LAB-ON-GLASS:
INTEGRATED ELECTRONIC DISPOSABLES FOR RAPID MOLECULAR DIAGNOSTICS

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ABSTRACT

In this paper we present for the first time our so-called “Lab-on-Glass” (LOG) technology platform which is an innovative generic electronic-fluidic integration approach for microfluidic total analysis systems and as such enables a versatile development platform for diagnostic devices. Here we focus on compact disposables for automated rapid molecular diagnostics (MDx) (i.e. nucleic acid testing). In particular, we discuss the first active-matrix driven thermocycler array suited for DNA amplification through Polymerase Chain Reaction (PCR).

KEYWORDS: Lab-on-Glass, micro-fluidic total analysis system, active-matrix multi-well thermocycler, PCR, LTPS, electronic-fluidic integration

INTRODUCTION

In the past decade a wide variety of bio-fluidic functions for total analysis systems has been reported using electrical actuation, e.g. droplet fluidics [1], gel-based valves [2], micro-mechanical actuators for mixing/flow [3], on-chip PCR [4], (di)electrophoretic techniques [5] and electric field based sensors [6]. Despite these and other advances, the use of the vast arsenal of electrically driven bio-fluidic functions in diagnostic applications is sofar limited, which is primarily due to the challenging system integration aspects: cost-effectiveness, performance (speed, sensitivity, reliability) and ease-of-use (automatic control). The Lab-on-Glass (LOG) technology presented here targets to overcome these challenges.

Figure 1 schematically shows the basic concept of the LOG platform approach for a generic DNA test device. An integrated LOG device consists of microfluidic structures (e.g. resists, plastics) stacked on an intelligent electronic glass substrate, which contains thin-film electronic components (e.g. resistors, transistors, diodes) that are deposited using technologies often applied in the display industry, such as low-temperature polycrystalline silicon (LTPS). The as such enabled application of active-matrix addressing (i.e. line-at-a-time), similar to that in a display, allows the rapid and individual control of a wide variety of biochemical and fluidic functionalities in parallel through a universal I/O interface (i.e. there is no need for large device peripheries).

Main advantages of LOG with respect to crystalline Si-based integration approaches is the natural fit of LOG with the need for electronics distributed over a relatively large area combined with the need for cost-effectiveness: costs of LOG are more than ten-fold lower per cm² than crystalline Si. In addition, the transparent and
biocompatible glass substrate puts fewer constraints on the cartridge and system design, e.g. the LOG technology can readily be applied in disposables that mainly consist of plastic.

![Diagram of Lab-on-Glass technology](image)

Figure 1. (a) basic concept of the Lab-on-Glass technology for an integrated DNA test device with the primary functions of sample preparation and nucleic acid amplification/detection, (b) cross-section of a Lab-on-Glass device (not to scale).

The options enabled by the LOG technology are demonstrated through presenting experimental results, thereby focusing primarily on thermal controlled functionalities for DNA testing, such as polymerase chain reaction (PCR). In particular, we report here, what is to the best of our knowledge the world’s first active-matrix (LTPS) controlled multi-well thermocycler arrays that are suited for DNA amplification through PCR.

**EXPERIMENTAL**

Demonstrators, ranging from single-well integrated thermocyclers up to 20-well thermocycler arrays with 180 heater and sensor pairs, were designed and realized in-house. The specifications include high ramping and cooling rates (>10 °C/s) combined with high temperature uniformity and accuracy within a single well (~1 °C). 3D thermal simulations were performed for the design, using the software package FLOTHERM [7]. The experimental work included the design of the on-chip circuits and processing masks for LTPS devices as well as the device processing itself, architecture and implementation of compact digital/analog hardware setups for driving the devices based on active-matrix (i.e. line-at-a-time) addressing, and the software to control the entire system (IT, communication and user interfaces).

**RESULTS AND DISCUSSION**

Figure 2 shows a photograph of a rapid miniature thermocycler for PCR with relatively large volume (~20 µL). It comprises eight individually addressable resistive heaters and three resistive sensors. Materials that may be used for the heaters/sensors include Chromium (Cr), Aluminium (Al) and Indium-Tin-Oxide (ITO). The fluidic frame may consist of resist (e.g. SU8), double-sided adhesive tapes, metal or plastics. Figure 3 shows the measured thermal response vs power characterization curve of a glass based (empty) thermocycler for heat sink temperatures of 20 °C and 30 °C.
Figure 2. Top view of a single-well microfluidic thermocycler (volume ~20 µL). The fluidic well is positioned on a heat sink to allow rapid cooling down.

Figure 3. Thermal response vs - power curve of glass based thermocycler comprising 8 heater segments, each consisting of 10 parallel resistive wires (200 nm thick CrAl, 50 µm width, 50 µm spacing).

Average heating rates (from 55 to 95 ºC) up to 100 ºC/s are obtained, as well as cooling rates as high as -30 ºC/s while keeping the heat sink at 20 ºC. Individual closed-loop control (1 kHz frequency) of the heaters/sensors enables the desired temperature control for PCR with high uniformity and accuracy (~1 ºC) combined with the heating rates (see Figure 4). PCR product was readily obtained using these thermocyclers. This 1-well study served as proof-of-concept towards multi-well thermocyclers.

We studied the feasibility of an integrated multi-well PCR array based on the LOG platform by building a 20-well thermocycler setup in which the temperature of each well can be individually controlled, in parallel with the others, without compromising on temperature uniformity (~1 ºC/s) and heating rate (>10 ºC/s).
Figure 4. Typical PCR cycle obtained with thermocycler using rapid (1 kHz frequency) and individual closed-loop control for the 8 integrated heaters.

Figure 5 shows a photograph of the active-matrix (LTPS) driven multi-well thermocycler array. It comprises 180 heater/sensor pairs that can all be driven individually in closed-loop with a frame time of 1 ms. The effective dimensions of the heating area per well are: 3 x 22 mm$^2$.

Figure 5. Top view photo of an active-matrix 20-well thermocycler array incorporating 180 heater and sensor pairs based on LTPS (9.0 x 7.5 cm).

With respect to the single-well design multiple innovations were made to overcome the challenges related to the array. Firstly, so-called thermal guards are included. These small heater segments (eight in total) with width 0.5 mm surround the central heater area of a well to allow for a compact design (minimal heater area, high well density) while minimizing the thermal cross-talk and maximizing temperature uniformity. Secondly, the multi-well arrays are driven by high voltage circuits to minimize voltage drop and power dissipation across the device, rather than using current driving. In particular, we employ on-chip circuits to switch 100 V whilst using only 20 V drivers to minimize the costs of the total system. Thirdly, to allow for
rapid thermal control we have implemented circuits for line-at-a-time addressing based on pulse width modulation. Also the architecture of the instrumental electronics (hard- and software) around the LTPS-glass were revised with respect to conventional display electronics. New approaches include: (i) the generation of the temperature profile setpoints for the 180 heaters with ms time resolution for periods >1 hour, (ii) real-time read-out and visualization of 180 sensors and (iii) PID loops per heater/sensor pair. All this is achieved within a frame time of 1 ms.

CONCLUSIONS

The “Lab-on-Glass” (LOG) technology platform is a generic electronic-fluidic integration approach for microfluidic total analysis systems and enables a versatile development platform for diagnostic devices. We present the active-matrix controlled thermocycler array suited for DNA amplification through Polymerase Chain Reaction, and as such we prove the suitability of the LOG technology for multi-well PCR cyclers. Besides the thermal control focused on here, the LOG platform is readily applicable to functions based on E&M field control.

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