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Thick film flow sensor for biological microsystems

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ABSTRACT

An anemometer for the in situ control of the flow rates in fluidic systems is designed, manufactured and characterized. For the first time, a flow sensor according to the boundary layer principle is manufactured with exclusive use of thick film technologies. This principle enables the application of the sensor for low fluid temperatures as required in biological fluid systems. The sensor is integrated in a retention module consisting of Low Temperature Cofired Ceramics (LTCC), which allow the cost-effective realisation of complex fluidic microsystems with integrated electronics by only using thick film technologies. Thermistor compositions are printed on a free-standing bridge and encapsulated to ensure biological compatibility. The encapsulation becomes possible by using an adapted technology. At the same time the design facilitates a maximal heat-insulation of the sensor element from the substrate. The control of the stress influences on the free-standing sensor bridge due to shrinking mismatch, TCE mismatch, density gradients and deformation during the lamination is investigated using design of experiments (DoE), resulting in an adapted design and fabrication process. The presented anemometer has a linear sensor characteristic for flow rates up to 80 μl/min. Compatibility investigations of LTCC with biological substances will be presented.

1. Introduction

Miniaturized systems on the meso scale level use Low Temperature Cofired Ceramics (LTCC) as a substrate material on account of the excellent dielectric and thermal properties offered and the fact that electrical and fluidic multilayers can be easily produced [1]. Additionally, their high chemical and thermal stability are valuable features for the construction of complex fluidic systems or the packaging of chemical sensors and BIO-MEMS. An increasing interest is therefore focused on the use of LTCC fluid systems for biological processes. Complex hybrid fluid systems have already been presented [2,3]. Previous work was focused on the realisation of a modular fluid system, as described in [4,5]. Several fluidic operations such as mixing and heating of microreaction devices are already demonstrated. Further developments are now in progress to enable handling of cell fluids and to mix reagents for enzymatic assays such as the polymerase chain reaction (PCR). A basic requirement for the integration of process control units into the fluid kit is the flow monitoring, which can be done by means of an integrated sensor in a retention module. Thus, in addition to routeing, the control unit can be situated on a fluidic component. Thick film flow sensors have already been presented. A simple component, which consists of a free standing ceramic bridge with a printed negative temperature coefficient (NTC) thermistor composition, is described in [6]. The same principle is also utilized [7] for the fabrication of gas flow sensors. Another example of a flow sensor combines LTCC technologies for simple via formation and thin film techniques to achieve a fast sensor for application in the harsh environment of a common rail diesel injection system at high pressures up to 135 MPa [8]. All of these sensors use the hot-wire principle, which requires high sensor temperatures for an adequate signal. A more accurate principle at lower temperatures, but also more demanding, is the boundary layer method, which has a linear dependency of measure and flow at small flow rates. This work demonstrates the design of a flow sensor which uses this principle and is compatible with biological processes. The exclusive use of thick film processes simultaneously guarantees a cost-effective solution. The sensor is built using LTCC Green Tape^{TM} 951 from DuPont Nemours, from here on called 951.

2. Sensor design

2.1. Function principle

A basic advantage of the boundary layer principle for use in biological environments is that the heater is electrically decoupled from the sensor elements. In this way, the maximal temperature of the biological fluids can be separately limited. Simultaneously, the

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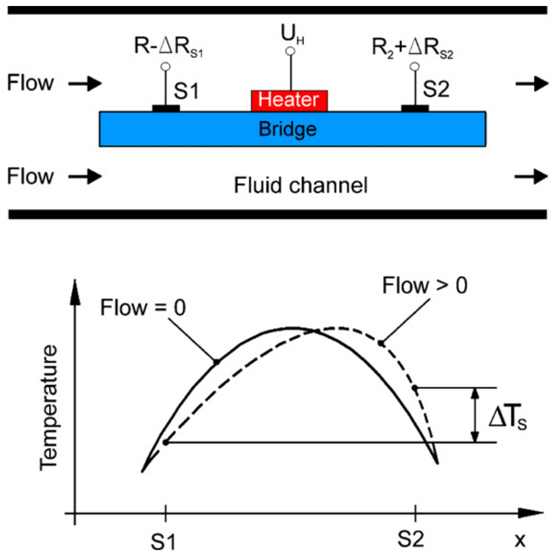

Fig. 1. Functional principle of the flow sensor with thermistor resistances R_1, R_2 for sensor S_1 and S_2, respectively.

differential measurement guarantees a linear characteristic. The sensor arrangement is explained schematically in Fig. 1.

The electric loss at the heater determines the temperature of the fluid. The thermal flow resulting from these losses can be divided into a convective part and an undesirable conductive part.

The convective part generates a symmetric temperature profile on top of the heater. Without any forced flow there is no temperature difference between the two sensors. A flow deforms the temperature profile and creates a temperature difference DT_S between the sensors, which is then measured. Its dependency on the flow rate can be approximated by a linear function for small mass flows [9]. The convective part depends on the heater surface area, the heater temperature, the dimensions of the fluid channel and the flow rate [10].

To minimize the conductive heat loss, the cross-sectional area of the bridge must be minimized.

2.2. Sensor dimensioning

The fluid channel with a fired cross-section of approximately 0.7 mm^2 is formed by means of a bottom and a top part of the 951 ceramic. Heater and sensor elements are situated on a free standing bridge, which is suspended between them to ensure good thermal coupling to the fluid. The three-dimensional arrangement is depicted in Fig. 2.

A meander of the platinum thick film paste DP 9896 (available from DuPont) forms the heater. It is screen printed with a line width of 100 μm and a pitch of 200 μm and has a resistance of 5 Ω. It covers an area of 0.77 mm^2 and the dimension in the direction of flow is 1.1 mm. A maximum temperature of 60 °C is allowed in order to avoid disturbing the handled biological substances, leading to an excess temperature T_e of 40 °C, which has to be generated through the heater element. The temperature characteristic of the heater is separately calibrated. The required excess temperature will not be exceeded, if the heater is supplied with a constant voltage of 2.3 V or less.

The thermistors are printed with a positive temperature coefficient composition (PTC paste 5093 D, available from DuPont). They have a theoretical resistance of 1 kΩ and a temperature resolution of approximately 2.75 Ω/K. The distance between heater and sensors amounts to 500 μm. All electrical elements are connected by means of 200 μm vias.

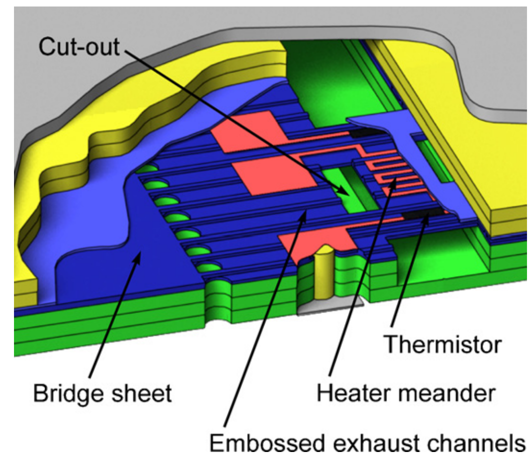

Fig. 2. Sensor design.

The bridge consists of two layers. All functional elements are screen printed between them to ensure the necessary encapsulation for biocompatibility. Exhaust channels are embossed to enable the use of the thickfilm compositions inside the multilayer. The necessity of this approach will be discussed in the next section. The thinnest commercially available layer combination is used to minimize the cross-section of the bridge. Furthermore, cut-outs decrease the thermal cross-section of the bridge and thus minimize the conductive heat loss.

Six modules are arranged on one tile with a dimension of 85 mm × 85 mm. The sensor is electrically connected by means of a standard plug. HPLC standard tubing is used for the fluidic supply.

3. Technological challenge resulting from the thick film technology

3.1. Biocompatibility of the LTCC tape

The compatibility of 951 with biological processes is investigated for some applications [11], but for the demanded polymerase chain reaction (PRC) and the widely distributed mammalian cell lines HEK 293 FT and CHO-K1 were no data available. Hence the compatibility of the 951 base tape and affiliated function compositions was evaluated in some assays.

Typical metal screen print compositions available from DuPont and low temperature sealing glasses were tested concerning their compatibility. From the DuPont Portfolio two cadmium-free sealing glasses, the QQ550 and QQ600 encapsulant were chosen. They are designed to cover thick film resistors. Additionally, the encapsulant FX 11-036 with a low thermal expansion coefficient available from Ferro Electronic Materials was investigated.

Various tests were run in which the PCR was carried out in the presence of the 951 ceramic as well as screen print compositions, and subsequently compared with a reference sample. The screen print compositions listed in Table 1 were applied to the substrates.

Both cell lines were grown on the ceramic surfaces, bare and printed with the pastes listed in Table 1, and their number was counted and compared with a parallel reference. The results are shown in Table 1.

The tests demonstrate that the base tape is well tolerated by all investigated biological processes, while all conductor compositions essentially have a negative influence. Sealing glass compositions strongly inhibit the PCR assay as well as the cell growth on the surface. This fact is a sign of toxic ingredients in the layer. The resulting consequence is that all functional layers should be covered with the basis tape to avoid the direct contact with the reagents. Thus, the sensor has to be encapsulated using the 951 base tape.