
</tr>
<tr>
<td>A(12,12)</td>
<td>$-1.5 \times 10^{-8}$</td>
<td>A(27,27)</td>
<td>$-1.6 \times 10^{-2}$</td>
</tr>
<tr>
<td>A(13,13)</td>
<td>$-3.0 \times 10^{-6}$</td>
<td>A(28,28)</td>
<td>$-8.9 \times 10^{-4}$</td>
</tr>
<tr>
<td>A(14,14)</td>
<td>$-7.0 \times 10^{-6}$</td>
<td>A(29,29)</td>
<td>$-8.9 \times 10^{-4}$</td>
</tr>
<tr>
<td>A(15,15)</td>
<td>$-4.0 \times 10^{-7}$</td>
<td>A(30,30)</td>
<td>$-8.9 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

The range of the eigenvalues is from $-3.723 \times 10^8$ to $-1.713 \times 10^2$, and the slowest time constant of the system is 5.8 ms. Remembering the main control aims, one must control the temperature at volume elements 23 and 26 and the temperatures at these sites must be independent from each other. The places where heat is generated are at volume elements 9 and 12. One observation about the main heat path, the thermal resistances along $x$ and $y$ (in the layers) are in the order of $10^{-5} (K/W)$ and/or $10^{-6} (K/W)$, the only exception to this, is in the bottom layer of Si which are for $R_{1.2} = R_{3.3} = 12.6 (K/W)$. See fig. 2 for the definition of the orientation frame. The thermal resistances along $z$ axis (between layers) are in the order of $[\sim 10^{-3} to \sim 10^{-2}] (K/W)$ this is for the volume element with larger surfaces. For $R_{7.14} = 3.1 \times 10^{-2}$, $R_{9.16} = 1.2 \times 10^{-10}$ and $R_{16.23} = 1.3 \times 10^{-3} (K/W)$. This has the consequence that the heat flux has an easy path down to the bottom of the chip and the bottom layer will not isolate the left/right from the right/left sides.

### B. Simulation results

In this subsection simulation results are shown to evaluate the temperature cross talk between sites 23 and 26 where drops of solution are placed. The results are shown in fig. 3. The power at volume element 23 was kept constant at 1.2 W during 500 ms, followed by a total cut for 500 ms. The heat generation at volume element 26 was kept constant at 6 mW. From the figure one can see that the sites 23 and 26 are not isolated because, when the power is cut down at $t = 500$ ms, both temperatures tend to the same value. As a consequence there is no control law that can be used to control the temperature at both sites by only manipulating the power. So the main conclusion is that the structure of the chip, the properties of the layers or an additional mechanism must be used to improve the performance of the chip.

![Diagram of chip](image)
IV. TEMPERATURE CONTROL

As was described in the last subsection, changes to the chip structure must be made in order to improve the thermal isolation between the hybridization sites, which are represented by volume elements 23 and 26. Because the bottom layer has a low thermal resistance, one way to improve thermal isolation between the sites is to change the thermal properties to this layer. The material selected for the bottom layer and for the layer above it, is SiO₂, which has a very low thermal conductivity. The results obtained with this change are shown in the fig. 4 and 5. A simple proportional controller was used to control the temperature at volume element 23, the power at the control volume 24 was kept constant to 6mW. From the results of figs. 4 and 5, one can observe that an improvement was obtained, the heat flow from the heater of the volume element 23 to the volume element 26 occurs at a lower rate. However there is a huge difficulty to remove heat from the chip. This means the other methods must be employed to obtain the desired performance of the chip, for example forced convection.

V. CONCLUSIONS

This paper presents the preliminary work on the analysis of the thermal behavior of a biochip for DNA detection. The aim is to have a chip with different zones, allowing the possibility to perform experiments at the same time but with independent temperature profiles. Due to the complexity of its structure, a lumped model was build based on the control volume methods (CVM). The volume elements were selected to capture the main path of heat inside the chip, until now it was not possible to validate the model with experimental data. This will carry out in the near future.

Several simplification were made at this stage, the thermal properties were assumed to be independent of the temperature, which is not correct, and the heat flow to the outside of the chip do not explicit includes the heat exchange by convection, this must be improved. Another important fact is the place of the temperature sensor which is not in the place where one must control the temperature, this must also be considered.

The state space model of the temperature in the chip has 30 state variables. The eigenvalues have an huge range of values, which can cause problems to the integration method. On possible solution is to use reduction of order methods and to change the time simulation scale.

An initial structure of the biochip was evaluate an changed, to improve the reduction of temperature cross talk between sites of interest. The main conclusion is that the control of temperature of this particular biochip must be done by exploring the structure of the chip and the thermal properties of materials. Using this approach simple control laws can be used.

Since the project is going on, it is expected that more results can be included in the final version oh the paper.
REFERENCES


