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DESIGN AND FABRICATION OF DIFFERENTIAL SCANNING NANOCALORIMETER

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ABSTRACT

This paper describes the design, fabrication, and characterization of a differential scanning nanocalorimeter that significantly reduces the sample volume to microliter and can potentially improve the temperature sensitivity to 10 μ K. The nanocalorimeter consists of a polymeric freestanding membrane, four high-sensitive low-noise thermistors based on the silicon carbide (SiC), and a platinum heater and temperature sensor. With the integrated heater and sensors, temperature scanning and power compensation can be achieved for calorimetric measurement. Temperature sensing SiC film was prepared by using sintered SiC target and DC magnetron sputtering under different gas pressure and sputtering power. The SiC sensing material is characterized through the measurement of current-voltage curves and noise levels. Thermal performance of a fabricated nanocalorimeter is studied in simulation and experiment. The experiment results show the device has excellent thermal isolation to hold thermal energy. The noise test together with the simulation show the device is promising for micro 10 μ K temperature sensitivity and nanowatt resolution which will lead to low-volume ultra-sensitive nanocalorimetry for biological process, such as protein folding and ligand binding.

Key words: nanocalorimeter, silicon carbide, platinum heater, polyimide, sputtering

1. INTRODUCTION

Virtually all biological phenomena depend one way or another on molecular interaction, which is either intramolecular as protein folding/unfolding or intermolecular as in ligand binding [1, 2]. As a label-free and immobilization-free method, calorimetry can evaluate the Gibbs free energy, enthalpy, entropy, specific heat, and stoichiometry, and thus provides a fundamental understanding of the molecular interactions. Calorimetric systems including isothermal titration calorimeters (ITC) and differential scanning calorimeters (DSC) are the gold standard for characterizing molecular interactions [1, 3, 4, 5].

Differential scanning calorimeters have been used in pharmaceutical hit confirmation and the secondary screening [3,4], bioprocess optimization [6], cell membrane protein [7],

formulation of biopharmaceuticals [8], cancer diagnosis [9,10], musculoskeletal disorder or injury [11], environmental monitoring, enzymatic turnover, and many others, as seen in the review [1,2,7]. However, several bottlenecks prohibit traditional calorimeter instruments for wide applications in biological study, especially in early drug discovery of membrane protein study. The traditional calorimeters require large amount of proteins and very long measurement time, while in practice it takes long time and cost a lot of money to purify and prepare small amount of membrane proteins. The early drug discovery typically needs the screen large numbers of compounds (from thousands to millions), which makes traditional calorimeters not suitable for early drug discovery of membrane protein study [6, 12, 13, 14].

The significance of the calorimeters to biological study has motivated researchers to minimize the calorimeters in the past decade including miniaturizing devices and reducing sample consumption. New technologies based on NEMS/MEMS (nano-/micro-electrical mechanical systems), integrated chip, or printed circuit design have boosted the miniaturized calorimeter development. Several recent published work, such as [15-21], made impressive progress to minimize the calorimeters in size and reduce protein sample volume. The sensitivity and signal noise ratio is still not enough [18-21].

Table 1. MEMS calorimeters and the sensitivity comparison

Group	sensitivity	noise level	power
VT(our group)	-0.1V/K	200nV	5nW
Kwak, B. S., et al[17]	428 μ V/K	4 μ V	
Lerchner, J., et al[18]	6.2V/W	124nV	20nW
PSU group[19]	0.94V/W	100nV	106.4nW
Columbia group[20]	4.07V/W	100nV	24.6nW

This paper describes our preliminary study on the design and micro fabrication of a power compensation differential scanning nanocalorimeter with aim of reducing the sample volume to 1-5 μ L and improving the temperature sensitivity to 10 μ K, which correspond to the requirement of typical

pharmaceutical drug screening or weak binder study. The nanocalorimeter consists of four thermistors which together form a full Wheatstone bridge and a feedback heater. In order to obtain high sensitive temperature sensing material, amorphous silicon carbide is chosen and the fabrication condition of DC magnetron sputtering are optimized. Thermal performance of a fabricated nanocalorimeter is simulated and experimentally analyzed.

2. DESIGN AND OPERATION PRINCIPLE

A schematic view of the differential scanning nanocalorimeter is shown in Figure 1. The nanocalorimeter unit consists of two thermal equilibration areas for sample and reference liquids. An important feature of the nanocalorimeter is that the thermometers, compensation heater, and electric traces are fabricated on a free-standing polymer diaphragm (Su8). The free-standing membrane significantly decreases the heat transfer from the sample or reference region to other area and reduces the thermal mass of the whole measurement region. Copper islands are formed on the backside of the membrane below the sample and the reference regions to improve their temperature uniformities. Because of the minimized thermal mass and the improved thermal isolation, the device can have a sufficiently fast time response to allow real-time measurement. Two high sensitivity micro-thermistors are formed on the membrane in each thermal equilibration areas for temperature sensing. They also will be used as main heaters for temperature scanning because of self-heating effect during the measurement. The feedback heater (platinum) is located on the sample area for power compensation. A thin layer of hydrophobic and biocompatible PDMS is then coated on the top as electrical insulator and moisture barrier. To minimize or prevent drop evaporation, the sample and the reference can be covered by a polymer cover.

The temperature difference between the sample and reference regions is detected by the full Wheatstone bridge formed by four thermistors on the membrane. The thermistor is an amorphous silicon (α -SiC) thin trace with high temperature coefficient resistance (TCR). The full Wheatstone bridge design doubles the sensitivity compared to the normal Wheatstone bridge. With the high TCR of the thermistor, and the full Wheatstone bridge design, this nanocalorimeter offers high temperature sensitivity. The temperature difference induced by molecular interactions is sensed by the resistance change of the thermistor, which will be picked up by the Wheatstone bridge. The output voltage is

$$\Delta V = \Delta R(2 \times R_t)V_{cc} = \frac{\alpha \Delta T}{2} V_{cc}. \quad (1)$$

where ΔR is resistance change, ΔT is the temperature difference, R_t is thermistor resistance, and V_{cc} is working voltage of the Wheatstone bridge. This differential measurement will afford excellent common mode rejection

in the sample and reference regions, such as room temperature fluctuations.

Figure 1. Schematic diagram of the calorimeter

Figure 2. The schematic diagram for the calorimeter system

The operation principal is similar to the standard DSC [1, 4]. A constant working voltage is applied to the thermistors which also act as main heaters, to heat up the reference and sample liquids. Temperature difference between the sample and reference cells caused by biomolecular interaction is sensed by thermistors and Wheatstone bridge, and is further compensated by additional heating power to the sample with the feedback heater shown in Figure 2. The electrical power of feedback heater (and thus excess heat capacity C_p) is recorded, the transition (for example, protein folding) temperature is the one where the maximum peak of C_p occurs, shifted baseline before and after transition is the change of heat capacity ΔC_p , and the area under the transition curve is defined as the unfolding enthalpy ΔH . The Gibbs free energy ΔG , entropic ΔS and affinity constant or disassociation constant can be obtained by comparing the unfolding processes of liganded and ligand-free proteins.

3. PROCESS OF DEVICE FABRICATION

The nanocalorimeters are fabricated using the BNL's user facilities at the Center for Functional Nanomaterials (CFN).

3.1 Overview of Fabrication Process

Figure 3 shows the fabrication process. It started with a silicon wafer with 500 nm silicon nitride (Si_3N_4) covered on both sides. 200 nm

Figure 3. The fabrication process for the nanocalorimeter unit.

chromium (Cr) were evaporated to its front side and backside respectively to serve as stop layer and mask layer for the later plasma etch processes. A photolithography step was then performed on the backside of the wafer to define a 5.5 x 7.5 mm² diaphragm window. The photoresist pattern was transferred to the Cr and then Si_3N_4 layers using wet etching (chromium etchant 1020, Transene Company Inc.) and plasma etching techniques, respectively. The Si exposed in the windows was thinned down to about 100 μm using a cryogenic deep reaction ion etch (DRIE) process in an Oxford Plasmalab 100 ICP (inductively coupled plasma) reactor. A 20 μm Su8 was spin coated onto the silicon carrier and then cured. In order to form free-standing diaphragm, the Si layer underneath the diaphragm was etched away using SF_6/O_2 plasma. 1-μm-thick copper was deposited on the backside of the membrane with the presence of a shadow mask to form two thermal conductive islands. A 100-nm-thick α -SiC film was then deposited onto the SU8 surface in a magnetron sputtering deposition tool (2 mTorr argon gas,

400 watts DC power), and patterned using photolithography and ICP etch techniques, to form four temperature sensing elements on top of the diaphragm window. The SiC film obtained has a resistivity of 10 Ω·m. The metal layers were deposited and patterned via lift-off process. Here, platinum (Pt) was chosen as the feedback heater material due to its stable thermal property and good compatibility, and a 10-nm-thick titanium (Ti) layer was introduced to improve the adhesion between platinum and SU8. The 100-nm-thick platinum layer was sputtering-deposited at 5 mTorr argon gas pressure and 200 watts DC power. This process was carried out sequentially without breaking the vacuum in the sputtering chamber. A stack of 10 nm titanium and 200 nm gold was deposited and patterned to form electric traces and electrodes. To encapsulate the thermometers, feedback heater, and electric traces, we use a PDMS cover to encapsulate the whole device. After oxygen plasma treatment on the bonding surfaces of the PDMS and SU-8 film, the PDMS cover can seal the device easily. The Figure 4 shows the nanocalorimeter device.

Figure 4. (a) The photo of the copper islands on the back of device. (b) Temperature sensors. (c) Feedback heater.

3.2 Detail of Thermistor Design and Process Optimization

Temperature sensing is the most important part of nanocalorimeters. Ideally the sensors should have high temperature sensitivity and low intrinsic noise. Thermal couples have been used in calorimetric biosensors [16, 18, 19], but the thermal Johnson noise is large because of large resistance. Resistance temperature detectors (RTDs) are usually made of metal materials and have low noise level, but the temperature sensitivity is small. Thermistors, such as amorphous germanium or silicon [22], silicon-germanium-

boron alloy [23] and amorphous YCBO [24] have excellent temperature sensitivity but the noises are also large due to their high resistivity. The sensing noise includes thermal noise (Johnson noise) and flicker noise (1/f noise), which is related to material conductivity and measurement frequency bandwidth. Some research results show that the wide band gap materials such as silicon carbide and diamond have high TCR and moderate resistivity values [25]. Furthermore, the wide bandgap semiconductors are very stable in the mechanical, thermal, chemical and biochemical properties, which make them suitable for the thermistor applications [26, 27].

Beside optimization of fabrication conditions, we propose a novel pattern design of thermistor with thermal noise two orders of magnitude lower than traditional design. The concept is illustrated in Figure 5. In this new design we sandwich thermistor trace with electrical conductor trace, therefore the electrical current flows in the side direction, and thus the whole resistance decreased greatly. A simple calculation based on $R=\rho \times L/A$ shows that the resistance of a 4-mm-long trace of $10\text{ }\mu\text{m} \times 0.2\text{ }\mu\text{m}$ cross-section can be decreased by a factor of 160,000, and the corresponding thermal noise can be reduced by a factor of 400.

Figure 5. (a) Novel pattern design of low-resistance high-sensitive thermistor in comparison with (b) conventional design.

The fabricated temperature sensing layer of nanocalorimeter is shown in Figure 6(a). Nominally 150 nm SiC film was deposited at comparatively low temperature via DC magnetron sputtering deposition using a sintered SiC target (purity 99.95%). Deposition of SiC thin film was performed in a Kurt Lesker PVD 75 magnetron sputtering deposition tool. DC power was applied to a 3 inch diameter SiC target in a pure argon (Ar) atmosphere. Amorphous SiC thin film was deposited on to Su8 substrates. Prior to sputtering process, the vacuum chamber was evacuated to 2×10^{-6} Torr and Ar working pressure was maintained by means of pump. The properties of the thermistor thin films depend on the Ar pressure and the power. The SiC film was patterned by ICP etching with a gas mixture of CHF_3 (11 sccm), SF_6 (43 sccm) and O_2 (6 sccm) (Figure 6(b)). The sample temperature was

maintained at 20°C , and RF power $W_1 = 150$ watt, ICP power $W_2 = 900$ watt. In the next step, a 300 nm aluminum was deposited by DC sputtering at a power $W = 300$ watt and pressure $P = 3$ mTorr. Finally, a lithographic step and wet etching is performed to obtain electrical traces, pads and contacts for contacting the sensing layer.

Figure 6. Illustration of the fabricated planar structure (a), and SEM micrograph of a typical amorphous SiC (b).

The properties of SiC film are sensitive to the deposition conditions. In order to obtain low intrinsic noise resistor, the electrical resistivity ρ of the order of $1\text{-}10\text{ }\Omega\cdot\text{m}$ are desired for the planar structure in our nanocalorimeter. The resistivity of the amorphous SiC films sharply increases from $9.5\text{ }\Omega\cdot\text{m}$ to approximately $6.3 \times 10^4\text{ }\Omega\cdot\text{m}$ when the Ar gas pressure increases from 2 mTorr to 10 mTorr at sputtering power 300 watts. Lower resistivity can be obtained at higher sputtering power. The lowest resistivity of $9.5\text{ }\Omega\cdot\text{m}$ at room temperature is obtained at 400 watt sputtering power.

Table 2. Resistivity variation of SiC films with increasing Ar gas pressure at sputtering power 300 and 400 watts.

#	Power(watt)	Pressure(mTorr)	Resistivity($\Omega\cdot\text{m}$)
1	300	2	20.2
2		3	110
3		5	1100
4		10	71000
5	400	2	9.5
6		3	76
7		5	720
8		10	50000

4. RESULTS AND DISCUSSIONS

4.1 Characteristics of Thermistor Materials

The performance of the thermistor SiC was characterized by the ohmicity of resistance, temperature coefficient of resistance (TCR), and noises. Ideally, we would like to have ohmic resistor with high TCR and low noise level.

We measured the current-voltage relation at temperature 295K and 313K using a Keithley 6517A electrometer, with

the applied voltages varied from -10 V to 10 V. The measured current-voltage I-U curves are shown in Figure 7, which indicate the current-voltage characteristics are linear and symmetrical for planar configuration at different current, and the resistance material is ohmic.

Figure 7. Current-voltage characteristics of thermal sensor with planar structure.

For temperature coefficient of resistance (TCR), we measured temperature dependence of the resistance in 20-100°C range in a Lakeshore probe station using an accurate sourcemeter. Since electrical conduction in amorphous materials is a thermally activated process, the temperature dependence on the resistance of semiconductor thermistors can be approximately represented using a relation of the form

$$R = \frac{U}{I} = R_0 \exp(E_a/k_b T) \quad (2)$$

where R_0 is the prefactor resistance, the k_b is the Boltzmann's constant, and E_a the activation energy, which is related to the TCR by $\alpha = -E_a/kT^2$. Therefore, the TCR can be calculated from the slope of $\ln R$ and $1/T$ plots. where the slope is E_a/k_b .

$$\ln R = \ln R_0 + \frac{E_a}{k_b} \frac{1}{T} \quad (3)$$

Figure 8 shows temperature coefficients of resistance at 25°C are -2.03%/K, and -2.04%/K for these two samples.

Figure 8. R-T characteristic of SiC thin films at two power levels of DC magnetron sputtering.

Noise is a major concern for any high-resolution nanocalorimeter. In this study we investigated the noise spectra using a low-noise current preamplifier and HP 35670 dynamic signal analyzer. The noise power spectral density of a DC biased amorphous SiC thin film consists of components of Johnson thermal noise and 1/f noise. The thermal noise power spectral density term can be estimated using $S_T = 4k_bRT$, where R is the resistance of SiC thin film, T is temperature. The relationship between the power spectral density and 1/f parameter is given as $S_{1/f} = \frac{K_f I^2 R^2}{f^\beta}$, where K_f is 1/f noise parameter, I is current across the film, β is the empirical factor which is close to 1, and f is the frequency. When the measurement system is used, an additional instrument noise spectral density (S_v) can be generated through the preamplifier, biasing circuit, and dynamic analyzer. The total noise can be expressed:

$$S_{\text{total}}(f) = 4k_bRT + \frac{K_f I^2 R^2}{f^\beta} + S_v = \frac{K_f I^2 R^2}{f^\beta} + S_{vb} \quad (4)$$

where we denote the sum of the test sample Johnson thermal noise and the instrument noise as background noise S_{vb} .

The background noise and the total noise were measured separately. The background noise was measured when the system was operating with no DC voltage across the thin film. And subtraction of both from the total noise obtains the 1/f noise. The thin film thermistor device was placed in a well-shield aluminum box. The current from the thin film was fed to a low current preamplifier (Stanford research systems SR570) which is battery powered for low intrinsic noise, and provides the biasing of the sample. The amplifier is also equipped with a comprehensive set of low-pass, high-pass and band-pass filters. In this application, we set it as band pass filter of the frequency range of interest, namely 0.03Hz to 30 Hz. The temporal current fluctuations were recorded with the signal analyzer HP 35670A and a noise spectrum was taken after 30 averages.

Figure 9. Spectral density of current noise as a function of frequency (room temperature).

From equation (2), the current noise could directly affect the value of the measured resistance of the thermistor, and further the temperature measurement. The current noise spectral density of one sample at different applied biases (0V, 1V, 2V) is shown in figure 9. It can be seen that with no bias, the background noise was measured to be 10^{-11} - 10^{-13} A/Hz^{1/2} in a frequency range of 0.1-10Hz. The noises measured at 1 V and 2 V are similar to the background noise and 1/f noise dominates at 0.1-10 Hz. By subtracting background noise from the total noise, we observed that a 1/f current noise spectral density in the 500 kΩ SiC film is approximately 10^{-13} A/Hz^{1/2}. In addition, the spectral density of thermal noise can be calculated in the order of 10^{-13} A/Hz^{1/2}. For a bandwidth of 0.1-10 Hz, the noise will be 0.2~0.3μV, which is corresponding to the temperature noise at 2~3μK for these thermistors. Therefore, a temperature of the SiC film of the order of 10 μK can be achieved and signal to noise ratio can be 4~5.

4.2 Characteristics of the Feedback Heater

Due to the thermal stability and good linear temperature coefficient, platinum was chosen as the feedback heater and temperature sensor (to monitor the temperature scanning). The properties of the sputtered Pt film also depend on the fabrication parameters. To assure the accuracy of power compensation and temperature measurement, it is necessary to calibrate the Pt film.

The device was placed in a Lakeshore probe station. We performed the current-voltage measurement at different temperature using an electrometer in the voltage range from -1 V to 1 V. Figure 10 shows the electrical resistance and its variation in 20-100°C range, in which $\Delta R = R(T_i) - R(T_0)$. The results demonstrate that the resistance varied linearly with the temperature and TCR is independent of temperature. In this work, the temperature coefficient of resistance was 0.12%/°C, which is lower than that of bulk pure platinum (0.39%/°C). This is possibly due to the porosity of the sputtered platinum film [28,29]

Figure 10. (a) Calibration curves of resistance vs temperature, (b) Resistance ratio of the sensing element vs. temperature.

4.3 Characteristics of Thermal Responses

Simulations and experiments are carried out to study the thermal performance of the nanocalorimeter, including the power resolution, temperature uniformity, and transient and steady response time.

To pursue ultra-sensitive low-noise temperature sensing at microliter sampling volume, it is necessary to have excellent thermal isolation, which means small parasitic energy loss. Figure 11 illustrates the heat flow paths. The PDMS cap is used to prevent the evaporation of the sample as well as to isolate the sample from the ambient temperature fluctuation. In this work the finite element analysis program ANSYS is used for the thermal and structure simulation. Other methods such as 3ω method which is extremely useful to study the thermal conductance of thin film and could be applied to the AC DSC which offers direct enthalpy measurement during the temperature scanning [30, 31].

According to our design, the nanocalorimeter is on the polymer membrane. In the steady-state thermal finite element analysis, the side face of the polymer membrane is set to be the ambient temperature T_{air} which is 293K. Another equivalent boundary condition is the boundary temperature gradient is zero. This setting can be explained by the sharp temperature attenuation in the non-heating area of the membrane. The size of the polymer membrane is $7 \times 8 \text{ mm}^2$. Solid 90 is used as the meshing element, and the free meshing method with local refinement in the heating area is used for the meshing process. We assume the SU8 is 20 μm and the thickness of conductive thermal island is 1 μm. Since the thermal conductance of copper is 1000 times larger than SU8, the total thermal resistance of the heating area is determined by the copper. A 5 nW power is applied in the sample, and 0 nW to the reference drop. Figure 12(a) shows the results of the temperature distribution on the thin film. The temperature variation in thermal equilibration area is small and temperature difference between sample and reference is over 10 μK which is 4 times larger than the

noise level of the system. Therefore, the nanocalorimeter is able to achieve 5 nW resolution.

Figure 11. Illustration of parasitic energy loss.

Figure 12 (b) compares the temperature along the central line in the equilibrium area with and without conductive thermal island on the backside of the membrane, where the relative error is defined as the normalized temperature variance. We see that the 1 μm copper thermal conductive island can effectively maintain the uniformity of the temperature in the measurement region, therefore it will increase the accuracy of the measurement.

Figure 12. (a) Simulation of the temperature distribution on the SU8 film, (b) temperature distribution comparison on equilibrium area.

Figure 13 (a) shows comparison of the temperature changes measured by the thermistor with (blue) and without (red)

PDMS cap when a hot drop ($\sim 50^\circ\text{C}$) was added to the sample measurement area. When a cap is present, the temperature increases very fast, and decrease rate is relative slower. After the system reached a steady state, the baseline doesn't shift. On the contrary, the baseline shifted almost 2% without a polymer cap. The reason is that the energy transport from the drop to the environment air via evaporation, heat conduction and convection without the aid of the cap, while the closed cap can effectively prevent the thermal evaporation and heat transfer. Figure 13 (a) illustrated the PDMS cap can minimize the liquid evaporation.

$$C \frac{dT}{dt} + h(T - T_{air}) = P \quad (5)$$

$$\tau = \frac{C}{h} \quad (6)$$

The thermal response characteristic of the device is determined by the thermal conductance h and the effective heat capacity C as illustrated in equation (5) and (6). To characterize the device's transient thermal response to the heating power, two 3 μl drops were added on the sample and reference measurement area. At the beginning, the device is in a steady state. A 100s electrically generated pulse was applied to the feedback Pt heater. The 100 s electrical pulse (45 mW) was enough to allow the system to reach a steady state. Figure 13 (b) shows the time constant of thermal dissipation is almost 9s, where longer time indicates better thermal isolation, thus smaller parasitic energy loss.

Figure 13. (a) Measured transient response of the device with cap (blue) and without cap (red, thin) when a hot liquid is

added to sample area, (b) transient response when the sample drop is subjected to 45mW heat power with cap.

5. CONCLUSIONS

This paper presents a preliminary study of design, fabrication and characterization of a nanocalorimeter for biological applications. The device was fabricated on a polymer membrane with four thermistor elements for differential temperature sensing and a feedback heater for power compensation. In order to increase the sensitivity and reduce the noise in temperature sensing, SiC film was prepared at various sputtering power and working gas pressure. The results show the deposition parameters significantly influence on the physical properties of SiC film. It presents an electrical resistivity of $\rho \approx 10 \Omega \cdot \text{m}$ at room temperature when the gas pressure is 2mTorr and power is 300 watt or 400 watt. A novel design is presented to attain reasonable high-sensitive low-noise thermistor. The measurement results show the SiC thermo-sensing material has advantages in temperature sensitivity (TCR -2.04%/K) and noise characteristics. The TCR of the Pt feedback heater is 0.12%/K with excellent linearity. Thermal performance of a fabricated nanocalorimeter is studied in simulation and experiments. The results show the device has nanowatt thermal power sensitivity and excellent thermal isolation to hold thermal energy, which promise ultrahigh sensitive nano calorimetry for biological process study. More realistic test with biological samples is undergoing work and the results will be reported later.

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