FLOW METROLOGY STANDARD FOR MICROFLUIDICS

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Abstract

Many current chemical, medical and pharmaceutical applications require precise measurement of fluidic flow in microfluidic regime where traditional flow metrology standards are obsolete or unavailable. It is often mandatory on the other hand for the flow metrology agency to provide certifications of any possible products in services. In this paper we present a systematic study from liquid from below 150µL/sec in the flow channels smaller than 800µm in diameter. The transportation, pressure, composition, temperature and other ambient effects are measured for the metrological effects. MEMS flow sensing technology with thermal time-of-flight operation mode and calorimetric mode is used as the benchmark to test various flow metrology standard methodology (e.g. gravimetrical, optical, and vibrational) such that a fast calibration metrology standard could be established to certify the available products on markets.

Introduction

Microfluidic devices have been the active topic in many current researches as their huge potentials in improvement of performance and process control in biomedical, pharmaceutical, chemical, environmental, aerospace, food and other industries. However, due to the complexity of the devices that involves multidisciplinary understandings of the process, commercial products are not popular and many of those have very high cost for the applications [1, 2]. There are still many technical issues which are not well demonstrated for solutions. The effects for fluid in the channels at micro-regime add the complexity of the possible interactions between the fluid and the channels that brings sometimes the poor repeatability due to the incapability for well-controlled schemes for the flow channels and the sensors. The current available instrumentations are also limited for the required characterization for both the micro structures and the fluid flow characters inside the micro-channels. The frequently discussed metrology tools for fluid flow in microfluidics are mostly based on optical technologies such as particle image velocimetry [3], infrared thermal velocimetry [4], and laser Doppler velocimetry [5]. These optical technologies are bulk in size and require optical transparent channels which may or may not be readily available. In particular these measurement tools are mostly for laboratory research purposes, and are not feasible to be incorporated into microfluidic devices for *in situ* measurement of the flow in the devices. In this paper, we present a design of a MEMS (micro electro mechanical system) thermal time-of-flight (TTOF) sensors that can be placed inside the microfluidic channel for *in situ* measurement of the flow characteristics. We will further discuss the metrology of a microfluidic system and the possibility to apply the TTOF sensors for the metrology standard.

MEMS TTOF sensor and metrology

MEMS TTOF sensor design and fabrication

The MEMS TTOF sensors were made on a silicon substrate of 1.5×3 mm where a 1.5µm thick low stressed silicon nitride prepared by low pressure chemical vapour deposition was used as the membrane support under which the thermal isolation cavity was made by etching away the bulk silicon materials using deep reactive ion etching process. Three thermistors disposed on the silicon nitride membrane were made of platinum via electronic beam evaporation. Each of the thermistors had a resistance about 1000 Ω and been separated with a distance of 70 µm. The length of each thermistor is 600µm. The thermistor at the middle was used as the heat wave transmitter while the other two thermistors placed symmetrically to the middle thermistor were designated as the receivers. In this configuration, the sensor could be employed to measure the bi-directional flow. An additional thermistor with a resistance of 7000 Ω was made for environmental temperature measurement. The surface of the sensor was passivated with a 350 nm low stress silicon nitride. The silicon nitride thin film prevents the fluid from interactions with the sensor. Additional thermistor deposited on the silicon chip substrate can be used to monitor the environment temperature for controlling the temperature of the heat pulse generation.

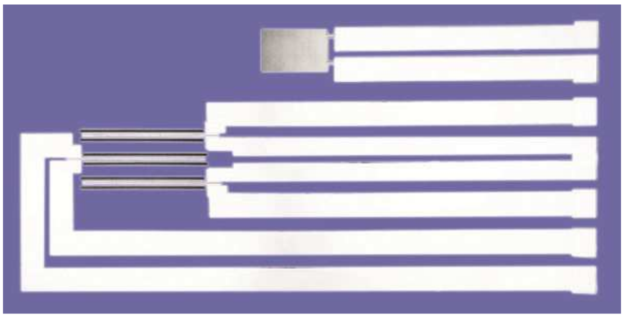

Figure 1. MEMS TTOF sensor

MEMS TTOF microfluidic device

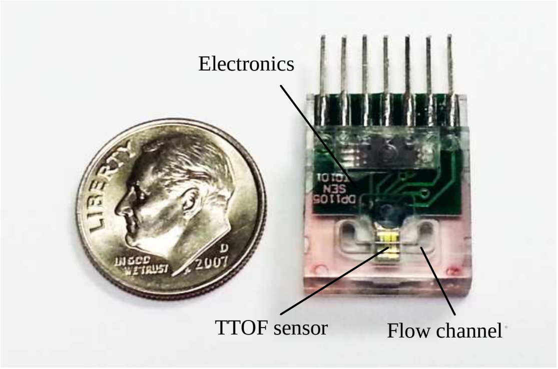

Figure 2. MEMS TTOF sensor package

Figure 2 shows the packaged microfluidic device for a medical infusion application. MEMS TTOF sensor chip is placed in a microfluidic channel that is designed for the fluid flow rate measurement for the complete infusion system control. The flow channel (package materials) is made of medical compatible polyphenylsulfone and is moulded in a base unit and a cover unit. Each unit has the half portion of the flow channel and the base unit also contains the space for the sensor chip. After the sensor chip is placed into the moulded space, the sealing of the two units is done with the ultrasonic bonding that shall have limited influence on the final channel dimensions (estimated <0.5% for the changes in dimension). The flow channel after the sealing is a rectangular shape with the dimension of 600×800 μm for the test flow range from 3 to 150 μL/sec. This dynamic range is for water based fluids. The active sensing area is in direct contact with the fluid and is aligned to the flow channel sidewall. The sensor chip is connected to an electronic circuitry that is embedded in the plastic package and has an electronic memory to store the metrology data. The package is then further connected through the pins as shown in the figure to the external control electronics that contains the interface for data processing.

Flow metrology standards and TTOF sensor calibration

One of the concerns during the tests with the different metrology standards is the interaction of the fluid with the microfluidic channels. Although the moulded flow channel surface is very smooth, there still exists a possibility for formation of gas bulbs during the fluid transportation. The bulbs will have significant impact to the accuracy for the metered fluid by the sensor. Therefore it is necessary to have the designed sensor to be capable of sensing the presence of the bulbs. This capability of the TTOF sensor is realized via the detection of the thermal conductivity of the fluids using one of the standby thermistor on the same sensor chip since the thermal conductivities for gas/air are significantly different from those of liquid, it is easy for the sensor to detect the formation of bulbs when they passed through the sensor. As the sensor has a fast response (<3 msec), it is also able to calculate the sizes of the bulbs when their sizes are comparable to that of the flow channel. Figure 3 shows the sensor output with the presence of the air bulb inside the flow channel. It should be noted that if the dimensions of air bulbs are far less that the size of the flow channel, the detection would be very difficult.

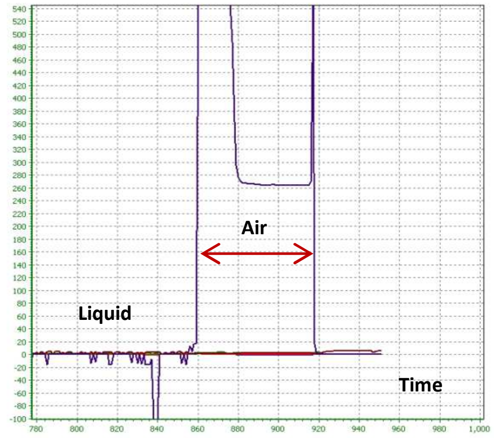

Figure 3. The TTOF sensor output at the presence of air bulb inside the flow channel.

Metrology standard for liquid flow using gravimetrical approach is well documented (*e.g.* OMIL R117 and R120). This approach is also applied in microfluidic flow measurement. As the electronic balance has a high precision and the reservoir can also be kept such that the gravimetrical induced delivery speed variation is kept constant, the amount of liquid delivered at a specific time span can then be accurately recorded as timer can also be very precise. The computer connects directly to the electronic high precision balance and records the start and stop of the pre-set time span. If the ambient conditions are controlled, then the non-system uncertainties of the measurement shall be minimal. The major concern for the microfluidic system is mostly dependent on the evaporation properties of the liquid since the flow velocity may be extremely slow. However, in practical measurements, it is often required to vary the inlet liquid flow velocities to evaluation the performance of the microfluidic devices, which is difficult to achieve with the gravimetrical approaches. The evaluation of the performance and calibration in the full dynamic range of the microfluidic system using the gravimetrical approach is then not the best option.

Another approach for a traceable liquid flow metering is using the Coriolis technology that utilize the resonant vibrational frequency of a tube arising from the Coriolis force or the gyroscopic force to measure the mass flow rate of the flow fluid. The meter made with this technology features a high precision and can serve as the master meter in a calibration system. The current available Coriolis mass flow meters that can be used as the metrology standard for the microfluidic regime are from Brooks Instrumentation (Quantim model) with a lowest measurable liquid flow rate of 0.3μL/sec but for meaningful metrology standard uncertainties of less than 0.5%, the minimal measurable flow rate shall be approximately starting from 10μL/sec. In addition to the incapability of the low flow metrology, there is another issue for the Coriolis technology that requires a minimal working differential pressure. For example, the Quantim meter at the flow rate of 10µL/sec requires at least 30 kPa pressures at the inlet of the meter for the normal operation. For many microfluidic applications this pressure might be over the specified range of the typical operation, although the pressure at this level may not be nontrivial to the measurement uncertainties for the most of fluids.

Many research works for measurements of the flow rates of a microfluidic system rely on optical velocimetry, such as the particle image velocimetry, laser Doppler velocimetry and infrared thermal velocimetry. These technologies can provide reasonably good data for the flow rates of interest. However, many factors are still not clearly documented for the resolution, uncertainty, and repeatability. In addition that there are no well-established standards, the above technologies require certain level of interactions to the measured fluid such as markers or temperature elevation which are undesired from the metrology point of view as such interactions would be another topic of research for the impact of such interactions to the performance of the designed microfluidic devices. Further, flow channel transparent and low loss of the optical signals is essential for an accurate data acquisition. These optical technologies are also bulky and good for laboratory studies. It does not provide convenience and efficiency for the batched process as required for manufacture.

Mechanical syringe pump is another technology that is frequently used to calibrate or test the microfluidic devices. The syringe pump can deliver constant flow rate as low as picoliters per minute that ideally matches to the microfluidic regime. The syringe piston presses forward at a pre-set speed from its control unit and the piston is driven by a linear motor that is controlled by a microprocessor for a precise revolution speed. The motor then drives the lead-screw putting the pressure arm in the syringe into a controlled motion. The small instability of the flow rate during the delivery can often be minimized via the average over time. Many manufacturers can now provide high precision syringe pumps that meet the minimal requirements for the metrology. In this study, A KD Scientific Legato 110 syringe pump with a 100µl syringe is then selected to be the primary metrology standard to test the metrology capability of the designed TTOF sensor. This model of syringe pump has a delivery accuracy of ±0.5% and a large accessible dynamic range. The digital outputs from both the syringe pump and the TTOF sensor are collected simultaneously by a computer and the calibrations and verifications for the metrology performance are then analysed with specially programmed software.

In situ measurement feasibility with TTOF

Conventional thermal sensing technologies are mostly used for process monitoring or set point repeatability applications. The available products are based on either calorimetric or anemometric principles as both have the advantages of independence on temperature and pressure but require well-established calibration process. These technologies are however prone to instability at low flow and therefore are not suitable for microfluidic applications. TTOF technology is more related to the direct measurement of the fluid flow velocity that shall be dependent on the temperature and pressure variations. Using the MEMS technology, the distance between the thermal pulse transmitter and the sensing element can be precisely determined. For example, the distance (length) uncertainty for a 100µm spaced transmitter and sensing element pair can be as low as 0.05%. Precise time measurement can also easily be achieved. There is then a possibility for a direct and *in situ* measurement of the fluid flow velocity in well-controlled environmental conditions. The calibration would be nullified if this approach could be truly established and verified. However, it is not nontrivial to obtain a pure time-of-flight signal with the thermal pulse approach. In addition to control or compensate the temperature and pressure variations, the impact of the thermal conductivity to the thermistors must also be carefully eliminated. At the very low flow regime, the thermal diffusivity may become a dominate factor over the thermal pulse time delay that suggests the TTOF will have a low flow rate detection cut-off. Besides these physical property limitations, one must also consider the fabrication of the thermistors, as the responses of the thermistors to the temperature variation is also a critical factor to be accounted for when developing the TTOF sensing that can meet with the necessary metrology standards.

One of the approaches to address the variation of the thermal property of the fluid is to integrate multiple sensing thermistors with different distances to the thermal pulse transmitter. A proposal by Bonne et al. [6] indicated that with two sensing thermistors, an independent accurate fluid flow velocity regardless of the fluid thermal properties can be measured with the MEMS sensing technology. For the thermistor thermal responses related transit time or time lag due to the non-zero thermal mass of the thermistors, a vacuum calibration process may be applied. The advantage for MEMS sensing chips is that they are made using massive production process. Variations among the thermistors are minimized. The calibration for each batch products rather than for individual product would be required in practical procedures.

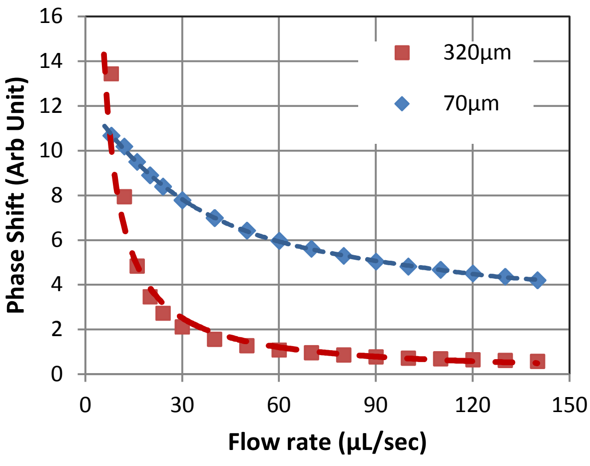

Figure 4. Sensor phase shift output vs. flow rate

Figure 4 shows the TTOF sensor phase shift outputs vs. flow rate. The two curves correspond to the different distances between the sensing thermistors to thermal pulse transmitter. The output from the sensing thermistor with 320µm distance can be approximated with a reverse power function while the outputs from the closer sensing thermistor cannot be approximate with a power function but a polynomial function to the third order. This indeed indicates that with a longer distance the time-of-flight is dominated while the other effects may be critical for the short signal transmission distance.

The time-of-flight technology has better low flow accuracy as the time span is longer resulting in a better resolution and stability as long as the domain is within the time-of-flight regime. Depending on the electronics, the TTOF sensor can achieve a better than 1% accuracy and a reasonably good dynamic range. As of today, the critical issue is that the data processing is not developed to identify each factors such that the pure time-of-flight velocity measurement approach can be established.

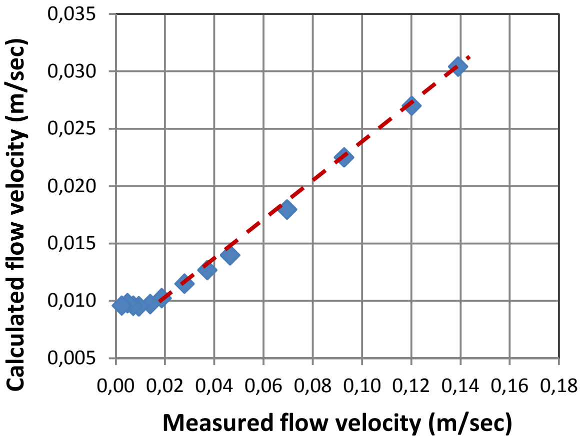

Figure 5. Measured flow rates vs. calculated flow rates

Figure 5 shows the measured flow velocities compared to those calculated directly from the measured phase shifts for a sensor with 150µm distance between the thermal pulse transmitter and the sensing thermistor. Apparently at the low flow rate regime, there are no correlations between these two set of values indicating that the time-of-flight would not be playing critical roles in the metrology of this regime. The observed low flow rate cut-off values are close to the theoretical estimations by Bonne et al. [6]. For the high flow velocities, the linear correlation suggested that we need additional work to understand the physics that contribute to the observed correlations.

The pressure effects to the metrology performance is minimal as long as the applied pressure is within the TTOF sensor membrane mechanical design limit as the compression of the liquid at low pressure is trivial. Temperature performance up to 60°C also showed no significant impact for the performance and can be easily compensated with the electronics.

Concluding remarks

Flow metrology for microfluidics is still an open topic to be addressed. There are many non-conventional factors that may play a role in the determination of the flow performance in the micro flow channels. Therefore it is nontrivial to develop an *in situ* metrology that can provide the true flow metrology values. Among the current available technologies, TTOF is promising as it could be integrated with the micro flow channel and the cost structure also makes it possible for a massive deployment. However, there are still some additional works required to clarify the details of the configuration and essential physics for the observed phenomena such as low flow rate cut-off, deviation from the theoretical value and ambient effects. Additional work is also needed to demonstrate the manufacture process that can provide the reliable and well performed products.

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