Master’s Thesis

Temperature control for PCR on a microfluidic MEMS

Ivo Leibacher

Advisor:
Philipp Rüst

Supervisor:
Prof. Dr. Jürg Dual

Institute of Mechanical Systems
Swiss Federal Institute of Technology (ETH) Zurich

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Ce n’est point le navire qui naît de la forge des clous et du sciage des planches. C’est la forge des clous et le sciage des planches qui naissent de la pente vers la mer et croissance du navire.

Antoine de Saint-Exupéry
## Contents

**Abstract** iii  
**Acknowledgements** iv  
**Nomenclature** v  

1. **Introduction** 1  
   1.1. Project outline and motivation .............................................. 1  
   1.2. State of the art ......................................................................... 3  

2. **Theoretical background** 5  
   2.1. The polymerase chain reaction (PCR) ........................................ 5  
   2.2. Thermodynamic basic equations ................................................ 6  
   2.3. Joule heating and the temperature-resistance relationship .......... 9  
   2.4. An analytical stationary, one-dimensional approach .................... 11  

3. **Numerical simulations** 14  
   3.1. Geometry, modeling and meshing .............................................. 14  
   3.2. Boundary conditions .................................................................. 16  
   3.3. Simulation results ........................................................................ 17  
      3.3.1. Steady-state simulations ...................................................... 17  
      3.3.2. Transient simulations .......................................................... 19  
      3.3.3. Simulation of a full PCR cycle ............................................. 24  

4. **Fabrication** 26  
   4.1. Fabrication of the heater and temperature sensor ...................... 26  
      4.1.1. Wafer processing ............................................................... 26  
      4.1.2. Fabrication process analysis and optimization .................... 30  
   4.2. Electrical connection and assembly of the pads ....................... 36  
   4.3. Fabrication of the lid for the fluidic chamber ............................ 37  
   4.4. Tubing of the chamber ............................................................. 39  

5. **Instrumentation and control** 40  
   5.1. Instrumentation setup .............................................................. 40  
   5.2. Modeling of the dynamic system for control engineering .......... 41  
   5.3. Controller design ...................................................................... 43  
   5.4. Data processing and graphical user interfaces (GUI) in LabView .... 44
6. Experimental characterization

6.1. Calibration of the temperature sensor ........................................... 48
6.2. First evaluations of complete PCR cycles ........................................ 50
6.3. Characterization of different cooling methods ..................................... 51
  6.3.1. Cooling by ventilation and fins ................................................. 51
  6.3.2. Cooling by a Peltier element ..................................................... 54
6.4. Measurements with a second temperature sensor within the device ............ 56
6.5. Final performance benchmark with multiple PCR cycles ........................... 59
6.6. Temperature-controlled cantilever sensor measurements .......................... 60

7. Conclusions .................................................................................. 62

8. Outlook ...................................................................................... 64

A. Appendix: Mask layouts .................................................................. 65

B. Appendix: Layout of the printed circuit board ...................................... 68

C. Appendix: Fabrication report of the heater and sensor structures ................. 69
  C.1. Processing recipe for the heater and sensor structures .......................... 69
  C.2. Parameters and logfile for the evaporation of the platinum layer ............ 70
  C.3. Factors of resistance increase ......................................................... 73
  C.4. Machine parameters for PECVD of silicon dioxide ............................ 73
  C.5. Machine parameters for wire bonding ............................................... 73

D. Appendix: Processing recipe for the mold of the PDMS lid ......................... 74

List of Figures .................................................................................. 74

List of Tables ................................................................................... 77

Bibliography .................................................................................... 78
Abstract

This study outlines the sketch, the simulation, the fabrication and experimental evaluation of a temperature control device for the on-chip polymerase chain reaction (PCR) method. The microfabricated device is integrated on a viscosity sensor with a fluidic chamber of 8.3 µl volume.

A three dimensional model of the device is developed with Comsol Multiphysics® in order to simulate the stationary and transient thermodynamical behaviour of the system. In the simulations, thermodynamics is coupled to the electrothermal Joule heating. A complete PCR cycle is simulated.

The microfabrication of a resistance heater and a resistance thermometer on an area of ∼ 4 × 4 mm with smallest feature sizes down to 20 µm is reported in detail. Photolithography, evaporation of thin platinum films, a lift-off process, and wire bonding are covered, and a process development is discussed in detail. Furthermore, a microfluidic lid is fabricated out of polydimethylsiloxane (PDMS) on a dry-etched microfabricated mold. Its assembly and tubing are also reported.

The control of the thermal system by a digital proportional-integral (PI) controller is developed. A ”lumped parameter” model of the system is experimentally derived. The instrumentation and operation with a LabView graphical user interface (GUI) are reported.

After calibration of the resistance thermometer, experiments with the temperature profile of rapid PCR are conducted. Different cooling methods, such as a fan, fins, Peltier elements and combined heat sinks are tested. The temperature distribution within the device is experimentally investigated by means of a second resistance thermometer, which is given by the viscosity sensor. Finally, first temperature-dependent measurements with the viscosity sensor are reported as proof of concept.
Acknowledgements

It is my great pleasure to hereby thank all the people who have supported me during this project, scientifically as well as personally.

I wish to thank Prof. Jürg Dual for his continuous guidance and the possibility to work in the laboratories of the IMES institute. I highly appreciate the proficient support of my advisor Philipp Rüst. He supported the advancement of my work on the project and my skills with dedication, whereas I also enjoyed the freedom I was given. I value his patience for my introduction to the cleanroom work and the micro engineering equipment. Many thanks to Ueli Marti for his essential support on the electronic systems as well as Jean-Claude Tomasina for his manufacturing work. Special thanks to Hansruedi Scherrer and his team from the laboratory of the physics department for the realisation and expertise regarding thin film evaporations.

Furthermore, I am grateful for the support from the whole group of the FIRST-Lab CLA, especially Dr. Stefan Blunier and Donat Scheiwiller, the IMES institute as well as various other institutes for their helpful discussions, so I could build on a wide experience of clean room processing.

Last but not least I would like to thank my colleagues in the student room, namely Johannes and Sabrina, for a great and friendly working atmosphere.
Nomenclature

All parameters are noted in SI units.

Roman alphabet

\begin{align*}
A & \quad [m^2] \quad \text{Area} \\
C & \quad [J/K] \quad \text{Heat capacity} \\
c & \quad [J/kg/K] \quad \text{Specific heat capacity} \\
d & \quad [m] \quad \text{Thickness} \\
E & \quad [J] \quad \text{Energy} \\
e & \quad [-] \quad \text{Control error} \\
h & \quad [W/m^2K] \quad \text{Heat transfer coefficient} \\
I & \quad [A] \quad \text{Current} \\
J & \quad [A/m^2] \quad \text{Current density} \\
K_i & \quad [-] \quad \text{Integral gain} \\
K_p & \quad [-] \quad \text{Proportional gain} \\
l & \quad [m] \quad \text{Length} \\
m & \quad [kg] \quad \text{Mass} \\
P & \quad [W] \quad \text{Power} \\
q & \quad [J] \quad \text{Heat energy} \\
\dot{q}'' & \quad [W/m^2] \quad \text{Heat flux per area} \\
\dot{q}'''' & \quad [W/m^3] \quad \text{Heat power source per volume} \\
R & \quad [\Omega] \quad \text{Resistance} \\
r & \quad [-] \quad \text{Setpoint} \\
T & \quad [K] \quad \text{Temperature} \\
t & \quad [s] \quad \text{Time} \\
U & \quad [V] \quad \text{Voltage} \\
u & \quad [-] \quad \text{Controller output} \\
w & \quad [m] \quad \text{Width} \\
y_s & \quad [-] \quad \text{Output signal} \\
x, y, z & \quad [m] \quad \text{Spatial variables}
\end{align*}
### Greek alphabet

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Unit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>( \frac{1}{K} )</td>
<td>Linear temperature coefficient of electrical resistance</td>
</tr>
<tr>
<td>( \delta )</td>
<td>( \frac{1}{K} )</td>
<td>Coefficient of thermal expansion</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>( \frac{W}{K \cdot m} )</td>
<td>Thermal conductivity</td>
</tr>
<tr>
<td>( \rho )</td>
<td>( \frac{kg}{m^3} )</td>
<td>Density</td>
</tr>
<tr>
<td>( \rho_{el} )</td>
<td>( \Omega \cdot m )</td>
<td>Specific electrical resistance</td>
</tr>
<tr>
<td>( \tau )</td>
<td>( [s] )</td>
<td>Time constant</td>
</tr>
</tbody>
</table>

### Mathematics

- \( a'' \): Expression divided by area
- \( \dot{a} \): Derivative with respect to time
- \( a_{,x} \): Derivative with respect to \( x \)
- \( n \): Nano \( (10^{-9}) \)
- \( \mu \): Micro \( (10^{-6}) \)
- \( m \): Milli \( (10^{-3}) \)
- \( k \): Kilo \( (10^3) \)
- \( M \): Mega \( (10^6) \)
# General

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al</td>
<td>Aluminum</td>
</tr>
<tr>
<td>Au</td>
<td>Gold</td>
</tr>
<tr>
<td>°C</td>
<td>Degree Celsius</td>
</tr>
<tr>
<td>Cr</td>
<td>Chromium</td>
</tr>
<tr>
<td>Cu</td>
<td>Copper</td>
</tr>
<tr>
<td>DI water</td>
<td>Deionized water</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DRIE</td>
<td>Deep reactive ion etching</td>
</tr>
<tr>
<td>et al.</td>
<td>et alii, and others</td>
</tr>
<tr>
<td>GPIB</td>
<td>General Purpose Interface Bus</td>
</tr>
<tr>
<td>GUI</td>
<td>Graphical user interface</td>
</tr>
<tr>
<td>HMDS</td>
<td>Hexamethyldisilazan</td>
</tr>
<tr>
<td>ICP</td>
<td>Inductively coupled plasma</td>
</tr>
<tr>
<td>IMES</td>
<td>Institute for Mechanical Systems, ETH Zürich</td>
</tr>
<tr>
<td>ITO</td>
<td>Indium tin oxide</td>
</tr>
<tr>
<td>MEMS</td>
<td>Microelectromechanical system</td>
</tr>
<tr>
<td>µ-TAS</td>
<td>Micro total analysis system</td>
</tr>
<tr>
<td>Ni</td>
<td>Nickel</td>
</tr>
<tr>
<td>PC</td>
<td>Personal computer</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PDMS</td>
<td>Polydimethylsiloxane</td>
</tr>
<tr>
<td>PI</td>
<td>Proportional-integral</td>
</tr>
<tr>
<td>PECVD</td>
<td>Plasma enhanced chemical vapour deposition</td>
</tr>
<tr>
<td>PMMA</td>
<td>Polymethylmethacrylate (Plexiglas)</td>
</tr>
<tr>
<td>Pt</td>
<td>Platinum</td>
</tr>
<tr>
<td>rpm</td>
<td>Revolutions per minute</td>
</tr>
<tr>
<td>RS-232</td>
<td>Recommended Standard 232 serial interface bus</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning electron microscope</td>
</tr>
<tr>
<td>Si</td>
<td>Silicon</td>
</tr>
<tr>
<td>SiO₂</td>
<td>Silicon dioxide</td>
</tr>
<tr>
<td>SU-8</td>
<td>A photoresist product line of MicroChem Corporation</td>
</tr>
<tr>
<td>Ti</td>
<td>Titanium</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasonic</td>
</tr>
</tbody>
</table>
1. Introduction

1.1. Project outline and motivation

The task of the thesis at hand is affiliated to the development of a microsensor at the Institute for Mechanical Systems (IMES). The sensor deploys a novel measurement method to determine the viscosity of a fluid sample which is placed in a fluidic chamber within the microelectromechanical system (MEMS).

The rheological properties of fluids are of great importance in research and industry. The measurement of viscosity has a wide range of industrial applications, ranging from the food industry to medical applications and the plastic industry, to name just a few. The applications of microviscosimeters in medicine, chemistry and biology have been reported by Jäger [16]: The analysis of chemical reactions involving changes in viscosity, blood rheology for diagnostic, prognostic and preventive medicine (hyperviscosity, diabetes mellitus), as well as further applications in clinical laboratories are seen as application fields for precise temperature-controlled viscosity measurements.

A main goal of this microsensor project aims at the biomedical analysis of fluid samples. The polymerase chain reaction (PCR) is intended to be carried out on the fluid sample within the sensor device prior to the viscosimetry measurement. The polymerase chain reaction is a method in molecular biology to amplify DNA sequences exponentially in vitro. As one of the most important methods of modern molecular biology, PCR is employed in biological and medical laboratories for a wide range of applications, such as for example the detection of hereditary diseases and viral infections, the preparation and testing of genetic fingerprints, DNA-based phylogeny and cloning [29].

The combination of the PCR method with read-out by viscosity measurements as a micro total analysis system (μ-TAS) on a portable device is the ultimate goal of the project. This combination of the PCR method with read-out by viscosimetry has been reported and patented by Dual et al. [8].

The main task of this thesis is to develop a heating and cooling device on the sensor in order to control the temperature of the fluid sample in the sensor. Temperature control on the MEMS is requested for two reasons:

- The aim to perform the PCR method on fluid samples within the device requires precisely controlled temperature cycling on the MEMS. The PCR method, widely used in biotechnology as outlined in chapter 2.1, includes temperatures from $\sim 55^\circ C$ up to $\sim 95^\circ C$. 

• The viscosity of fluids is highly dependent on their temperature. In order to measure at different temperatures with an assured repeatability, the sample temperature has to be held constant during the viscosity measurements.

Figure 1.1: Crossectional sketch of the sensor with attached temperature control devices

Figure [1.1] shows a crossectional sketch of the intended device geometry. The fluid sample of 8.3 µl is held within a volume of 0.72 mm height and 3.5 × 3.5 mm outside dimension. The bottom of the chamber includes the actuator and sensor for the temperature control. Based on the literature review of chapter 1.2, a resistance heater is chosen as a flexible, fast and simple heating method. For the viscosity measurements, a cantilever sensor is protruding in the fluid sample. The cantilever sensor is subject of a dissertation at the institute, it is micromachined out of a silicon substrate and has a metal film forming a loop on top.

The motivation for a micromachined device lies in several advantages compared to conventional, macro-scale devices. A thermodynamic advantage of µ-TAS lies in their small fluid sample volumes. They allow much faster temperature cycling, since the smaller thermal masses lead to higher heating and cooling rates. Faster temperature cycling renders a decreased analysis time possible. The reduced consumption of biological samples as necessary for PCR are of special importance for fluids with limited availability. Decreased cost of fabrication, reduced usage of PCR additives, increased portability and integration of the final device as well as the possibility of parallelization are further benefits.

The thesis at hand covers the sketch, the simulation, the fabrication and experimental evaluation of a device to control the temperature of a fluid sample volume in a microfluidic sensor with a focus on the application of the PCR method.
1.2. State of the art

In a literature review, papers concerning PCR microfluidic devices for DNA amplification were studied in order to find a starting point for this project. Zhang et al. [32] provides a summarizing overview on the work in this field. For the design, mainly two types of microfluidic systems for PCR are discussed: one for chamber stationary PCR and the other one for flow-through PCR. The focus for our purpose lies on single chamber stationary PCR microfluidics, as the sensor for viscosimetry includes a fluid chamber where PCR will take place.

Whereas most devices described in literature base on a silicon substrate (Cui et al. [6], Lao et al. [17], Lee et al. [18], Lee et al. [19], Poser et al. [22], Schabmüller et al. [26], Yoon et al. [30], Zhao et al. [33]), there are several examples of devices fabricated on a glass substrate (Bäch [1], Bestmann [2], El-Ali et al. [10], Fukuba et al. [11], Liao et al. [20]). Other materials include Polydimethylsiloxane (PDMS), Polymethylmethacrylate (PMMA) and SU-8.

All mentioned papers describe a heater wire in the form of a meander, whereas the design of the heater sensors is either also a meander (Bestmann [2], Lee et al. [19], Yoon et al. [30], Schabmüller et al. [26], Fukuba et al. [11]) or just a single loop (Cui et al. [6], El-Ali et al. [10], Lao et al. [17], Lee et al. [18], Poser et al. [22], Zhao et al. [33]). The thicknesses of the heater and sensor substrate layers vary from 100 nm up to 1000 nm.

In order to cool down the sample fluid, most devices use passive cooling by convection to the ambient air. Other approaches include cooling with a Peltier element (Bestmann [2]) and cooling by forced convection with a fan (Poser et al. [22], Schabmüller et al. [26], Yoon et al. [30]).

The in-house experience within the Institute of Mechanical Systems (IMES) includes an on-chip PCR device which has been developed by Bestmann [2] for a total nucleic acid analysis system. The described device is built of several layers, including a copper heater and sensor layer and a Peltier element for cooling. Furthermore, the dissertation of Bäch [1] at the same institute covers heater wires, although for a different purpose.

An overview on the reviewed papers and the performances of the described devices is given in Table 1.1. Out of a large number of papers in this field, the most adequate for our purpose were chosen. These papers were a clue for all further questions regarding fabrication, design, choice of materials, heating and cooling methods, biocompatibility, bonding and control. Comparing the heating rates of the reported devices in Table 1.1 with the heating rate of 1° − 2° C/s of conventional PCR devices (Zhang et al., [32]), a much better temperature cycling performance of microfabricated devices can be stated. Roche’s Light Cycler® 2.0, a well-known, rapid and proven thermal cycler, has a heating rate of more than ~3.7° C/s in the range of 40° − 95° C [24].
Table 1.1: Literature review on PCR microfluidic devices: A paper overview

<table>
<thead>
<tr>
<th>Author</th>
<th>Fluid sample volume</th>
<th>Heating/cooling rate</th>
<th>Heater material</th>
<th>Speciality of the paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bestmann [2]</td>
<td>100 nl-2 μl</td>
<td>30°C C/s</td>
<td>Cu</td>
<td>Multi-layered</td>
</tr>
<tr>
<td>Cui [6]</td>
<td>2.5 μl</td>
<td>15°C C/s</td>
<td>Pt/Ti</td>
<td>Thermal stress</td>
</tr>
<tr>
<td>El-Ali [10]</td>
<td>20 μl +50°C/-30°C C/s</td>
<td>Pt/Ti</td>
<td>FEM simulations</td>
<td></td>
</tr>
<tr>
<td>Lao [17]</td>
<td>20 μl +20°C/-10°C C/s</td>
<td>Pt/Ti</td>
<td>Design rules</td>
<td></td>
</tr>
<tr>
<td>Lee [18]</td>
<td>8 μl +15°C/-3.5°C C/s</td>
<td>Pt/Ti</td>
<td>Design rules</td>
<td></td>
</tr>
<tr>
<td>Lee [19]</td>
<td>0.2 μl +80°C/-60°C C/s</td>
<td>Pt/Ti</td>
<td>PMMA lid</td>
<td></td>
</tr>
<tr>
<td>Liao [20]</td>
<td>10 μl +20°C/-10°C C/s</td>
<td>Pt/Cr</td>
<td>PDMS walls</td>
<td></td>
</tr>
<tr>
<td>Poser [22]</td>
<td>5–10 μl +80°C/-40°C C/s</td>
<td>Pt/NiCr</td>
<td>Fan cooling</td>
<td></td>
</tr>
<tr>
<td>Schabmüller [26]</td>
<td>1 μl</td>
<td>-</td>
<td>Pt/Ti</td>
<td>Packaging</td>
</tr>
<tr>
<td>Yoon [30]</td>
<td>3.6 μl +36°C/-22°C C/s</td>
<td>Pt/Ti</td>
<td>Thermodynamics</td>
<td></td>
</tr>
<tr>
<td>Zhang [32]</td>
<td>3 nl-50 μl</td>
<td>-</td>
<td>all</td>
<td>Review paper</td>
</tr>
<tr>
<td>Zhao [33]</td>
<td>2 μl +15°C/-10°C C/s</td>
<td>Pt</td>
<td>Bottom thicknesses</td>
<td></td>
</tr>
</tbody>
</table>
2. Theoretical background

2.1. The polymerase chain reaction (PCR)

The procedure for the polymerase chain reaction (PCR) includes cycles of repeated heating and cooling of a fluid sample where the reaction takes place. Figure 2.1 shows a typical temperature profile for a rapid PCR. Conventionally, these thermal cycles are carried out by placing small reaction tubes in a macroscale thermal cycler. In this thesis, thermal cycling will be implemented within a microfluidic device, aiming for a lab-on-a-chip. The fundamentals of the PCR will be outlined here in order to understand the requirements for the temperature control on the chip for such a thermal cycling.

Before thermal cycling begins, the fluid sample containing DNA sequences has to be mixed with several biological and chemical components and reagents. Then this prepared fluid sample undergoes typically 20-40 times the temperature cycle which is shown in Figure 2.1. Each cycle consists of 3 different steps as numerated in this figure. Figure 2.2 illustrates these three steps as following (13, 29):

- **Denaturation step ①**: Double-stranded DNA containing the target sequence is separated into two single strands by heating of the fluid sample to typically 94° – 98°C. The separation is achieved by DNA melting which disrupts the hydrogen bonds between the two strands.

- **Annealing step ②**: Now the so-called primers, which were inserted before into the fluid sample, can anneal to its designated primer-binding sites on the single strands of DNA. A primer is an oligonucleotide, serving as a starting point for the following DNA polymerase. The primer is illustrated as a red strand in Figure 2.2. The annealing works best at a temperature of about 50° – 65°C.

- **Elongation step ③**: Now the Taq-polymerase synthesizes and replicates a new DNA strand complementary to its DNA template by proceeding along the template in the direction of the arrow, extending from the primer. The resulting double-stranded DNA molecule is now identical to its double-stranded parental DNA molecule. Taq polymerase is an enzyme which is usually employed at 72°C, where it has its optimum activity.

After these steps, the number of target DNA strands has nearly been doubled, and the cycle begins afresh at step ①. After 25 cycles, the target sequence has been amplified about 10^6-fold. By this amplification of the chosen target DNA, its subsequent read-out and analysis becomes possible. Usually a gel electrophoresis follows, where the target
2.2. Thermodynamic basic equations

Thermodynamics distinguishes 3 different types of heat transfer: heat conduction, heat convection and heat radiation. Whereas the first two will be discussed in the following, heat radiation is neglected since it occurs mainly at higher temperatures than in our system.
2.2. Thermodynamic basic equations

Figure 2.2: The PCR method from a molecular perspective [13]: The initially double-stranded DNA undergoes a denaturation step ①, an annealing step ② and an elongation step ③ during a temperature cycle. This procedure leads to an amplification of the target DNA sequence.
2.2. Thermodynamic basic equations

Heat conduction

Heat convection can also be seen as diffusion of thermal energy \[23\]. It is present in all kinds of materials, but most determining in solids. It is described by Fourier’s law:

\[
\dot{q}'' = \frac{\dot{q}}{A} = -\lambda \cdot \nabla T
\]  

(2.1)

with the heat flux per area \(\dot{q}''\), the thermal conductivity \(\lambda\) and the temperature \(T\). The thermal conductivity is a material parameter, which is normally slightly temperature dependent. Fourier’s law states that the heat flux per area is proportional to the temperature gradient with a proportional factor \(\lambda\). Table 2.1 lists typical values for the materials which will be present in the device.

<table>
<thead>
<tr>
<th>Material</th>
<th>Thermal conductivity ([\frac{W}{K\cdot m}])</th>
<th>Specific heat capacity ([\frac{J}{g\cdot K}])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>0.599</td>
<td>1.012</td>
</tr>
<tr>
<td>Glass</td>
<td>0.76</td>
<td>0.84</td>
</tr>
<tr>
<td>PDMS</td>
<td>0.21</td>
<td>1.5</td>
</tr>
<tr>
<td>Platinum</td>
<td>71.6</td>
<td>0.133</td>
</tr>
<tr>
<td>Si</td>
<td>148</td>
<td>0.712</td>
</tr>
<tr>
<td>SiO₂</td>
<td>(\sim 1.2 - 1.3)</td>
<td>(0.70)</td>
</tr>
<tr>
<td>Water (at 55-95°C)</td>
<td>(\sim 0.64 - 0.68)</td>
<td>(\sim 4.2)</td>
</tr>
</tbody>
</table>

Heat convection

Heat transfer by heat convection bases on the movement of a fluid, namely a liquid or a gas. When a fluid flows against a solid, heat is transferred between the solid and the fluid which carries heat energy away. Convective heat transfer is proportional to the temperature difference \[23\]:

\[
\dot{q}'' = \frac{\dot{q}}{A} = h \cdot (T_{\text{hot}} - T_{\text{cold}})
\]  

(2.2)

with the heat transfer coefficient \(h\) and the temperatures \(T_{\text{hot}}\) and \(T_{\text{cold}}\) of solid and fluid or vice versa. The heat transfer coefficient is highly dependent on the type of flow, the surface roughness, the geometry of the solid, the kind of fluid, and phase transitions. Thereofore this coefficient is not generally known, it has to be determined undividually for a given case.

Two types of convection are distinguished: forced convection where the flow is externally generated by e. g. a fan, and natural convection where the flow is induced by the slow rise and descent of fluids, as caused by its non-uniform temperature distribution. Whereas Pouflikakos et al. \[23\] states \(h = 2 - 25 \frac{W}{m^2 K}\) for natural convection of gases, forced convection is listed with coefficients of \(h = 25 - 250 \frac{W}{m^2 K}\). With liquids, these
values are \( h = 50 - 1'000 \frac{W}{m^2K} \) for natural convection and \( h = 50 - 20'000 \frac{W}{m^2K} \) for forced convection.

**Heat capacity and the energy conservation equation**

The heat capacity \( C \) characterizes the amount of heat \( \Delta q \) that is required to change a body’s temperature by a given amount \( \Delta T \) \[2.3\]:

\[
C = \frac{\Delta q}{\Delta T}
\]

The heat capacity \( C \) is also called *thermal mass* as it describes how inertial a body reacts thermodynamically. The formulation of the heat capacity \( C \) per mass leads to the *specific* heat capacity \( c \) with:

\[
c = \frac{\Delta q}{m \cdot \Delta T}
\]

The specific heat capacities at constant pressure \( c_p \) of several materials which will be applied for this thesis are listed in Table 2.1. Of all listed materials, remarkably water has by far the highest heat capacity. Therefore the chamber walls will be heated much faster than the fluid sample, which consumes the most heating energy.

After the introduction of heat conduction and heat capacity, the basic time-dependent partial differential equation for an arbitrary three-dimensional temperature field can be written as following \[2.5\]:

\[
\rho \cdot c \frac{\partial T}{\partial t} = \frac{\partial}{\partial x} \left( \lambda \frac{\partial T}{\partial x} \right) + \frac{\partial}{\partial y} \left( \lambda \frac{\partial T}{\partial y} \right) + \frac{\partial}{\partial z} \left( \lambda \frac{\partial T}{\partial z} \right) + \dot{q}_{sources}
\]

with the density \( \rho \), the specific heat capacity \( c \), the temperature \( T \), the time \( t \), the thermal conductivity \( \lambda \), the spatial variables \( x \), \( y \) and \( z \) and the volumetric heat sources \( \dot{q}_{sources} \). This equation bases on the formulation of the principle of energy conservation over a control volume.

The outlined theoretical background will be applied in chapter 2.4 on an analytical model.

### 2.3. Joule heating and the temperature-resistance relationship

Joule heating, also known as ohmic heating and resistive heating, is the process by which the passage of an electric current through a conductor releases heat \[2.9\]. Joule’s first law, also known as the Joule effect, reads:

\[
\dot{q} = I^2 \cdot R = \frac{U^2}{R}
\]
2.3. Joule heating and the temperature-resistance relationship

with the dissipated heat power $\dot{q}$, the current $I$, the resistance $R$ of the conductor and the voltage $U$. This relation follows from the electrical power $P = U \cdot I$ with Ohm’s law $U = R \cdot I$.

The resistance $R$ can be calculated for a cuboid as

$$R = \rho_{el} \cdot \frac{A}{l}$$  \hspace{1cm} (2.7)

with the electrical resistance $\rho_{el}$, the cross-sectional area $A$ and the length $l$. Platinum, which will be used for this project, has an electrical resistance of $1.05 \cdot 10^{-7}\Omega m$ at $20^\circ C$ \cite{14}; for Titanium the same value accounts to $3.9 \cdot 10^{-7}\Omega m$ at $0^\circ C$ \cite{14}.

Actually the electrical resistance $\rho_{el}$ is slightly temperature dependent. This effect is employed to build a temperature sensor: Once calibrated, a measurement of the resistance $R$ of a conductor reveals its temperature $T$. The temperature-resistance relationship is usually linearized according to Lao et al. \cite{17} to

$$R(T) = R_0 \cdot (1 + \alpha (T - T_0))$$  \hspace{1cm} (2.8)

with the resistance $R(T)$ at temperature $T$, the resistance $R_0$ at reference temperature $T_0$ and the linear temperature coefficient of electrical resistance $\alpha$. This equation is simplified from the Callendar-Van Dusen equation for temperatures $T > 0^\circ C$, which is also used in the DIN EN 60751:

$$R(T) = R_0 \cdot (1 + A \cdot T + B \cdot T^2)$$  \hspace{1cm} (2.9)

Platinum is the material of choice for temperature sensors because of a high coefficient of resistance $\alpha$, resulting in a better sensitivity, and because of its good linearity. Furthermore platinum temperature sensors do not suffer from measurement drift, and chemically, platinum is also a relatively inert material.

An important design criterion for a resistance heater is the electromigration limit, as outlined by Lao et al. \cite{17} and Lee et al. \cite{18}: If the current density $J$ is higher than a material dependent electromigration limit, the heater will degrade over time. Electromigration is material transport by gradual ion movements in a conductor, caused by electrical current \cite{29}. The current density $J$ is calculated as follows:

$$J = \frac{U}{R \cdot d \cdot w} = \frac{U}{\rho_{el} \cdot l}$$  \hspace{1cm} (2.10)

with the heater line thickness $d$ and width $w$. For platinum, Lao et al. \cite{17} give a limit of $\sim 10^6 \frac{A}{cm^2}$. This limit was undermatched for the heater designs in this thesis.
2.4. An analytical stationary, one-dimensional approach

This chapter outlines an analytical stationary, one-dimensional approach for the given problem, based on the fundamentals of thermodynamics as outlined in chapter 2.2. The geometry of the device can be simplified to a cuboid. Its length and width are about the same, whereas the height is relatively smaller. Therefore, the only modeled dimension here is along the height axis of the device. As follows, the model is constituted by 4 layers: a lid layer, here modeled as polydimethylsiloxane (PDMS), then the layer of sample fluid, the bottom layer of silicon and a thin metal layer representing the heater wire. Figure 2.3 illustrates the model.

Thermodynamically speaking, convection, conduction and a volumetric heat source will be modeled. Convection appears at the top lid layer and the metal layer into the air. Conduction is present within all 4 layers, and the metal layer is the heat source in the model.

In the 3 layers without heat sources, the governing equation 2.5 simplifies to

\[ \rho c \dot{T} = \nabla \cdot (\lambda \nabla T) \] (2.11)

in the stationary case with \( \dot{T} = 0 \), so the temperature distribution will be linear:

\[ T(x) = C_1 x + C_2 \] (2.12)

In the heater layer, from the equation

\[ \rho c \dot{T} = \nabla \cdot (\lambda \nabla T) + \dot{q}_{heater}'' \] (2.13)

the following general quadratic solution can be derived:

\[ T(x) = -\frac{\dot{q}_{heater}''}{2\lambda} x^2 + C_1 x + C_2 \] (2.14)

These equations, formulated for all layers, result in 9 unknowns, including \( \dot{q}_{heater}'' \), the heat power per volume which is necessary to hold a specific temperature. 6 of these
unknowns can be eliminated by formulating the internal boundary conditions: The temperature curve is continuous at the internal boundaries (3 equations), and the heat flux \( \dot{q}'' = -\lambda \frac{\partial T}{\partial x} \) leaving one layer is the incoming heat flux of the adjacent layer (3 equations). Two more equations are formulated by the convection at the top and lowermost layer. For the final ninth equation, the temperature in the middle of the chamber was assigned a designated value.

Figure 2.4 shows the model solved for the parameters as listed in Table 2.2 and Table 2.1 for the thermal conductivities \( \lambda \). As operating point, 95 °C was chosen, whereas the ambient temperature was set 20 °C. For the heat transfer coefficient, \( h = 8 \frac{W}{m^2\,K} \) was chosen based on the script of Poulikakos et al. [23]. The plot outlines the changes in slope depending on the heat conduction coefficient: The higher the heat conduction coefficient is, the more even the temperature distribution results. Since the bottom layer has a high thermal conductivity, its temperature is nearly uniform. At the chosen operating point and an expected size of 4mm × 4mm of the device, the necessary power to hold 95 °C in this model accounts for \( \dot{q} = 0.019 \, W \), a relatively small power compared to the stored heat energy in the system. The heating power is dissipated into the air at the top and the lowermost layer approximately one half each. Another important value which can be analyzed here is the temperature uniformity within the sample fluid. Here, the temperature difference between the uppermost and the lowermost point in the sample fluid accounts for 0.61 °C.

This model describes a stationary analysis, or in other words the final state of the device long after a temperature transition. Therefore the parameters of heat capacity, which become important to reach rapid temperature cycling, did not appear in the equations.
Table 2.2: Parameters of the model

<table>
<thead>
<tr>
<th>Layer</th>
<th>Thickness [µm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lid, PDMS</td>
<td>1000</td>
</tr>
<tr>
<td>Sample fluid, water</td>
<td>720</td>
</tr>
<tr>
<td>Bottom, silicon</td>
<td>300</td>
</tr>
<tr>
<td>Heater, platinum</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Furthermore, the influence of the chamber walls can not be considered as the model is one-dimensional. Hence the outward heat flux caused by convection at the walls is neglected. Nevertheless this model is a first approach to the calculation of the device’s thermodynamic behaviour. The effects of heat conductivity, heat sources and heat sinks could be studied.
3. Numerical simulations

For prediction, analysis and optimisation of the device’s thermodynamical behaviour, a three-dimensional numerical simulation was set up in the Comsol Multiphysics® software. Both steady-state and transient simulations were calculated. The effect of Joule heating is also simulated, resulting in a realistic heat source behaviour.

Two modules were combined to a multiphysics simulation: the "General Heat Transfer" module (htgh) and the "Shell, Conductive Media DC" module (emdcsh). The latter allows to model the Joule heating in a quasi-two-dimensional manner, so to be considerate of the small heater layer thickness. This modeling speeds up the calculations significantly since the number of numerical mesh nodes is reduced. Comsol Multiphysics® also offers an electro-thermal module where Joule heating is calculated alternatively by coupling the "Heat transfer by Conduction" module (ht) with the "Conductive Media DC" module (dc), but this option was not chosen because of the aforementioned drawbacks in terms of calculation speed.

3.1. Geometry, modeling and meshing

Figure 3.1 shows the three-dimensional geometry of the model. Inside the MEMS, an octagonal cavity builds the chamber where the sample fluid will be filled in. For the simulations, the fluid is assigned to be water, which is a reasonable assumption for the designated sample fluids. The walls around the chamber, its bottom as well as most bulk material is made from silicon, as it is processed on a wafer. A solid loop protrudes from the chamber walls in the cavity; this is the sensing element for the measurement of the fluid viscosity. Expect of its geometry, it is not further simulated here. The cover on the chip is a glass plate. The side boundaries of the fluidic chamber are modeled as thin walls, however the actual MEMS is micromachined within a $10 \times 10 \times 0.52$ mm cuboid of silicon. The modeled thin-walled device is proposed as a further development with reduced thermal mass, as inspired by Yoon et al. [30].

In fact there will be a solid connection of the MEMS to the surrounding devices, at least at one edge, whereas the model is spatially limited. Heat will be lost at this connection through conduction, but this unwanted effect should be minimised and it is neglected here.

As already mentioned, the heater wire is only modeled as a shell in the conductive media module. Similarly, Comsol’s software allows to define a so-called "highly conductive layer" in the heat transfer module. This modeling was also chosen for the thin heater wire layer, which is then modeled quasi-two-dimensional as the layer is really thin anyway and it has a high thermal conductivity. A three-dimensional modeling of the heater
wire would result in an extremely fine mesh to resolve the thin structure, which would require a much larger computation time. Despite the difference in computation time, the results are the same for both modeling methods as outlined in Comsol’s Heat Transfer User’s Guide [3]. For the mesh, different refinements were tested. Up to quite coarse meshes, the results differed only slightly. So numerically the solution is quite stable, and the computation time could be held reasonably short (several minutes) with the chosen mesh parameters.

Whereas the device with the geometry from above uses passive cooling by convection, a second device with active cooling was also modeled. This second model has the same chamber and heater geometry, but a Peltier element for active cooling is attached at the heater side of the device. The Peltier element is modeled as a $8 \times 8 \times 2 \text{ mm}^3$ cuboid, based on the $TB-31-0.6-1.5$ type from Deltron AG [7]. A Peltier element has a complex structure inside, which was simplified to a cuboid in order to avoid much longer computation times. The cuboid was modeled with half the conductivity of silicon, and three times the heat transfer coefficient on the backside in order to come up to the inner structure of the element. Then, a heat sink of $1 \text{ W}$ in total was introduced as a power per area on the Peltier side which faces the device. The chosen total power equals the maximum heat pumping power minus half of the heat power by the Peltier element’s dissipation loss, $q_{\text{max}} - \frac{F \times R}{2}$. However, this value remains an approximation, since it depends on the further attachment of the Peltier’s hot side to a bulk heat sink, where the heat finally leaves the system. The main idea of this second model is to study the
Table 3.1: Boundary/edge Conditions

<table>
<thead>
<tr>
<th>Domain</th>
<th>Boundary</th>
<th>Boundary condition</th>
<th>Quantity in Fig. 3.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heater wire</td>
<td>First heater end</td>
<td>Ground</td>
<td>$U_{in}$</td>
</tr>
<tr>
<td></td>
<td>Second heater end</td>
<td>Electric potential</td>
<td>$U_{in}$</td>
</tr>
<tr>
<td></td>
<td>Free surface</td>
<td>Convection</td>
<td>$q'' = h \cdot \Delta T$</td>
</tr>
<tr>
<td></td>
<td>Inner surface</td>
<td>Conduction</td>
<td>$q''_{heating}$</td>
</tr>
<tr>
<td>Chamber</td>
<td>Free surfaces</td>
<td>Convection</td>
<td>$q'' = h \cdot \Delta T$</td>
</tr>
<tr>
<td>Sample fluid</td>
<td>Inner surfaces</td>
<td>Conduction</td>
<td></td>
</tr>
</tbody>
</table>

cooling impact as well as the effects of an additional thermal mass.

3.2. Boundary conditions

The conductive media DC module as well as the general heat transfer module require boundary conditions in the domains where they are active. Table 3.1 summarizes the chosen boundary conditions which will be discussed below.

First, the conductive media DC module needs an applied voltage in order to simulate the Joule heating. A voltage difference is introduced between the two ends of the heater wire by setting one of them to an electrical ground, whereas the other end has an electric potential of $U_{in}$. Since this condition is introduced on a line element, it is an edge condition. The value for $U_{in}$ is then defined as a constant or in some simulations as a function of time, entered in the "Global expressions" menu of the software. All other edges are set as electric insulation/continuity. The conductive media DC module is only active in the heater wire, therefore no more settings have to be entered here.

The general heat transfer module is active in all domains. Whereas inner boundaries simulate heat conduction by default (as outlined in Comsol’s User’s Guide [3]) and ensure temperature continuity, the boundary conditions for free surfaces have to be defined. The device is operated at ambient temperature of 293 K in ambient air, thus convection will occur. A convective heat flux can be entered by defining the heat transfer coefficient $h$ as well as the ambient temperature, so a heat flux of $q'' = h \cdot (T_{chip} - T_{air})$ results. For the value of the heat transfer coefficient $h$, literature was reviewed. For natural convection of gases, Poulikakos et al. [23] gives values in the range of 2-25 W/m²K. The exact value is influenced by the type and state of the gas, the horizontal/vertical placement of the chip, the air movement and the surface properties of the device. Comsol’s tutorials [4] suggest $h = 5 \ W/\text{m}^2\text{K}$, whereas El-Ali et al. [10] calculate with $h = 7.5 \ W/\text{m}^2\text{K}$, and Lao et al. [17] reached realistic results with an assumption of $h = 12 \ W/\text{m}^2\text{K}$. In our model, a middle value of $h = 8 \ W/\text{m}^2\text{K}$ was chosen based on these literature values, as in chapter 2.4. Finally, in order to link the two modules, the heat produced by Joule heating has to be introduced as a heat source $q''_{heating}$ at the interface boundary between the heater
3.3. Simulation results

Figure 3.2: Steady-state temperature plotted against applied voltage on the heater. The power \( P = U^2/R \) introduced by the heater compensates heat losses of convection to the ambient air. The temperature is calculated as the mean value in the sample fluid.

The results and insights gained by simulations are summarized in this chapter. Steady-state and transient simulations have to be distinguished.

3.3.1. Steady-state simulations

Steady-state simulations are necessary to understand the behaviour between two subsequent steps according to Figure 2.1. As it will be shown by transient simulations in chapter 3.3.2, steady-state can be reached within seconds for the given system. Thermodynamically, at steady-state the heater will introduce heat to compensate the heat loss by convection. In order to evaluate the applied voltage on the heater which is necessary for a certain equilibrium temperature, Figure 3.2 was plotted based on simulation results. Voltages in the range of 1 - 1.5 V are necessary to keep the temperature of the device at our designated temperatures, hence a voltage control with appropriate resolution in this range will be necessary. For the simulations with attached Peltier element, the required heat power to hold a certain temperature is approximately twice as high because of the
3.3. Simulation results

Figure 3.3: Temperature difference of measuring points at the top, middle and bottom of the fluid sample, plotted against the reference sensor temperature at steady-state.

A uniform temperature distribution within the device at steady-state is a crucial criterion for the success of the PCR method, since the behaviour of the reagents in the sample fluid is expected to be highly dependent on the temperature. Therefore Figure 3.3 was plotted to provide answers to the question of temperature uniformity. It summarizes the simulation results on 4 different measuring points for the passively cooled device. The first point is chosen at the top of the fluid sample just below the lid. A second point is chosen in the middle of the chamber, far away from the loop. The third point is located at the bottom of the fluid sample at the border to the silicon bottom. The fourth point is chosen right at the temperature sensor, it gives the reference temperature which is plotted on the x-axis. The plot shows the temperature difference of a measuring point compared to the reference at different temperatures. As it can be seen, higher operating temperatures cause higher temperature differences within the device, since the heat flow by convection is higher. At 95° C, the temperature difference within the fluid sample is found to be ∼ 0.6° C, matching the analytically calculated value of 0.61° C in chapter 2.4. Such a value should not be problematic for PCR, since in reality it is expected to be lowered because of the free fluid motion within the sample. Finally, the measuring point at the bottom of the chamber has a marginally higher temperature than the sensor, since it is located just above a heater wire.

A comparison with the model from chapter 2.4 confirms the simulation: The normal conductive heat flux through the lid results in 0.0054 W at 55° C in the Comsol model, whereas the one-dimensional model results in 0.0056 W. The heat loss through the walls
3.3. Simulation results

Figure 3.4: Applied voltage (feed forward control) and the resulting simulated temperature step (averaged over the fluid sample) from 2 to 3 in Figure 2.1 sums up to 0.0046 W. This heat flux is not negligible compared to the former one, so the importance of a three-dimensional modeling is shown.

3.3.2. Transient simulations

Simulation of a heating step

Transient simulations were calculated for a heating step from 55°C to 70°C according to the step from 2 to 3 in Figure 2.1. The goals of these simulations are to characterize the feasible heating rates, to determine the necessary heating power and to estimate the duration to reach steady-state.

In order to simulate a heating step, the applied voltage profile on the heater has to be determined. A chosen voltage of 8 V was applied and iteratively simulated with different heating times until the correct heating time to reach 70°C was found. Figure 3.4 shows the resulting voltage profile and the resulting simulated temperature step, averaged over the fluid sample volume. A heating time of ~1 s at 8 V was necessary. After the heating, the voltage is set to the necessary steady-state voltage to hold 70°C according to Figure 3.2. For the following simulations, the shown voltage profile was applied as a feed forward control.

Figures 3.5-3.8 outline the spatial temperature distribution at different times. The initial temperature for all domains of the device was set to 55°C, and a voltage difference of 8 V on the heater caused heating. This voltage results in a heating power of $P = 0.91$ W,
Figure 3.5: Transient simulation at the beginning of a heating step from 55°C to 70°C, resulting in a nonuniform temperature distribution. The walls heat up much faster than the fluid.

Figure 3.6: Temperature distribution at $t = 1$ s, whereas heating stopped at $t = 0.9$ s. Temperatures above and below the target temperature of 70°C are temporarily present.
3.3. Simulation results

Figure 3.7: Equilibration of the temperature towards $70^\circ C$ advances $1.5$ s after the heating stop at $t = 0.9$ s. The protruding loop supports the heat flow from the walls into the fluid.

Figure 3.8: Steady-state temperature distribution at $70^\circ C$ is almost reached at $t = 4.8$ s
which is not yet exploiting the maximum possible heating power concerning the elec-
tronmigration limit ($\sim 25$ $W$ in the current configuration).

Figure 3.5 was recorded at $t = 0.6$ $s$: Whereas the outer silicon walls were already heated
up to $75^\circ$ $C$, the fluid in the chamber is still at about $58^\circ$ $C$, which is only $3^\circ$ $C$ higher
than at $t = 0$ $s$. The low thermal conductivities and the high specific heat capacity of
the fluid cause a rather nonuniform temperature distribution. At $t = 0.9$ $s$, the applied
voltage was reduced to $1.3$ $V$ as evaluated by Figure 3.2 in order to stop heating and
hold $70^\circ$ $C$, following the temperature profile of Figure 2.1. The residual heat power is
necessary to compensate the heat losses from convection to the ambient air, which is at
$20^\circ$ $C$. Figure 3.6 shows the device $1$ $s$ after the start of the simulation: Whereas the
walls are still up to $7^\circ$ $C$ warmer than the target temperature of $70^\circ$ $C$, the fluid is up
to $9^\circ$ $C$ too cold, resulting in a temperature difference of $\sim 15^\circ$ $C$ in the device. Figures
3.7 and 3.8 outline the subsequent equilibration at times $t = 2.4$ $s$ and $t = 4.8$ $s$, where
the temperature approaches $70^\circ$ $C$ all over the device.

The heat flows from the walls into the fluid, whereas the protruding loop supports the
heat flow, resulting in higher fluid temperatures around the loop. As an important re-
result, steady-state is almost reached after a few seconds as shown in Figure 3.8. The
remaining temperature differences are caused by convection, which cools the outer areas
of the device.
3.3. Simulation results

Evaluation and comparison of the device’s time constant

The aim of this chapter is to calculate the time constant of the device, in order to prepare an appropriate control of the system and to provide a value for comparison of different devices. In addition to the geometry of Figure 3.1, a second geometry as shown in Figure 3.9 is considered. The additional geometry is not modeled with thin silicon walls, rather the fluid chamber is within a $10 \times 10 \times 0.52 \text{ mm}$ cuboid of silicon, which adds more thermal mass to the system. All other parameters remain the same. This geometry is closer to the prototype, where thin walls were not etched.

Based on the equations of chapter 5.2, the step function response of the temperature obeys basically the solution of a first-order differential equation. So for the mean temperature $T$ of the fluid and an initial temperature $T_0$ which equals the ambient temperature, we expect the following step response upon a voltage step on the heater, as derived in chapter 5.2:

$$T(t) = T_\infty \cdot \left(1 - e^{-\frac{t}{\tau}}\right) + T_0 \quad (3.1)$$

with the steady-state temperature $T_\infty$ and the time constant $\tau$. The time constant $\tau$ is defined as the duration of the temperature change process to reach 63.2% of the complete steady-state temperature step $T_\infty - T_0$.

$T_\infty$ for an arbitrarily chosen voltage step is determined first by a steady-state simulation. Then, the time-dependent mean heating rate $\dot{T}$ of the fluid sample at $t = 3 \text{ s}$ was inserted into the equation

$$\dot{T}(3) = \frac{T_\infty}{\tau} \cdot e^{-\frac{3}{\tau}} \quad (3.2)$$

for the evaluation of $\tau$. This derived equation is chosen for the calculation of $\tau$ as it is less prone to errors by dead times in the system, because the heating rate is almost constant for some tenths of a second around $t = 3 \text{ s}$. The evaluation time $t = 3 \text{ s}$ was also chosen since the temperature curve showed a reliable first-order response at this time.

For the main design with thin walls, $\tau = 145.5 \text{ s}$ resulted. The geometry with more silicon mass had a shorter time constant of $\tau = 143.7 \text{ s}$ despite its higher thermal mass, because its increased heat losses by convection lead to a faster temperature equilibration. However, as evaluated during these simulations, the heating rate is about 4 times higher for the thin-walled device: With $T_0 = 55^\circ \text{C}$, it showed a heating rate of $2.2^\circ \text{C/s}$ after $t = 1 \text{ s}$ for an applied voltage of 3 V, whereas the larger device only heated up with $0.52^\circ \text{C/s}$ with the given parameters. In other words, the thin-walled device has longer to reach its steady state upon a given voltage step, but its heating rate and temperature step is higher than in the prototype device with higher silicon mass.
3.3.3. Simulation of a full PCR cycle

A complete PCR cycle with heating from $55^\circ C$ up to $95^\circ C$ and cooling down to $55^\circ C$ was simulated in order to predict the period of one cycle and to characterize the behaviour of the system in terms of control and transient temperature distributions. Figure 3.10 shows the result for two different devices: The blue curve represents a thin-walled device with passive cooling by convection only, whereas the black curve shows a temperature profile with active cooling by a Peltier element with common properties, also on a thin-walled device. The temperature values on the left axis are mean values: A subdomain integration over the fluid sample was calculated and divided by its volume. For the heating steps, $8 \, V$ were applied on the device with passive cooling, whereas $16 \, V$ had to be applied on the device with attached Peltier element to reach a comparable heating rate. An applied voltage profile for the whole cycle is also shown in Figure 3.10, whereas the axis on the right side gives the voltage values.

![Figure 3.10: Simulation of a complete PCR cycle as in Figure 2.1. This simulation reveals the need for an active cooling of the device. The applied voltage on the resistive heater for feed forward control of the PCR cycle on the device with passive cooling is plotted with its axis on the right side.](image)

This simulation shows the need for an active cooling of the device, since the convection can only make up for a cooling rate of $\sim 0.8^\circ C/s$. However, the attachment of a Peltier element has some minor drawbacks: Twice the voltage, equalling four times the power, is necessary compared to the device alone in order to reach a similar heating rate. This can be explained as half of the heating power is lost by conduction into the Peltier el-
3.3. Simulation results

Figure 3.11: Temperature sampling of measuring points at the top, middle and bottom of the fluid sample during a simulated PCR cycle with the same feed forward control as shown in Figure 3.10.

The Peltier element had an actively cooled device, whereas the passively cooled device had a heater-air interface with almost no heat loss. Furthermore, the Peltier element adds a relatively high thermal mass to the system. Due to the higher thermal mass, the temperature curve is also less sharp and tends to overshoot, as the Peltier element heats up faster than the material around the sensor.

Finally, Figure 3.11 is an evaluation of the same simulation of a complete PCR cycle. In this plot, the temperatures of measuring points at the top, middle and the bottom of the fluid sample as well as the temperature at the sensor location are shown, unlike the mean values of Figure 3.10. The crucial insight here is the overshoot of the temperature at the bottom of the fluid sample, which is problematic as soon as the boiling point of the sample fluid, e.g. 100° C for water, is surpassed. This plot demonstrates the importance of a non-aggressive control algorithm in order to avoid bubbles of boiling liquid.
4. Fabrication

4.1. Fabrication of the heater and temperature sensor

This chapter covers the microfabrication as well as the assembly of the PCR device, including a heater and sensor unit and a lid for the microfluidic chamber. Figure 4.1 shows the cross-sectional sideview of the final assembly in order to give an overview. A photographic top view of the final assembly can be found in Figure 4.15, a bottom view is shown in Figure 4.13b. The following chapters outline the particular fabrication steps.

![Cross-sectional sideview of the assembled device (not to scale).](image)

4.1.1. Wafer processing

The heater and temperature sensor pads are fabricated with MEMS technology in the cleanrooms of the institute. The primary material is a 4 inch silicon wafer with a thickness of 300 $\mu m$. It is p-doped with a resistivity $\rho_{el}$ of $0.07 - 0.13 \, \Omega \cdot cm$, and the surface is polished on both sides.

The fabrication of the quasi-two-dimensional platinum heater and sensor structure on the wafer bases on a so-called lift-off process. The single fabrication steps are illustrated in Table 4.1 and the final optimized version of the corresponding processing recipe with the parameters and technical details is attached in appendix C.1.

The general layout of the heater and sensor structure is shown in Figure 4.2. Two circuits of platinum will be deposited on the substrate, one for temperature measurements as a resistance thermometer, one for resistance heating. The resistance thermometer is designed to have a high resistance, in order to prevent self-heating, which would influence the measurement. Furthermore a high resistance results in a higher sensitivity.

The resistance heater is designed according to the power requirements: $\dot{q} = \frac{U^2}{R}$ with the
heating power $\dot{q}$, the applied voltage $U$ and the resistance $R$, as outlined in equation 2.6. For a given supply voltage $U$, the maximum heat power can be enlarged by a design with low resistance $R$.

(a) In this prototype version, 4 large contact pads on the left and right side are provided for electrical connection. The widths of the two circuits are designed to be 20 $\mu m$ and 200 $\mu m$.

(b) A design version of the second series with widths of 40 $\mu m$ for the thermometer and 450 $\mu m$ for the heater is shown. The contact pad size and therefore the overall size could be reduced.

Figure 4.2: General layout of the heater and sensor structures: The finer one of the two electrical circuits represents the resistance heater, the large meander is a resistance heater.
4.1. Fabrication of the heater and temperature sensor

Table 4.1: Fabrication steps

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>The substrate is covered with an oxide layer of 200 nm by PECVD. This layer is intended as an electrical insulation between the silicon and the following structures. Furthermore, an oxidized surface is passivated in terms of biological reactions with an adjacent fluid sample.</td>
</tr>
<tr>
<td>2.</td>
<td>A negative photoresist is spin-coated and photolithographically patterned with a mask as shown in appendix A, Figure A.1. The mask represents 56 devices of 4 different designs, one of them as shown in Figure 4.2. Figure 4.3a is a microscopic photograph of the wafer after this stage.</td>
</tr>
<tr>
<td>3.</td>
<td>A titanium layer of 20 nm is deposited as an adhesion layer, then a platinum layer of 180 nm is deposited on top, both times by evaporation. Sputtering was also considered as an alternative to evaporation, but it requires a large bulk mass as a target, so it is too expensive for the deposition of platinum. The evaporation had a yield of 5%. Figure 4.3b shows the platinum layer.</td>
</tr>
<tr>
<td>4.</td>
<td>Lift-off with N-Methyl-2-pyrrolidone (NMP). The excessive platinum is removed. In order not to damage the thin structures, a gentle lift-off was found to be crucial with no use of the ultrasonic bath; blowing by pipettes supported the lift-off instead. Figure 4.4 shows the results after this step.</td>
</tr>
<tr>
<td>5.</td>
<td>A protective photo resist layer is spin-coated since the subsequent dicing is a rather muddy process. Figure 4.5a shows the coated wafer. The protective layer can easily be removed after dicing with acetone and isopropanol, so a clean surface is educed, as confirmed in Figure 4.5b.</td>
</tr>
</tbody>
</table>
4.1. Fabrication of the heater and temperature sensor

(a) The negative photoresist (red surface), patterned by photolithography. Structures of 40 $\mu$m width are correctly represented on the centerline of this example, thinner structures of 20 $\mu$m were problematic in some cases.

(b) A surface view of the deposited platinum is shown. A brittle layer results when the platinum is deposited on the photoresist, as in the left half of the image. On the right half, a neat surface of platinum on the wafer evolved.

Figure 4.3: Microscopic images before the lift-off process

(a) A neatly looking example as most devices on the wafer

(b) A poorly developed device towards the border of the wafer

Figure 4.4: After lift-off, the bright structures show the platinum layer, whereas the dark surfaces represent the wafer surface.
4.1. Fabrication of the heater and temperature sensor

(a) The processed wafer is protected by a layer of photoresist before the abrasive dicing process

(b) A clean surface is visible under the light microscope after dicing and removal of the protective photoresist layer

Figure 4.5: Final process steps

4.1.2. Fabrication process analysis and optimization

After the fabrication of the prototype series, the devices were analyzed in terms of their performance. Since some measurements have shown irregularities with the resistance of the heater and the sensor, the fabrication process was analyzed in detail in order to find the reason for the irregularities, as described in this chapter. More precisely, in the prototype series the resistances of the heater and the sensor were measured to be up to 10 times higher than calculated with the bulk value of the specific electrical resistance of platinum \( \rho_{el} \). Thin films are known to have different physical properties than described by the bulk values, but this discrepancy might be caused by a fabrication problem. Furthermore, the resistances of different devices showed a high variance. In order to overcome these irregularities, an in-depth analysis of the fabrication process was started, and its conclusions are drawn at the end of this chapter.

Surface profilometer measurements of the platinum film

In order to confirm the layer thickness of the deposited platinum and titanium, the wafer surface was measured with a surface profilometer, type Tencor P10. Figure 4.6 shows the result of 3 measurements on different locations on the wafer. The measurement needle was set to a speed of 100 \( \mu m/s \) and 50 \( \mu m/s \). The target thickness of 300 \( nm \) is achieved with a precision of about \( \pm 10\% \). The layer thickness decreases towards the border of the wafer, as shown in the measurement of sample 2. Sample 1 shows a runaway value at a distance of 600 \( \mu m \), which is assumed to be caused by a dust particle on the surface.
4.1. Fabrication of the heater and temperature sensor

Figure 4.6: The height of profile of the heater and sensor wires on the pad surface, measured with a profilometer.

Identification of film irregularities in the Scanning Electron Microscope (SEM)

For the analysis of the film’s surface microstructure, inspections by a scanning electron microscope (SEM) were considered. A Zeiss DSM 962 delivered valuable insights as described in this chapter.

(a) A large crack, beginning at the film border
(b) Cracks within the film
(c) Relatively small cracks on the surface

Figure 4.7: SEM images reveal cracks in the platinum film.

Whereas the film surfaces looked fine under the light microscope for most devices on the wafer as shown in Figure 4.4a, Figure 4.7 shows a different result: Cracks on the film surface can be seen in these three images. These cracks may increase the film resistance and cause a variation, as the crack size and distribution varies on different spots on the wafer. Some cracks are as small as 2 \( \mu m \), whereas others cross the whole film width. The SEM machine parameters such as magnification, acceleration voltage and working distance are shown on the lower border of the images. Discussions with various stakeholders and experts in the house helped to find reasons and explanations for these cracks, as listed below.
• Since the cracks are deep and not filled with additionally evaporated platinum, the cracks are assumed to occur after and not during the evaporation process.

• The film adhesion is not considered problematic, otherwise an ablation beginning at corners and edges would be visible. Furthermore, scratching with a metal tip on the film showed a good adhesion of the film.

• The team from the evaporation laboratory suspected residues of photoresist between the film and the substrate to be a possible reason.

• The prototype film thickness of 20 nm Ti/280 nm Pt is rated to be critically high.

• Among experienced experts at the FIRST-Lab CLA, the use of an ultrasound bath (1 min, power 2) for a better lift-off is assumed to cause these cracks.

• Intrinsic stresses might be a reason, because many cracks are perpendicular to the film border. Since the film borders are strainless, cracks which are perpendicular to the film border are an indication of intrinsic stresses.

• Another explanation for the cracks are stresses because of different coefficients of thermal expansion: At 25 °C, the coefficient of thermal expansion for platinum is $\delta_{Pt} = 8.8 \cdot 10^{-6} \, K^{-1}$ [14], whereas for silicon the coefficient is $\delta_{Si} \approx 2.5 \cdot 10^{-6} \, K^{-1}$ [28]. During the lift-off, a temperature of 65 °C was set for this first series.

• The target wafer was installed at half height in the evaporation chamber in order to reduce the platinum usage. This method was not assumed to be problematic by the team from the evaporation laboratory, so it was continued. However it might be a main difference to the fabrication methods of other research groups.

Based on these insights of various discussions, a second wafer was processed and analyzed in detail. The wafer was controlled in the SEM after every fabrication step in order to find the reason for the described irregularities. The following chapters report the outcome of this analysis.

Photolithography process analysis

Based on the insights from the SEM images, amongst other reasons the photoresist was suspected to cause the irregularities of the platinum film. More precisely, the photoresist can cause problems if it is not adequately developed by photolithography. In this case residues of photoresist between the substrate and the platinum film would reduce the film quality. Mainly because of this concern, a process analysis and development was started as described in this chapter.

The following principal photolithography process changes were considered:

• A flask of fresh AZ nLOF2070 was ordered, since photoresist is prone to expiration.
The processing recipe was changed in order to avoid residues of photoresist:
- A sample with a prolonged exposure was processed
- A sample with a prolonged development time was processed

Figure 4.8 shows the resulting photoresist layer after photolithography, photographed through a light microscope. First, Figure 4.8a is a reference with the original recipe. The large areas with darker color are covered with photoresist. The large areas with lighter color should be free of photoresist, so that the evaporated platinum stays on these surfaces. At the border between these large areas, a transition zone indicates the so-called undercut of the photoresist. Figure 4.9 sketches the desired undercut profile: The evaporated platinum on top of the photoresist is not connected to the platinum film which stays on the substrate after lift-off. Figure 4.8a shows the achievement of this undercut and its width. (By adjusting the focus back and forth, this undercut could be seen more clearly than with the limited depth of focus of a single image.)

![Microscopic images of the photoresist after photolithography.](image)

Figure 4.8: Microscopic images of the photoresist after photolithography. The shown loops have a width of 20 µm. Different variations of the processing recipe are compared: Longer exposure or development lead to thinner photoresist structures. The contours are twofold visible, revealing the desired undercut of the photoresist layer.

![Sketch of the desired undercut profile for an optimal lift-off.](image)

Figure 4.9: Sketch of the desired undercut profile for an optimal lift-off.
Figure 4.8b shows the same section for a wafer which was exposed with 175 \( mJ/cm^2 \) (15% higher than before). As it can be seen, the vertical stripe of photoresist in the center of the image was narrowed by the stronger exposure. In Figure 4.8c, the same effect is observed after a development of 2.5 minutes (25% longer than before).

These photoresist layers of these differently processed wafers were now measured by the surface profilometer. Figure 4.10 shows the result: A photoresist thickness of \( \sim 6 \, \mu m \) resulted. The spin curve of the manufacturer’s data sheet indicates a thickness of 7 \( \mu m \) at 2500 \( rpm \), which matches the measured thickness approximatively. Furthermore, the profilometer indicates the surface roughness. Whereas the photoresist has a clearly visible roughness in Figure 4.10, the lower surface where the platinum film will adhere was measured to be exactly 0 \( \mu m \) along the measurement path for all three measured wafers.

If there were substantial residues of photoresist, a roughness would probably be visible. Furthermore, the thickness of the three wafers would be different if a residual layer of photoresist remained on the substrate. The wafer was also analyzed in the SEM, where no problematic residues of photoresist were found.

Figure 4.10: The height of profile of the photoresist layer before evaporation.

This analysis led to the insight that the photoresist and the photolithography did most probably not cause the irregularities which were discovered in the SEM. The recipe for the photolithography showed a reliable result, and the original photolithography parameters concerning exposure and development time were resumed.

**Process improvements and conclusions**

Based on the insights of the previous chapters, the process improvements as listed in the following were introduced. Because of the high costs for a platinum film evaporation, all those changes were applied at the same time, unlike the photolithography analysis, where the effects of particular changes could be studied.
• The total film thickness was reduced from initially 20 nm Ti/280 nm Pt to 20 nm Ti/180 nm Pt.

• The lift-off process was performed without the ultrasound bath. Liquid blowing with a pipette was chosen instead.

• The substrate heating during evaporation was turned off.

• The temperature of the NMP bath for the lift-off was decreased from originally 65°C to 50°C.

• Hexamethyldisilazane (HMDS), an adhesion promoter for photoresist, was applied.

• The wafer was cleaned in the plasma asher for 20 s at 100 W between the photolithography and the evaporation, rather than 14 s as the prototype.

• The oxide layer thickness was reduced from 500 nm to 200 nm.

• Residual water was evaporated at 110°C for 90 s before the photolithography step.

• The following evaporations were processed in a different machine because of a technical breakdown of the former machine.

The wafer was monitored by light microscope, an example is shown in Figure 4.11. The wafer was also analyzed in the SEM after every fabrication step, examples of images are shown in Figure 4.12. The formerly described cracks did not occur again with these process improvements. As an important result of the process development, the variation, the reproducibility and the constancy of the resistance values could be improved. However, compared to the bulk values the resistances of the devices were still 3 times higher on one wafer side and up to 7 times higher on the other wafer side, as further outlined in appendix C.3. The team from the evaporation laboratory considers such variations as not surprising, but rather higher than expected. Possibly the evaporation quality
was decreased because the target wafer was installed at half height in the evaporation chamber in order to reduce the platinum usage.
As such a result had to be expected, various different heater and sensor designs were drawn on the mask. Due to this measure of precaution, devices with suitably low resistances were processed on the wafer even so, allowing the further progress of the project.

(a) Before the lift-off: A stripe of photoresist, covered with Pt, protrudes into the image. The photoresist’s undercut profile can clearly be seen.
(b) Also before the lift-off, a photoresist layer forms a step of 6 \( \mu m \) at the upper right side of the image. The undercut profile creates a gradual increase of the Pt film thickness at the border.
(c) With the new recipe, an even film surface without cracks resulted as shown here. The surface was focussed on a dust particle on the surface.

Figure 4.12: A selection of SEM images which were taken to examine the fabrication process.

4.2. Electrical connection and assembly of the pads

For the electrical connection of the pads, 4 different options can be considered: Conductive silver, conductive epoxy, soldering and wire bonding. The first three methods were applied for prototypes because of their simplicity, however they require a relatively large contact pad of \( > 1 \text{mm}^2 \), whereas wire bonding is the only one of those 4 techniques which allows electrical connections in the micrometer range.

Conductive silver is a fast and easy way for the electrical connection, however the mechanical stability of the connection is poor. Figure 4.13a shows an example of the electrical connection by conductive silver on a prototype. Conductive epoxy has a sufficient mechanical stability, but it is more delicate to apply on small pads. Soldering is possible, however the bond is not optimal, and the soldering temperature of 330 \( ^\circ C \) might damage the devices. As an advantage, soldering inherently provides a fuse, since the connection breaks at high temperatures.
4.3. Fabrication of the lid for the fluidic chamber

Wire bonding is the best suited and most widely used method for the electrical connection of microsystems. A DELVOTEC 5425 wirebonder with an ultrasound source was used with parameters as listed in appendix C.5. Wire bonding can bridge only short distances, so a second pad where the wire can be connected to is required. Therefore a printed circuit board (PCB) was drawn and ordered at Eurocircuits GmbH. In appendix B the design of the PCB is depicted with four connections on the backside for the heater and the sensor as well as two connections on the frontside for the viscosity sensor, the gold wire loop. Figure 4.13b shows the electrical connection between a pad and the PCB.

As it can be seen, multiple wires were bonded on each pad in order to allow a larger current and increase the mechanical robustness. The wire which is used here was tested to withstand a current of up to \( \sim 0.4 \) A, above this limit it begins to glow and subsequently break.

For the bond between the pad and the silicon chip as it is shown in Figure 4.13b the adhesive Vitralit 6108T was ordered at IBZ AG, Adliswil. The main requirement for the adhesive is its biocompatibility. The fluid sample in the fluidic chamber should not be contaminated. Bestmann [2] reported successful tests with the Vitralit product line. Vitralit 6108T is a multifunctional medical adhesive of 4000 – 6000 mPa · s viscosity. The adhesive was cured at 120° C for 30 min.

4.3. Fabrication of the lid for the fluidic chamber

As material for the fabrication of the lid on top of the fluidic chamber, polydimethylsiloxane (PDMS) is chosen. PDMS, a clear silicone, is well-known as an ideal material for the rapid prototyping of microfluidic devices. It offers the necessary biocompatibility for our purpose and allows to view into the fluidic chamber, since it is transparent. Furthermore, measurements with a laser Doppler vibrometer through this lid were ex-
4.3. Fabrication of the lid for the fluidic chamber

The product "Sylgard® 184" from Dow Corning was chosen. It consists of two originally liquid components which have to be well mixed with a fork in a 1 : 10 ratio by weight. After mixing, the liquid contains small air bubbles, so the mixture has to be degassed for about 20 minutes in a vacuum chamber. The liquid PDMS can now be poured on a mold in a petri dish, as it can be seen in Figure 4.14. The silicone needs about 48 hours to cure at room temperature, alternatively a faster curing can be achieved in an oven.

Figure 4.14 shows two different molds which were developed during the project. The mold in Figure 4.14a was fabricated by traditional manufacturing out of aluminum by Jean-Claude Tomasina at the workshop of the institute. The mold has a profile height of 200 µm and was a valuable prototype. Since traditional manufacturing allows only geometric shapes at this scale, a next mold was fabricated by bulk micromachining, as shown in Figure 4.14b. This mold also includes fluidic channels for an improved filling of the chamber. For this mold, a silicon wafer of 500 µm thickness was patterned by photolithography with a positive photoresist, then the wafer was dry-etched by deep reactive ion etching (DRIE) (Bosch process) on an equipment of Surface Technology Systems with inductively coupled plasma (ICP). A depth of 200 µm was etched. The recipe for this process is listed in appendix D. The mask layouts with several microfluidic channel designs are shown in appendix A in figure A.3. Different designs were tested in order to optimize the fluid sample filling process, where air bubbles in the chamber should be avoided.

![Figure 4.14: Clear PDMS is cured on a mold within a petri dish](image)

(a) A traditionally machined aluminum mold  (b) A bulk micromachined mold, fabricated with DRIE out of a silicon wafer

After curing of the PDMS on the mold, the material stays flexible and a cutter was used to cut the lids. For most designs, two holes in the lid are intended for the filling. These holes were punched with a sharpened thin-walled metal tube. Then the lid can be bonded onto the MEMS. As widely reported in literature, PDMS can be bonded by oxygen plasma activation without any adhesives. Duffy et al. [9] explains the bond by
a conversion of $-OSi(CH3)2O-$ groups at the surface to $-O_nSi(OH)_{4-n}$ by a plasma discharge oxidation, as indicated by experimental evidence. Covalent siloxane (Si-O-Si) bonds between two surfaces are then believed to be formed, resulting in a bond. For activation of the surfaces, a device called "Laboratory Corona Treater BD-20ACV" was used, which is also reported by Haubert et al. [15]. Test series revealed an optimal bond when the silicon substrate as well as the PDMS were treated by a back and forth movement of the corona over the pieces for 40 s, however the results depend on many parameters such as the distance between the corona and the surfaces, the underlay, the surface cleanliness and the surface properties of the pieces to bond. Therefore silicon substrate was previously cleaned by isopropanol. After light clamping for 30 seconds, the bond needed about one more day to complete as experience has shown. The activation changes the surfaces from hydrophobic to hydrophilic, what can easily be checked by the placing small water drops on the surface. Whereas this method is ideal in terms of fabricational simplicity and biocompatibility as it does not require any adhesives, a clean handling was crucial in order to reach a fluidic chamber without leakages.

### 4.4. Tubing of the chamber

The tubing for the chamber in the chip has to fulfill two main tasks: First it has to allow a reliable filling with a fluid. Secondly, it should form a closed, airtight system together with the chamber during the PCR cycles in order to prevent evaporation of the fluid. Figure 4.15 is a photograph of the tubing. Small tubes were inserted in the punched holes on the PDMS lid, so a form fit resulted. Flexible silicone tubes are imposed on the rigid small tubes as shown on the right side of the image. These silicone tubes can then easily be connected to syringes.

![Figure 4.15: Tubing on the square chip of 10 × 10 mm](image)
5. Instrumentation and control

5.1. Instrumentation setup

The concept of the instrumentation is the connection of all devices to a personal computer (PC). A PC allows to automate, control and record experiments on the devices in a flexible manner. Figure 5.1 shows a schematic diagram of the instruments and their connections.

The instrumentation can be divided into actuation and sensing tasks. For this thesis, actuation means resistive heating and sensing means one or multiple temperature measurements.

For the actuation of the heating, a Hameg® Instruments HM7044 controllable voltage source is connected to a PC by the serial interface RS-232. This device allows to set a direct current voltage output of $0 - 32 V$ with a precision of $10 mV$.

For the primary sensing of the temperature, the resistance thermometer on the device has to be calibrated. After calibration of this thermometer, the temperature can be determined by measuring resistance. For this purpose, a Keithley Model 2000 6 1/2-Digit Multimeter is connected to the same PC by a General Purpose Interface Bus (GPIB). This instrument allows to measure resistances ranging from $100 \mu \Omega$ to $100 M\Omega$ with an accuracy of $0.008\%$. A second Multimeter of the same type was occasionally connected in order to measure a second temperature value simultaneously, as it is reported in chapter 6.4.
5.2. Modeling of the dynamic system for control engineering

In order to define an appropriate model of the plant, the dynamics of the thermodynamic system will be analysed in the following chapter. A more profound understanding of the dynamics supports the analysis of the following experiments. Following an example in the control engineering lectures of Guzzella [12], first a temperature $T(s)$ of the system is assumed to be spatially uniform, including the fluid sample and the chamber walls. This approach is called a "lumped parameter assumption". Then a level variable $T(t)$ is defined with

$$T(t) = T_s(t) - T_0(t)$$  \hspace{1cm} (5.1)

whereas $T_0(t)$ represents the temperature of the environment. Now the internal energy $E$ stored in the system has to fulfill the following energy balance:

$$\dot{E}(t) = m \cdot c_p \cdot \dot{T}(t) = \dot{q}_{\text{in}}(t) - \dot{q}_{\text{out}}(t)$$  \hspace{1cm} (5.2)

with the inward and outward heat flows $\dot{q}_{\text{in}}$ and $\dot{q}_{\text{out}}$. They are defined by resistive heating and convection, respectively:

$$\dot{q}_{\text{in}} = \frac{U(t)^2}{R}$$  \hspace{1cm} (5.3)
$$\dot{q}_{\text{out}} = h \cdot A \cdot T(t)$$  \hspace{1cm} (5.4)

following equation 2.6 for Joule heating, and equation 2.2 for convection. So the model formulation reads

$$m \cdot c_p \cdot \dot{T}(t) = \frac{U(t)^2}{R} - h \cdot A \cdot T(t)$$  \hspace{1cm} (5.5)

As it can be seen, for a constant voltage $U$ the dynamic system is of first order. Division by $m \cdot c_p$ yields

$$\dot{T}(t) = \frac{U(t)^2}{R \cdot m \cdot c_p} - \frac{h \cdot A}{m \cdot c_p} \cdot T(t)$$  \hspace{1cm} (5.6)

so the time constant $\tau$, the inverse factor in front of $T(t)$, can be read as $\tau = \frac{m \cdot c_p}{h \cdot A}$. The higher the time constant gets, the more slowly the system will respond.

An analytical solution for $T(t)$ in equation 5.6 can be determined in the case where the input voltage $U(t)$ is constant, as outlined by Storey [27]. The analytical solution is the sum of the homogeneous solution $T_h(t)$ and the particular solution $T_p(t)$. For $T_h(t)$, we find

$$T_h(t) = C \cdot e^{-\frac{t}{\tau}}$$  \hspace{1cm} (5.7)
with an integration constant $C$. For the particular solution, the equilibrium point with $\dot{T}(t) = 0$ can be chosen, so the particular solution yields

$$T_p(t) = \tau \cdot \frac{U^2}{R \cdot m \cdot c_p} \quad (5.8)$$

The overall solution $T(t) = T_h(t) + T_p(t)$ reads

$$T(t) = C \cdot e^{-\frac{t}{\tau}} + \tau \cdot \frac{U^2}{R \cdot m \cdot c_p} \quad (5.9)$$

By choosing the initial condition $T(t = 0) = 0$, the integration constant $C$ can be determined, so the solution becomes

$$T(t) = \tau \cdot \frac{U^2}{R \cdot m \cdot c_p} \cdot \left(1 - e^{-\frac{t}{\tau}}\right) \quad (5.10)$$

Some parameters in this equation are not precisely known for the real system. The mass $m$ is not precisely known since the chamber walls as well as the clamping of the device will be heated too, and the heat transfer by convection and conduction through the clamping is not quantifiable a priori. Therefore the "lumped parameters" of this model have to be determined experimentally. Namely two parameters, $\tau$ and $m$, have to be found. These two parameters can be determined by fitting the model to experimental data [27], as outlined in the following.

Figure [5.2] shows the recorded curve during the experiment as well as a fitted curve. The fitted curve has a resulting mass of $m = 6.1 \cdot 10^{-5} \text{ kg}$. Since the water inside the chamber has a weight of $\sim 8 \cdot 10^{-6} \text{ kg}$, this determined value seems feasible: The chamber walls and the PCB add additional thermal mass to the system. The time constant was determined to be $\tau = 20.8 \text{ s}$. This value is much smaller than in the simulations of chapter [3.3.2]. The difference is considered to be caused by the heat conduction through the PCB, which was neglected in the simulations, where the devices had no suspension. Convection accounts for a relatively small heat flux, therefore the heat flux by conduction might change the system significantly. As it can be seen in equation [5.6], heat losses let the time constant $\tau$ decrease.

Finally, comparing equation [5.6] with the state space representation for linear time-invariant systems for a state $x$,

$$\dot{x} = A \cdot x(t) + b \cdot u(t) \quad (5.11)$$

it can be noted that the input $u$ for the plant is proportional to the heating power and $u(t) \sim U(t)^2$. Therefore the square of the voltage $U$ has to be the controlled parameter.
5.3. Controller design

The temperature of the devices is controlled by a discrete proportional-integral (PI) controller, which is implemented in LabView 8.5 on a PC. A PI controller obeys the following equation:

\[ u(t) = K_p \cdot e(t) + K_i \cdot \int_0^t e(t') \, dt' \]  \hspace{1cm} (5.12)

with the input signal \( u(t) \) on the plant at time \( t \), the error \( e(t) = r(t) - y_s(t) \) between the setpoint \( r(t) \) and the output signal \( y_s(t) \) of the plant \([29]\). \( K_p \) and \( K_i \), the proportional gain and the integral gain, are constants which have to be determined for the plant and task at hand.

For the task of this thesis, a PI controller can be simplified to a time-discrete iteration with integration by the Euler method:

\[ u(t_{n+1}) = K_p \cdot e(t_n) + K_i \cdot \sum_{i=0}^{t_n} e(t_i) \Delta t \]  \hspace{1cm} (5.13)

Figure 5.2: The model of the thermodynamic system is determined by the analysis of a voltage step response: The parameters of a first-order system are fitted to the experimental step function response of equation 5.10.
with the error $e(t_n)$ at time $t_n$ between the measured temperature output $T_m$ and the temperature setpoint $T_s$,

$$e(t_n) = T_m(t_n) - T_s(t_n)$$  \tag{5.14}

as introduced in a LabView course [25]. The proportional gain $K_p$ and the integral gain $K_i$ were determined experimentally by analysis of the step function response. A compromise between a large overshoot with oscillations and a slow controller response had to be found for each fabricated device.

In order to optimize the control behaviour, some limitations were introduced on the numerically integrated error $\sum_{t_0}^{t_n} e(t_i) \Delta t$ of equation 5.13: This term was coerced to a range between a lower limit 0 and an upper limit. The lower limit 0 is reasonable since the resistance heater can only receive positive voltages, corresponding to an increase of temperature. However the summed error would contribute to a negative voltage during a cooling step, which is physically not meaningful. Therefore this lower limit prevents a large undershoot after a cooling step. Figure 6.2 shows an example what happens without setting this lower limit. Similarly, the upper limit is introduced in order to prevent a large overshoot after a heating step.

5.4. Data processing and graphical user interfaces (GUI) in LabView

The data processing is also realized with a LabView 8.5 program. The controllable voltage source as well as the multimeters are driven by this program. The drivers for the instruments are provided by the manufacturers for the corresponding interfaces RS-232 and GPIB.

During the project, three main LabView programs with graphical user interfaces (GUI) were developed for the operation of the system:

- A basic manual program is intended for testing, experiments and fault diagnostics. A voltage on the heater can be adjusted at runtime in the GUI, and the system temperature is monitored.

- A program with controller allows to enter a temperature setpoint, which is then controlled on the system. The control parameters, namely the proportional and the integral gain, have to be entered in the GUI. The controller is implemented within LabView. The controller calculates an appropriate voltage output which is passed to the voltage source.

- A program for a complete automated PCR procedure with timer, basing on the latter program with controller, allows to set the cycling parameters such as the
temperatures and the timing for the PCR procedure. The cycling parameters define a timed operating sequence of temperature setpoints, which is passed to the controller.

The basic structure of these programs is the same: First, the instruments have to be initialized. Then the program enters a loop. In each iteration of this loop, the program determines the system temperature first by a multimeter measurement. Then the output value for the controllable voltage source is actuated. In each iteration, the values of time, temperatures and voltage are written in a textfile in order to evaluate the experiments afterwards.

The GUI of the program with controller is represented in the following screenshot images:

Figure 5.3: The panel for the heater keeps track of the voltage $U$ which is set on the voltage source. The resistance of the heater has to be entered in order to calculate a corresponding voltage to the controlled heating power. A voltage limit can be entered to prevent overheating damages during test runs.

Figure 5.4: The sensor panel allows to set the measurement mode of the multimeter, and the resistance of the sensor wire is monitored.
5.4. Data processing and graphical user interfaces (GUI) in LabView

Figure 5.5: The temperature panel shows the measurement values of the resistance thermometer. According to the temperature-resistance relationship from equation 2.8 in chapter 2.3 the resistance $R_0$ at reference temperature $T_0$ has to be entered as well as the linear temperature coefficient of electrical resistance $\alpha$ in order to calculate the temperature from the measured resistance value $R$.

Figure 5.6: In the controller panel, the temperature setpoint $r$ is entered. The proportional gain $K_p$ and the integral gain $K_i$ can be adjusted, also at runtime. The step time indicates the time which is needed for one iteration of the whole control loop. The momentary value of the summed error $\sum_{t=0}^{t_i} e(t_i) \Delta t$ in equation 5.13 is displayed for a better understanding of the control behaviour.

The program for a complete automated PCR procedure bases on the latter GUI, and the panel of Figure 5.7 is added for the definition of the timing. Finally Figure 5.8 gives an example of the graphical programming behind these GUIs by showing the implementation of the PI controller.
Figure 5.7: The timer for the automated PCR procedure is configured here. An initial denaturation step can be defined, then the number of temperature cycles as well as the duration of the denaturation step, the annealing step and the elongation step according to chapter 2.1 can be adjusted. At runtime, the current cycle number is displayed.

Figure 5.8: As an example for the graphical programming in LabView, the implementation of the discrete PI controller is shown.
6. Experimental characterization

6.1. Calibration of the temperature sensor

The resistance thermometer has to be calibrated in order to determine the relation between resistance and temperature. According to chapter 2.3, equation 2.8, a linear relation is usually assumed.

For a precise temperature calibration, the whole device was placed in a climatic chamber of the type "Clima Temperatur Systeme CTS C-40/200" at different temperatures. Alternatively a temperature-controlled oven was used for fast prototype calibrations. Figure 6.1 shows the measurement values of a first calibration, a linear curve and a quadratic curve, both fitted by the least squares approach, as well as the measured values of a second calibration. The quadratic curve conforms to the Callendar-Van Dusen equation 2.9. The linear temperature coefficient of electrical resistance yielded \( \alpha = 0.84 \cdot 10^{-3} \frac{1}{\text{K}} \), whereas \( T_0 = 20^\circ \text{C} \) was chosen. The corresponding bulk value of platinum is \( \alpha = 3.9 \cdot 10^{-3} \frac{1}{\text{K}} \) at 26.85\(^\circ\)C according to Zhang et al. [31], but for thin films of platinum the same author reports significantly lower temperature coefficients, for example \( \alpha = 1.4 \cdot 10^{-3} \frac{1}{\text{K}} \) for a film of 28 nm thickness. Lao [17], Lee [18],[19], Poser [22], Yoon [30] et al. report values between 1.6 \( \cdot 10^{-3} \frac{1}{\text{K}} \) and 2.5 \( \cdot 10^{-3} \frac{1}{\text{K}} \) for similar thin film platinum resistance thermometers. Evaporated thin film properties and structure defects formed during fabrication are considered to be the reason for the difference to the bulk values [31].

A second calibration two days after the first one is also shown in Figure 6.1. This calibration is intended to analyze the repeatability of the sensor. Whereas the slope of the curve remained rather constant, the resistances were found to be lower. This variability might result since the lid of the chamber was bonded in between the two calibrations, and the film resistance itself has a certain variability. In order to increase precision, a resistance \( R_0 \) at a reference temperature \( T_0 \) was calibrated periodically for each device; the coefficient \( \alpha \) was assumed to be constant. About one month later, the resistance at 20\(^\circ\)C was measured a third times as plotted in the same figure. The resistance was reduced by 2.6 \( \Omega /0.5 \% \), whereas this difference might also be caused by the application of thermal conductance paste on the sensor surface for the attachment of heat sinks.

In order to follow up the matter of calibration error, the resistance of the sensor on a different device was measured 6 times during a range of 9 days at room temperature, which was also recorded. The resistance value at 25\(^\circ\)C was then calculated with the known coefficient \( \alpha \). Then a standard deviation of only 0.32 \( \Omega \) resulted for the 6 measured resistances, representing a temperature variation of \( \pm 0.13 \)\(^\circ\)C, which is much smaller than in Figure 6.1. These findings underline the importance of a careful sensor monitoring and handling.
6.1. Calibration of the temperature sensor

For a calibration which is optimized for PCR, a linear calibration in the range of $55 - 95^\circ C$ with $T_0 = 75^\circ C$ is reasonable. Such a linear calibration with the values of Figure 6.1 results in a maximal error due to nonlinearity of $\sim 2^\circ C$ in this range. For the viscosity measurements of the main sensor, a gold loop is protruding in the fluid sample as visualized in Figure 3.1 and as visible in Figure 4.15. Similar to the platinum resistance thermometer, this loop can be used as a second temperature sensor for test purposes. The calibration yielded a linear temperature coefficient of $\alpha = 2.6 \cdot 10^{-3} \frac{1}{K}$ for the gold loop. As an advantage, the gold loop can measure the temperature within the MEMS and partially within the fluid sample, contrarily to the platinum sensor, which is placed at the bottom of the fluidic chamber. However, sensing with the gold loop is less suitable for control purposes, since its measurement is time-delayed compared to the platinum sensor, which is placed right at the acting heater. It has to be considered that the measured temperature value of the gold loop is only a middle value, as large parts of the loop are not protruding into the fluid sample. Furthermore, platinum is the material of choice for resistance thermometers rather than gold, because of its beneficial relation between resistance and temperature. Experiments with both sensors are presented in chapter 6.4.
6.2. First evaluations of complete PCR cycles

The experimental data of first temperature-controlled PCR cycles on the fabricated devices are discussed in this chapter. The shown experiments helped to find room for improvement at an early stage of the project.

Figure 6.2 shows the result of an experiment on a stand-alone device which was not yet assembled with the sensor, and no fluid load was placed on the device. This development stage helped to tune the parameters of the controller. Figure 6.3 shows an experiment where the device was assembled with the viscosity sensor, and a fluid sample was injected into the fluidic chamber. As it can be seen, for a rapid PCR cycling an active cooling of the fluid sample is necessary. Therefore the next chapters report the tests of different cooling methods. The heating rate is generally not an issue for rapid PCR, because here it was intentionally limited by means of a voltage limit on the voltage source in order to prevent an overheating damage of the devices during the experiments.

Figure 6.2: Control experiment with a PCR temperature profile on a stand-alone pad without fluid sample. A method to avoid the large undershoot at the end of the cooling step is reported in chapter 5.3.
6.3. Characterization of different cooling methods

The results of chapter 6.2 have shown the need for an active cooling of the devices. Therefore different cooling methods are considered in this chapter, and the optimal solution is aspired.

6.3.1. Cooling by ventilation and fins

As outlined in chapter 2.2, forced convection has a heat transfer coefficient which is severalfold higher than the one of natural convection. In literature, Poser et al. [22] as well as Schabmueller et al. [26] report fast PCR cycling with cooling by a fan, and Yoon et al. [30] analyzed the effects of fan cooling in detail. A standard fan for chip cooling of 4 cm diameter was used for an experiment with forced convection. Figure 6.4 compares two PCR cycles with and without fan cooling, whereas the fluid chamber was filled with DI water. The fan was turned on at the beginning of the cooling step with a power of 0.9 W, and a much faster temperature decay can be observed. Automation of the fan cooling is possible with the used equipment, since the controllable voltage source offers 4 voltage outputs. Cooling with a fan showed to be an effective improvement for cooling, and it is easily installed since it doesn’t have to be assembled on the MEMS itself. However the fan needs a relatively large installation space compared to the microsystem, and it increases
6.3. Characterization of different cooling methods

the power consumption of the system.

In a next step, fins were attached at the bottom of the MEMS. Figure 6.5 shows the setup. Thermal conductance paste (Cooler Master® thermal compound kit) was applied between the microchip and the fins in order to guarantee a proper heat flux. Fins increase the convection as they enlarge the surface area.

Figure 6.4: Experiment with fan cooling.

Figure 6.5: Fins of different sizes were attached at the bottom of the MEMS in order to increase convection.
Figure 6.6 shows the result of 5 experiments with fins and water in the fluidic chamber. First, a small fin was attached. A better cooling than in Figure 6.3 was expected, however the added thermal mass led to an only slightly improved cooling speed. Therefore a next experiment was started, where the fin was supported by ventilation with the aforementioned ventilator. As shown in Figure 6.6, this combination led to a cooling from $95^\circ C$ to $55^\circ C$ in 7 s. Furthermore, a large fin as shown in Figure 6.5 was found to result in a faster cooling even without ventilation. However, it has to be considered that the fins are at room temperature when the PCR cycling starts, but after a few cycles, the fins will be heated up, resulting in a worse cooling performance. In order to consider this effect, in a next experiment a fin was preheated by holding the setpoint of the device at $75^\circ C$ until a steady-state was reached with a stable output voltage of the controller. Then the PCR cycle was recorded, and a slightly slower cooling resulted. In a last experiment, the maximal cooling performance was found with continuous ventilation of the large fin and a better alignment between the fin and the device. The continuous cooling of the fin avoids the heating of the fin during prolonged temperature cycling. A sharp bend in the curves of the three fastest cooling methods in Figure 6.6 can be seen at $t \approx s$. It is assumed that these bends are caused by time delays in the control system: The sampling rate as well as the actuation speed of the voltage source might be at their limits at such high cooling rates, resulting in a slightly delayed response of the control system, which tries to dampen the cooling step at its end. Summing up, cooling with fins and ventilation showed to increase the cooling speed significantly: Whereas the cooling step from $95^\circ C$ to $55^\circ C$ lasts $\sim 30$ s without active cooling (see 6.3), only $\sim 3$ s were necessary with the fastest cooling method presented.
in this chapter.

6.3.2. Cooling by a Peltier element

Bestmann [2] reports fast cooling by means of a Peltier element. A Peltier element, also called thermoelectric heat pump, transfers heat from one side of the device to the other side against the temperature gradient, with consumption of electrical energy [29].

A Peltier element was attached to the microsystem as a heat sink as illustrated in Figure 1.1. In order to guarantee a proper contact, thermal conductance paste (Cooler Master® thermal compound kit) was applied between the microsystem and the Peltier element as well as on the backside of the Peltier element. On this backside, a metal block was attached where the heat can be finally dissipated into the ambient air.

First, an innovative Micro-Peltier element of the type $MPC - D701 - M22 - C$ from Micropelt GmbH, Freiburg/ Germany was received as a test sample. At a hot side temperature of 25° C, this product is specified to have a $Q_{\text{max}}$ of 4.6 W. For first tests, the chip was heated to a steady state of 60° C and the voltage was held constant. After the Peltier element was turned on, a steady state of 54° C resulted. This preliminary tests were intended to find the optimal operation voltage of the Peltier elements, which was found to be $\sim 3 \text{ V}$.

![Figure 6.7: Experiment with cooling by a Micro-Peltier, without water.](image)

After the operating point of the Peltier element was found, complete PCR cycles were tested, here with an air-filled chamber. Figure 6.7 shows the results of three runs: A run
without attached Peltier element as a reference, a run with attached Peltier without any operating voltage, and a run where the Peltier element was turned on at the beginning of the cooling step. As it can be seen by comparing the latter two, even an inactive Peltier element acted as a reasonable heat sink by heat conduction. However this effect is only present at a cold start of the system: After a few cycles, the Peltier and the metal block on its backside will be heated up themselves, and therefore they will dissipate less energy than after a single cycle.

In these experiments, the Peltier effect improved the cooling speed only slightly. Presumably the free Peltier test specimens had a lower power than in the specifications. On the other hand, as it can be observed at the two heating steps, the attachment of the Peltier element causes a slower heating rate because of heat conduction.

In order to reach a better cooling by the Peltier effect, a standard macroscale Peltier element (Supercool® 4 × 4 cm, 5 V) was installed instead of the former Peltier elements. (This Peltier element was available at the institute for first tests, however its size is larger than necessary.) Figure 6.8 shows the results for a water-filled fluidic chamber. Even when the Peltier element was not active, the attached mass dissipated the heat energy much quicker than without active cooling. However, again the Peltier element and the underlying metal block will heat up at repeated temperature cycles, therefore the cooling speed is assumed to decrease at longer experiment durations. Experiments with repeated cycling are reported in chapter 6.5.

![Figure 6.8: Experiment with cooling by a standard macroscale Peltier element.](image)

In summary, the cooling speed in these experiments was quite high, so after less than
5 s the cold temperature of $55^\circ C$ was reached. Because of this short time period, the influence of the Peltier effect resulted only in a small improvement. However, the heat on the hot side of the Peltier element has to be dissipated effectively into the environment, otherwise the whole system will heat up after repeated temperature cycles. In order to prevent this effect, the dissipation of heat at the hot side of the Peltier would have to be supported by a fan and fins. Compared to the cooling of the device by direct ventilation, cooling by a Peltier element with backside ventilation results in a higher effort, whereas the cooling speed of both methods showed to be comparable.

### 6.4. Measurements with a second temperature sensor within the device

The temperature distribution within the MEMS and the fluid sample will be non-uniform as already discussed in the simulations in chapter 3 and in the analytical approach of chapter 2.4. Whereas the bottom of the fluidic chamber has almost the same temperature as at the sensor, the top of the chamber is expected to have a lower temperature because of convection and heat conduction. In order to quantify the temperature difference experimentally, measurements with a second temperature sensor are outlined in this chapter.

For the measurement of the viscosity, the MEMS includes a cantilever sensor which is protruding into the fluid. The cantilever sensor is sketched in Figure 3.1. On top of the cantilever, a thin film of gold was evaporated, forming a wire loop as it can be seen in Figure 4.15. The wire loop is originally intended for viscosity measurements, but it can also be used as a resistance thermometer after the same calibration procedure as described for the platinum resistance thermometer. The gold wire loop is located on the silicon chip just underneath the PDMS lid, and one third of its length is protruding into the fluid sample. The other two thirds of the gold wire loop are farther away from the heater, so the temperature decreases in this region. Therefore this sensor provides an important but limited insight into the spatial distribution of the temperature.

Figure 6.9 shows an experiment with the PCR temperature profile, whereas the temperature was measured simultaneously with both resistance thermometers. The temperature at the second sensor in the middle of the device is lower than at the bottom during the three heating steps, as expected. The signal of the second temperature sensor reacts more slowly, therefore at the cooling step the temperature is slightly higher in the middle of the device.
6.4. Measurements with a second temperature sensor within the device

Figure 6.9: Transient analysis of the temperature distribution within the device by means of a second resistance thermometer of gold in the middle of the device. The signal of the second sensor shows a higher time constant and lower temperatures during the heating.

Generally speaking, the temperature difference of the two sensors is larger at higher temperature setpoints, because of increased heat losses. Figure 6.10 further outlines this relation: The temperature difference between the temperature setpoint and the two sensors is plotted against the temperature setpoint. The values were averaged over 5 measurement values after the controlled system reached a steady-state. As it is showed, the difference increases disproportionately with the setpoint temperature.

These results are important in order to allow a precisely controlled average fluid sample temperature. A compensation by means of a higher temperature setpoint can be derived. Alternatively, a weighted average between the two measured temperatures could be calculated and passed to the controller as the measured output.
Figure 6.10: Steady-state temperature difference between the setpoint and the measured temperature for two sensors at the bottom and middle of the chamber. Below 80°C, the difference is < 1°C, but at higher temperatures, the difference should be compensated by a higher setpoint.
6.5. Final performance benchmark with multiple PCR cycles

Figure 6.11: Multiple rapid PCR cycles at 95°/55°/70° C with periods of 15 s/15 s/15 s.

In order to test the maximally achieved performance of the developed device, this section shows an experiment with several rapid PCR cycles. A device with a heater of 113 Ω resistance was linearly calibrated around $T_0 = 75° C$. The voltage source was set to the maximal voltage of 32 V, so the maximal heating power accounted to 9.1 W. As described in chapter 6.3.1, the device was attached to the large fin of Figure 6.6, and a ventilator was installed on the fin. The ventilator was continuously running, also at heating steps, as reported by Yoon et al. [30]. In this way, the cooling rate is expected to be constantly high even after multiple cycles. For the denaturation/annealing/elongation steps of the PCR, a temperature profile of 95°/55°/70° C was chosen for 15 s/15 s/15 s, and a section of multiple cycles are shown in Figure 6.11. A small air bubble in the chamber used to expand at 95° C to about 10 – 20% of the chamber volume and shrank at lower temperatures. Such small air bubbles at one edge of the chamber occurred more often for the lid design which is shown in the first row, third column of the mask in Figure A.3. The design just underneath showed to allow a better filling. However evaporation could be avoided by water-filled tubes on the chamber inlet and outlet. Figure 6.11 outlines the performance of the developed device in terms of the heating/cooling rate and the control precision as well as the feasibility of multiple rapid PCR cycles. The shown temperature profile of 15 s/15 s/15 s clearly exceeds the speed of a conventional PCR, which achieves a typical temperature profile of 30 s/60 s/30 s as mentioned by Yoon et al. [30].
6.6. Temperature-controlled cantilever sensor measurements

As formerly described, the temperature-controlled fluidic chamber is built on a MEMS with a novel cantilever sensor for viscosity measurements. This sensor consists of a gold/silicon wireloop which protrudes into the fluidic chamber, as shown in Figure 4.15. The aim of this chapter is to report first temperature-controlled measurements with the novel sensor, combining the work on the novel cantilever sensor with the work of this thesis. The working principle of the cantilever sensor is not explained in detail, as it will be reported in the dissertation of the advisor of this thesis.

As test fluids, DI water and a 5% glycerin solution were considered to be filled in the fluidic chamber. The cantilever sensor is excited to oscillate at its first resonance frequency, which is dependent on the fluid sample properties. The oscillation of the cantilever sensor was measured with a laser Doppler vibrometer through the clear PDMS lid. Figure 6.12 shows the resulting resonance frequency for the two fluids in a temperature range from 35° − 60°C. The values were averaged over three measurements at a measurement run, whereas the values differed less than 10 Hertz. The glycerin solution was measured in two experimental runs in order to demonstrate the repeatability of the system. For both fluids, the resonance frequency was observed to increase at higher temperatures. The reason for an increasing resonance frequency is the decrease of the fluid’s density and viscosity at higher temperatures. Above 60°C, the measurements showed irregularities, possibly due to the expansion of small air bubbles within the fluidic chamber.

In order to measure the viscosity of the fluid sample, the cantilever sensor is excited to an oscillation with a ±45° phase shift compared to the phase between the excitation and the oscillation at the first resonance. The difference between the frequency at these two phase shifts of ±45° reveals the damping of the system, which allows to calculate the viscosity of the fluid sample. Figure 6.13 shows the described frequency differences which were measured in the same experiment as above. The values were again averaged over three measurements, and the particular measurement values are also plotted. In the shown temperature range, the frequency difference decreases with increasing temperature. This reveals a lower damping and therefore a lower viscosity of the test fluids at higher temperatures.

The measured values were compared to an analytic model of the resonator. Whereas the measured resonance frequency was well calculable by the model, the predicted frequency difference values were rather lower. Since the resonator had only a distance of 200 µm to the lid, it is assumed that wall effects, which are not covered by the actual model, have come into play.

Summing up, the developed MEMS allowed to observe the temperature-dependency of the cantilever oscillation, which leads to the calculation of the fluid sample viscosity.
6.6. Temperature-controlled cantilever sensor measurements

Figure 6.12: First resonance frequency of the cantilever sensor for different fluids and temperatures. The mentioned voltage in the plot legend refers to the excitation voltage of the cantilever sensor.

Figure 6.13: Frequency difference between two operating points with a phase of $\pm 45^\circ$ of the cantilever sensor around its first resonance frequency for different fluids and temperatures.
7. Conclusions

The master’s thesis at hand reports the development of a temperature control device for the on-chip PCR method. The conclusions which can be drawn from the main chapters in particular concerning the theoretical background, the numerical simulations, the fabrication, the instrumentation and control and the experimental characterization are reported below.

The theoretical background provided a foundation for all following chapters. The interdisciplinary nature of the project asked not only for a knowledge of the basic equations in thermodynamics, but also for a diversified understanding of the PCR method. Stationary analytical calculations were shown, however the complex geometry as well as the dynamics of the problem began to limit the application of the analytical approach.

The numerical simulations allowed a three-dimensional, dynamic modeling of the thermodynamics, coupled with Joule heating. The model allowed to simulate a complete PCR cycle, whereas all required information could be read out. These simulations were important to estimate the feasibility of the project, whereas a deeper understanding of the device’s physical behaviour could be gained. However, the significance of the simulations depends strongly on an appropriate definition of the boundary conditions, which were not always straightforward to estimate. Especially the dissipation by heat conduction through the clamping could not be modeled adequately, therefore the required heating power was smaller in the simulations than in the experiments. Although the device’s geometry and parameters were changed and further developed after the simulations, the qualitative answers from the simulations were of great value for the development process.

In terms of fabrication, step by step the device was developed from a rudimentary prototype to the final version. This stepwise development helped to overview and timely assess the difficulties on all stages of development. Most development work has been done in order to reach a better platinum film quality, and this concern is still crucial. The quality of the platinum film is of importance as it affects the precision of the temperature sensor, whereas the heater is less dependent on the film quality. The process development with different recipes was educationally valuable and led to process improvements.

The instrumentation and control benefits from the comparably slow dynamics of the thermal system, so the stability of the controller was not a critical point. However, the serial interface RS-232 showed to be prone to errors if the LabView program did not provide enough waiting time between two requests. Finally the device was properly
controlled with a sampling time of 0.2 s.

The experimental characterization delivered the most interesting results, as the setup allowed diversified experimental evaluations. Mostly practical issues occurred, such as the expansion of small air bubbles within the fluidic chamber at higher temperatures, the evaporation of the fluid sample at temperature overshoots and leakages at the lid of the fluidic chamber. The advantages and disadvantages of different cooling methods are discussed. Attachment of a fin on the chamber backside with ventilation by a fan resulted in the best cooling performance, whereas the fan was continuously running, even at heating steps. Whereas ventilation dissipates the heat energy directly into the environment, Peltier elements only pump the heat on one side, where it has to be dissipated by e. g. an additional ventilation. Therefore cooling by direct ventilation offers a more practical solution.

Whereas conventional thermal cycling has denaturation/annealing/elongation steps with a duration of 30 s/60 s/30 s as mentioned by Yoon et al. [30], the developed device allows rapid thermal cycling with shorter PCR processing times. A temperature profile of 15 s/15 s/15 s has been shown experimentally in this thesis. Even faster cycling is feasible, however the temperature steps are rounded down because of a finite heating and cooling rate. Heating rates with an average of more than 10°C/s could be reached for a temperature step from 70°C to 95°C, whereas peak values of up to 50°C/s were measured at the transition from 55°C to 70°C in chapter 6.5. A cooling rate of up to 19°C was achieved with a large fin and ventilation. The heating rate could still be increased by a lower resistance of the resistance heater, which results in a larger maximum heating power.

The experiments with a second resistance thermometer were not only of importance to observe the spatial temperature distribution, but also a verification of the resistance thermometer. The sensors of two different materials at two different locations showed a coherent result. In a last chapter, the successful combination of the novel viscosity sensor and the device for temperature control has been reported.

Finally, the thesis benefits from the widespread approach from the theory over the simulations to the experiments in order to give a conclusive result.
8. Outlook

This chapter first outlines the fields where a further development is promising, then an outlook on the applications of the device for temperature control is given. The presented device was at prototype stage at half time of the thesis, and was further developed since then. Nevertheless, improvements concerning the fabrication are feasible.

- The precision of the temperature sensor could be increased, e. g. by a further improved evaporation of the platinum film. The higher the coefficient of electrical resistance $\alpha$ can be fabricated, the more precise the temperature sensor will measure.

- So far the fabrication process is intended for the production of unique specimens. A development towards batch fabrication is left open.

- Up to now, the test set-up suffers from its fragility, so an elaborated test equipment would increase the reliability of the device.

- The thermal mass of the device could be reduced by an etching of thin walls around the fluidic chamber, as proposed in the model of the simulations.

- The lid of the fluidic chamber might be optimized in order to prevent small air bubbles within the chamber which were formed during the filling of the fluid sample. Small air bubbles in the chamber are problematic because of their expansion at higher temperatures.

- First measurements with the viscosity sensor revealed distracting influences of wall effects at the lid of the chamber. These wall effects might be studied in further work, so the lid geometry can be designed to minimize the wall effects.

Regarding the applications of this thesis, the presented device is ready for temperature-controlled experiments with the built-in viscosity sensor. Whereas the development focused on the engineering of the device, a next step is the actual application with biological sample fluids. A real time quantitative PCR with read-out by fluorescence as described by Bestmann [2] could be a next intermediate step. Finally, the viscosity difference of the fluid sample before and after a PCR is intended to be read out on the MEMS. A micro total analysis system ($\mu$-TAS) on a portable device is the ultimate goal of the project. The combination of rapid PCR and viscosimetry opens a wide range of applications in medicine, chemistry and biology.
A. Appendix: Mask layouts

The masks below were drawn with Adobe Illustrator CS4. For photolithography, they were printed on a A4 foil with a resolution of 3800 dots per inch, exposure positive, size 100 % at Salinger AG, 8050 Zurich.

Figure A.1: Heater and sensor mask first version, 4 different designs, enlarged \times1.4. Smallest feature size: 20 \mu m
Figure A.2: Heater and sensor mask, second version, 6 different designs, enlarged $\times 3.8$. Smallest feature size: $40 \, \mu m$
Figure A.3: Mask for the mold for the chamber lid, enlarged ×1.6. 8 different microfluidic channel designs were drawn to optimize the filling of the chamber.
B. Appendix: Layout of the printed circuit board

Figure B.1: The layout of the printed circuit board with 6 electrical connections. The PCB was drawn with the software Protel99 and fabricated by Eurocircuits GmbH.
C. Appendix: Fabrication report of the heater and sensor structures

C.1. Processing recipe for the heater and sensor structures

Table C.1: Recipe for the lift-off process of the surface-micromachined heaters and sensors

<table>
<thead>
<tr>
<th>Process step</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.) Cleaning and preparation</strong></td>
<td></td>
</tr>
<tr>
<td>Acetone bath</td>
<td>3 min in US power 1</td>
</tr>
<tr>
<td>Isopropanol bath</td>
<td>3 min in US power 1</td>
</tr>
<tr>
<td>Quick dump rinser/rinser dryer</td>
<td></td>
</tr>
<tr>
<td>Evaporate water on hot plate</td>
<td>110 °C 2 min</td>
</tr>
<tr>
<td>Plasma asher</td>
<td>600W 2 Minutes</td>
</tr>
<tr>
<td><strong>2.) Deposition of SiO₂</strong></td>
<td>Details: see chapter C.4</td>
</tr>
<tr>
<td>PECVD 6 minutes</td>
<td>300°C, goal: 200 nm double-sided</td>
</tr>
<tr>
<td><strong>3.) Photolithography</strong></td>
<td></td>
</tr>
<tr>
<td>Evaporation of residual water</td>
<td>110° C, 90 sec</td>
</tr>
<tr>
<td>Surface preparation</td>
<td>5 min N₂, 30 sec HMDS, 5 min N₂</td>
</tr>
<tr>
<td>Spin coating with AZ nLOF2070</td>
<td>2000 rpm 3 sec/ ramp 300 rpm/min</td>
</tr>
<tr>
<td>(a negative resist)</td>
<td>2500 rpm 45 sec/ramp 500 rpm/min, 3.6 mL</td>
</tr>
<tr>
<td>Prebake</td>
<td>110° C 90 sec</td>
</tr>
<tr>
<td>Exposure</td>
<td>152 mJ/cm²</td>
</tr>
<tr>
<td>Post bake</td>
<td>110° C, 90 sec</td>
</tr>
<tr>
<td>Development</td>
<td>AZ 826 MIF, 2 minutes, mild agitation</td>
</tr>
<tr>
<td></td>
<td>last ~15 sec in fresh AZ 826 MIF</td>
</tr>
<tr>
<td>Quick dump rinser/rinser dryer</td>
<td></td>
</tr>
<tr>
<td>Plasma asher</td>
<td>100W 20 sec</td>
</tr>
<tr>
<td>Inspection</td>
<td>Light microscope and surface profiler</td>
</tr>
<tr>
<td><strong>4.) Evaporation</strong></td>
<td>Details: see chapter C.2</td>
</tr>
<tr>
<td>Titanium</td>
<td>20 nm</td>
</tr>
<tr>
<td>Platinum</td>
<td>180 nm</td>
</tr>
<tr>
<td><strong>5.) Lift-off</strong></td>
<td></td>
</tr>
<tr>
<td>Bath in N-Methyl-2-pyrrolidone (NMP)</td>
<td>50° C, ~30 min, periodic agitation</td>
</tr>
<tr>
<td></td>
<td>Blowing with a pipette</td>
</tr>
</tbody>
</table>

...
<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.)</td>
<td>Coating with a protective layer</td>
<td>Surface preparation: 5 min N$_2$, 30 sec HMDS, 5 min N$_2$; Spin coating with AZ 4562; Softbake: 100° C 10 min</td>
</tr>
<tr>
<td>7.)</td>
<td>Dicing</td>
<td>Dicing saw: 30000 rpm, 10 mm/sec</td>
</tr>
<tr>
<td>8.)</td>
<td>Cleaning</td>
<td>Acetone bath, Isopropanol bath: ~2 min until photoresist is dissolved, ~1 min</td>
</tr>
</tbody>
</table>

### C.2. Parameters and logfile for the evaporation of the platinum layer

The evaporation steps were conducted at the laboratory of Hansruedi Scherrer at the department of physics, HPR E86, by Thomas Kälin and Sandro Tiegermann. The first evaporation was accomplished on the following system: Classic 500 Pfeiffer Vacuum chamber, Pfeiffer Turbo pump (1600 l/s), electron beam with up to 6 kW. The second and third evaporations were accomplished on the following system: Univex Pfeiffer Balzers PLS 570, Electron beam HVS 107, 10kV, electron gun control EKS 110A. For the latter two evaporations, the following parameters were set: Target half height, deposition rate: 1.2 nm/s first up to 20 nm, then ramping of 20 s up to 2.4 nm/s. No substrate heating. The logfiles of the second and third evaporation are shown in Figure C.1 and Figure C.2 respectively.
Figure C.1: Evaporation logfile of the second evaporation
Figure C.2: Evaporation logfile of the third evaporation
C.3. Factors of resistance increase

For the wafer of the third series, the factors of resistance increase between the measured values and the calculations with bulk values were evaluated. The devices B1 to K10 were arranged as following on the wafer:

\[
\begin{bmatrix}
B1 & \ldots & B5 & B6 & \ldots & B10 \\
C1 & \ldots & C5 & C6 & \ldots & C10 \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
J1 & \ldots & J5 & J6 & \ldots & J10 \\
K1 & \ldots & K5 & K6 & \ldots & K10
\end{bmatrix}
\]

The corresponding factors were evaluated as following:

\[
\begin{bmatrix}
6.4 & \ldots & 6.2 & 5.9 & \ldots & 6.7 \\
6.0 & \ldots & 5.7 & 5.4 & \ldots & 6.1 \\
5.4 & \ldots & 5.1 & 4.9 & \ldots & 5.5 \\
5.1 & \ldots & 4.8 & 4.5 & \ldots & 5.1 \\
4.6 & \ldots & 4.4 & 4.2 & \ldots & 4.6 \\
4.4 & \ldots & 4.2 & 4.0 & \ldots & 4.4 \\
4.1 & \ldots & 3.9 & 3.7 & \ldots & 4.1 \\
3.9 & \ldots & 3.8 & 3.6 & \ldots & 3.9 \\
3.5 & \ldots & 3.6 & 3.4 & \ldots & 3.8 \\
2.9 & \ldots & 3.5 & 3.3 & \ldots & \text{–}
\end{bmatrix}
\]

C.4. Machine parameters for PECVD of silicon dioxide

\[\text{SiO}_x \ 3.5 \ \text{min} \ 300^\circ\text{C}, \ \text{SiH}_4: \ 340 \ \text{sccm}, \ \text{N}_2\text{O}: \ 700 \ \text{sccm}; \ \text{low frequency power}: \ 30 \ \text{W},\]
\[\text{power pulsed} \ 10 \ \text{s}; \ \text{high frequency power}: \ 30 \ \text{W}\]

C.5. Machine parameters for wire bonding

Wire bonding was conducted on a Delvotec 5425 with the following settings:

<table>
<thead>
<tr>
<th>Bonding substrate</th>
<th>Ultrasonic power</th>
<th>Ultrasonic time</th>
<th>Bond weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaporated platin layer</td>
<td>120</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>PCB contact pads, gold coated</td>
<td>135</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Evaporated gold layer</td>
<td>140</td>
<td>60</td>
<td>8</td>
</tr>
</tbody>
</table>
## D. Appendix: Processing recipe for the mold of the PDMS lid

### Table D.1: Recipe for the etching of the mold for the PDMS lid

<table>
<thead>
<tr>
<th>Process step</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.) Cleaning and preparation</strong></td>
<td></td>
</tr>
<tr>
<td>Acetone bath</td>
<td>3 min in US power 1</td>
</tr>
<tr>
<td>Isopropanol bath</td>
<td>3 min in US power 1</td>
</tr>
<tr>
<td>Quick dump rinser/rinser dryer</td>
<td></td>
</tr>
<tr>
<td>Evaporate water on hot plate</td>
<td>110 °C 2 min</td>
</tr>
<tr>
<td>Plasma asher</td>
<td>600W 2 Minutes</td>
</tr>
<tr>
<td><strong>2.) Photolithography</strong></td>
<td></td>
</tr>
<tr>
<td>Evaporate water on hot plate</td>
<td>100 °C 5 min</td>
</tr>
<tr>
<td>Surface preparation</td>
<td>5 min N₂, 30 sec HMDS, 5 min N₂</td>
</tr>
<tr>
<td>Spin coating with AZ 4562</td>
<td>700 rpm 5 sec/ ramp 500 rpm/sec, 1700 rpm 35 sec/ ramp 1000 rpm/sec, 3.3 mL</td>
</tr>
<tr>
<td>Softbake</td>
<td>100° C, 10 min</td>
</tr>
<tr>
<td>Waiting for rehydration</td>
<td>10 min</td>
</tr>
<tr>
<td>Exposure</td>
<td>700 mJ/cm²</td>
</tr>
<tr>
<td>Waiting for degassing</td>
<td>5 min</td>
</tr>
<tr>
<td>Development</td>
<td>AZ 351 (120 ml) and DI water (480 ml), 1:4, 290 sec, mild agitation</td>
</tr>
<tr>
<td>Quick dump rinser/rinser dryer</td>
<td></td>
</tr>
<tr>
<td>Optical inspection by light microscope</td>
<td></td>
</tr>
<tr>
<td><strong>3.) Dry etching</strong></td>
<td></td>
</tr>
<tr>
<td>Bosch process DRIE with ICP</td>
<td>0.65 μm/cycle, 320 cycles, recipe MR_C1_TE</td>
</tr>
<tr>
<td><strong>4.) Cleaning</strong></td>
<td></td>
</tr>
<tr>
<td>Acetone bath</td>
<td>~2 min until photoresist is dissolved</td>
</tr>
</tbody>
</table>
List of Figures

1.1. Sketch of the sensor with attached temperature control devices . . . . . . 2

2.1. Temperature curve of rapid PCR cycling [10] . . . . . . . . . . . . . . . . 6
2.2. The PCR method from a molecular perspective [13] . . . . . . . . . . . . 7
2.3. A one-dimensional model with 4 layers . . . . . . . . . . . . . . . . . . . . 11
2.4. Temperature profile along the x-axis of Figure 2.3 . . . . . . . . . . . . . . 12

3.1. The simulation geometry . . . . . . . . . . . . . . . . . . . . . . . . . . . . 15
3.2. Steady-state temperature plotted against applied voltage on the heater . . 17
3.3. Temperature difference of different measuring points . . . . . . . . . . . . 18
3.4. Applied voltage (feed forward control) for a temperature step . . . . . . . 19
3.5. Transient simulation at the beginning of a heating step from 55°C to 70°C 20
3.6. Temperature distribution at $t = 1 s$ . . . . . . . . . . . . . . . . . . . . . 20
3.7. Equilibration of the temperature towards 70°C . . . . . . . . . . . . . . . . 21
3.8. A steady-state temperature distribution at 70°C . . . . . . . . . . . . . . . 21
3.9. Geometry of a prototype . . . . . . . . . . . . . . . . . . . . . . . . . . . . 22
3.10. Simulation of a complete PCR cycle . . . . . . . . . . . . . . . . . . . . . 24
3.11. Temperature sampling during a simulated PCR cycle . . . . . . . . . . . . 25

4.1. Crosssectional sideview of the assembled device . . . . . . . . . . . . . . . 26
4.2. General layout of the heater and sensor structures . . . . . . . . . . . . . . 27
4.3. Microscopic images . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 29
4.4. After lift-off . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 29
4.5. Final process steps . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 30
4.6. Profilometer measurement of the heater and sensor wires . . . . . . . . . . 31
4.7. SEM images . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 31
4.8. Microscopic photoresist images with variations . . . . . . . . . . . . . . . 33
4.9. Undercut profile . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 33
4.10. Profilometer measurement of the photoresist . . . . . . . . . . . . . . . . . 34
4.11. The evaporated platinum film before the lift-off . . . . . . . . . . . . . . 35
4.12. A selection of SEM images . . . . . . . . . . . . . . . . . . . . . . . . . . . 36
4.13. Electrical connection . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 37
4.14. Lid of PDMS . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 38
4.15. Tubing . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 39

5.1. Schematic diagram of the instrumentation setup . . . . . . . . . . . . . . . 40
5.2. Step function response of the first-order system . . . . . . . . . . . . . . 43
List of Figures

5.3. Heater GUI ......................................................... 45
5.4. Sensor GUI ........................................................ 45
5.5. Thermometer GUI ............................................... 46
5.6. Controller GUI .................................................. 46
5.7. PCR timer GUI .................................................... 47
5.8. Graphical programming in LabView ......................... 47
6.1. Platinum resistance thermometer calibration .................. 49
6.2. Control experiment with a PCR temperature profile ............... 50
6.3. A prototypic temperature-controlled experiment of a PCR cycle ... 51
6.4. Experiment with fan cooling .................................... 52
6.5. Fins at the bottom of the MEMS .................................. 52
6.6. Experimental results with different fin types ................. 53
6.7. Experiment with cooling by a Micro-Peltier ..................... 54
6.8. Experiment with cooling by a standard macroscale Peltier element ... 55
6.9. Measurement with two temperature sensors .................. 57
6.10. Steady-state temperature difference ........................... 58
6.11. Multiple PCR cycles ............................................ 59
6.12. First resonance frequency of the cantilever sensor .............. 61
6.13. Frequency difference between two operating points with a phase of ±45° . 61
A.1. Heater and sensor mask version 1 .............................. 65
A.2. Heater and sensor mask version 2 .............................. 66
A.3. Mask for the mold for the chamber lid ......................... 67
B.1. The layout of the printed circuit board ......................... 68
C.1. Evaporation logfile ................................................ 71
C.2. Evaporation logfile ................................................ 72
# List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Literature review on PCR microfluidic devices: A paper overview</td>
<td>4</td>
</tr>
<tr>
<td>2.1</td>
<td>Thermal material properties at room condition ([14], [21], [23], [29])</td>
<td>8</td>
</tr>
<tr>
<td>2.2</td>
<td>Parameters of the model</td>
<td>13</td>
</tr>
<tr>
<td>3.1</td>
<td>Boundary/edge Conditions</td>
<td>16</td>
</tr>
<tr>
<td>4.1</td>
<td>Fabrication steps</td>
<td>28</td>
</tr>
<tr>
<td>C.1</td>
<td>Recipe for the lift-off process of the surface-micromachined heaters and sensors</td>
<td>69</td>
</tr>
<tr>
<td>C.2</td>
<td>Machine parameters for wire bonding (in machine units)</td>
<td>73</td>
</tr>
<tr>
<td>D.1</td>
<td>Recipe for the etching of the mold for the PDMS lid</td>
<td>74</td>
</tr>
</tbody>
</table>
Bibliography


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Temperature control for PCR on a microfluidic MEMS

Master-Arbeit, 17. September 2010

Philipp Rüst

Ivo Leibacher
livo@student.ethz.ch
05-915-475
9