Integrated Differential Silicon Nano-Calorimeter with on-chip Microfluidic for Real-Time High-Throughput Drug Discovery

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The optimization design rules for an integrated poly-silicon chip as well as the optimization of the surrounding microfluidic platform module for liquid-phase picocalorimetry are discussed [1]. The sensor is made of two separate devices, which are placed adjacent to each other for possible differential operation to improve the common mode rejection ratio (e.g. canceling the fluidics injection, 60-Hz, thermocouple thermal resistance, and temperature fluctuation noise). Then each device is made of two suspended 1.6-micron Silicon Nitride membranes aligned on top of each other with 300-micrometer separation, which creates a microchannel with the height of 300-um between them. On each membrane an array of more than hundred (n-p) polysilicon thermocouples are fabricated. The thermocouple array are connected in series creates a thermopile on each side of the dual-sided device.

Combining both thermopile signals results to 40% increase in sensitivity. In addition, the device with the two suspended membranes those facing each other results to more than 50% increase in thermal isolation from the surface of the reaction volume, results to sensitivity of 39 V/W, an improvement to all the reported works with similar structures.

The accuracy of the device through two independent measurement of a single event is also improved. A schematic of one of the two-nanocaloriemter sensors in differential format and a top view of the sensor is shown in the figure 1 Left. Two micrographs of the device are shown in the Fig 1. Right. Our collaborators in Xensor Technology, Germany completed the fabrication of the device.

This device has been originally fabricated toward the recent developments of Thermoseqencing, a new label-free method of DNA sequencing based on direct measurement of heat incorporation in the DNA polymerization reaction; It has been discussed why Thermosequencing, could potentially reduce both the cost and complexity of DNA sequencing by using a picocalorimetric assay in microfluidic platform [2]. In addition to the DNA Thermosequencing, can be used for other applications in biomedical detection such as monitoring drug binding events to a specific protein, antibody-antigen interaction, metabolism or small molecule bindings which are critical for drug discovery.

We have tested the device for different range of bio-molecule detection. Fig. 2 shows the detection of the reaction of Urease with Urea solution at different concentration with our nanocalorimeter device. The reaction has 14.5 Kcal.mol reaction enthalpy. As it shown in the right, the experimental results (square) are in a great agreement with the theoretical values (line) expected for the reaction power at different concentrations.

References:

[1] H. Esfandyarpour, et al., JVST.B V.26, 2, pp. 661-665.
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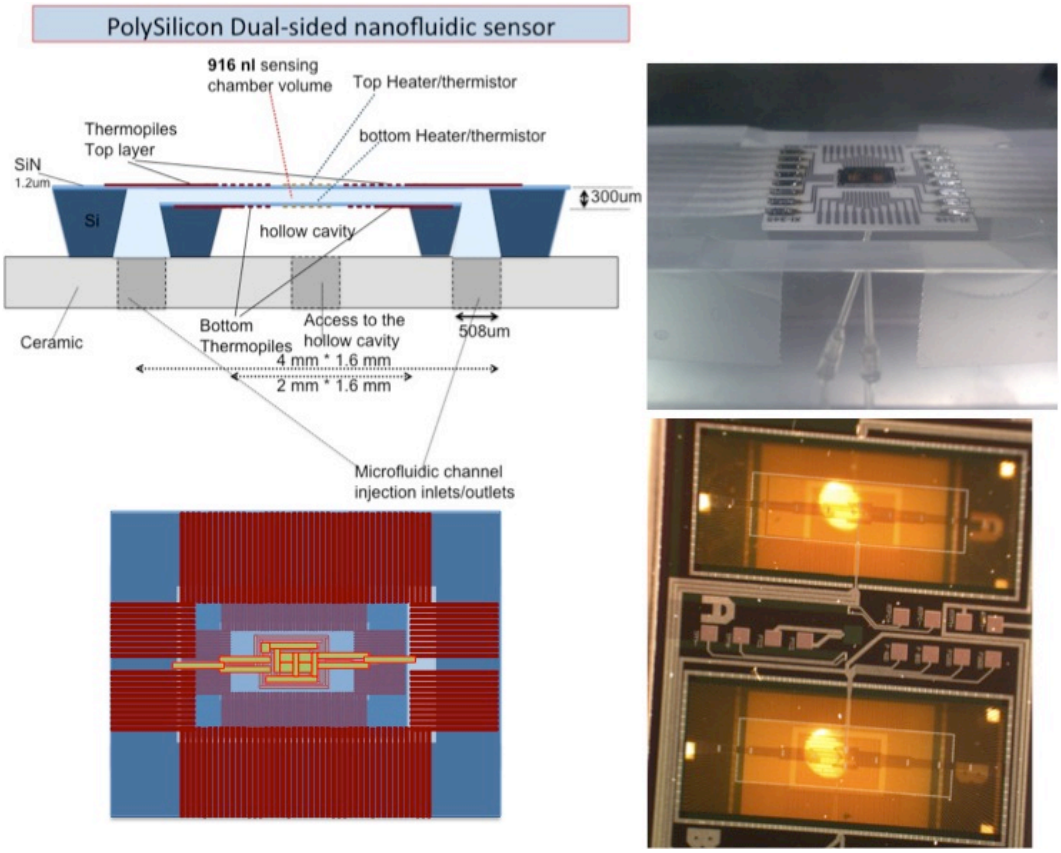

Fig. 1 The schematic and micrographs of the integrated poly-silicon nanocalorimetric sensors with on-chip microfluidics.

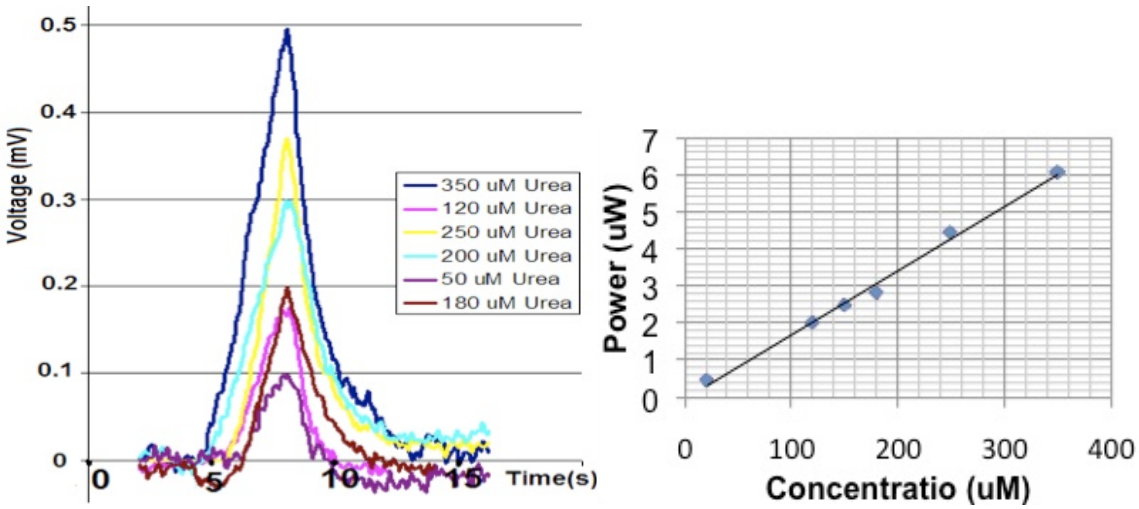

Fig. 2. Successful demonstration of Urease detection with integrated differential nano-calorimeter device at different concentration: left) the output voltage vs time; right) power versus the concentration confirmed the sensitivity and accuracy of the device.