

Calibration of Microfluidic Flow Meters

Y. Liu¹, X. Feng¹, Y. Yao¹, L. Lei², P. Zhao², T. Meng³, L.J. Huang¹

¹Siargo Ltd., 3100 De La Cruz Boulevard, Suite 210, Santa Clara, California 95054 USA

²National Institute of Measurement and Testing Technology, Chengdu 610021, China

³National Institute of Metrology, Beijing 100029, China

E-mail: Liji@Siargo.com

Abstract

Calibration of a microfluidic meter is conventionally done with a precision reference such as a high accurate balance or a precise syringe pump system. These processes normally are very time consuming and are not the feasible approaches for high volume flow meter manufacture. In this paper, we will discuss the comparison of the calibration options of the thermal time-of-flight microfluidic meter including the precise syringe system, balance and Coriolis flow meter. The flow range of the meter covers from 20 μ L/min to 400mL/min. The comparison of the metrology features and the procedure of each system is discussed. Further, for the hygienic sensitive applications, the liquid calibration often leads to concerns for the cleaning procedure after the calibration. Comparison of the calibration with the calculated values and DI water and the conversion between the fluids is also discussed.

1. Introduction

In recent years, demands for the precision flow rate measurement in microfluidic applications become more and more pronounced. Examples are the applications in drug delivery, DNA sequence analyser, liquid analytical instrumentation (such as HPLC), pharmaceutical equipment and monitoring of the physiological fluid in medical intensive care units. For these applications, traditional Coriolis mass flow meters or thermal calorimetric sensors are often too expensive and manufacture of those products in high volume is also not feasible. As of today, there is still no suitable products that can meet the market demands. Although a couple of companies are offering microfluidic flow sensor products for evaluation [1,2,3], but these products are still having a very high cost while the performances are not as desired.

The current available products targeting for high volume applications are made of three different measurement principles. The MEMS Coriolis mass flow sensors were initially proposed for the drug infusion applications, but it had a very complicated manufacture process and in a foreseeable time it could not reduce the manufacture cost for the disposable options. The MEMS calorimetric sensors have a path for the cost-effective sensor chips, and is also proposed for drug infusions but the required package makes the final product yield and cost

problematic for the high-volume production. Another microfluidic flow rate product with energy dispersion approach was also having a high manufacture cost, and therefore the desired high-volume applications are not feasible.

For medical and/or pharmaceutical applications, while the precision of the products is required, these applications also ask the products to be disposable to avoid cross contamination since the cleaning is very challenge within the tiny microfluidic flow channels. In a previous report [4], the authors proposed a micromachined thermal time-of-flight sensing technology aiming to provide the desired performance of large dynamic range with a high accuracy. While the performance could meet the current market requirements, the cost is critically dependent on the manufacture of such, in particular the time-consuming calibration process to maintain the desired accuracy. For the thermal time-of-flight sensing technology with the micromachined chips, the distances between the thermal source and the sensing element is well defined and known once the design is fixed. In theory, if the thermal time-of-flight sensing can be well established, the flow speed can be readily calculated by a precise measurement of the time lag for the thermal register travelled at the known distances. However, in reality other thermal effects could not be completely eliminated, a calibration shall still be required. In this paper, we discuss the various calibration approaches and the

correlations between the calibration data and the theoretical values.

2. The design of the thermal time-of-flight flow meter

Figure 1 shows the design and final formality of the thermal time-of-flight flow meter LF6000 for microfluidics. The products have two models. The differences of these two models are the sensing chips on which the distances between the microheater and the sensors are different. One of the sensor chips with the shorter distances among the microheater and sensing elements measures the flow rate from 20 μ L/min to 3 mL/min, while another with longer distances measures from 2 mL/min to 400mL/min.

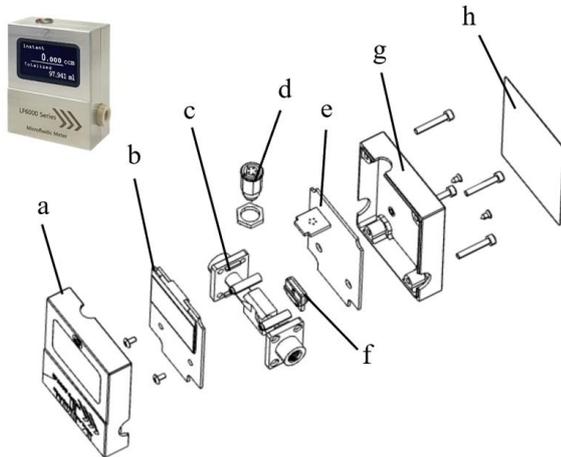


Figure 1: The explosive view of the thermal time-of-flight flow meter for microfluidics. The insert photo is the actual product, LF6000. a – the front cover; b – the OLED display; c – the flow channel with ¼ - 28 standard connectors; d – the interface connector; e – control electronics on PCB; f – MEMS sensor assembly; g – back cover and h – product plate/label.

In the explosive view shown above in Figure 1, the meter was made with stainless steel cover for both front- and backside. The OLED display presents a clear view even with a strong light. The flow channel as designed has a venturi type of structure and has a pressure rating of 10 MPa, and the flow channel materials was moulded PEEK which provide a wide spectrum of fluid compatibility. The connectors at the both end of the flow channel are the standard ¼"-28 UNF fittings providing each tubing for the measurements. The MEMS flow sensor chip was moulded into a polypropylene flow channel base where the surface was made flat and aligned with the channel while the sensor connection was isolated by the moulding materials from the flow channel. The meter's control electronics provide all signal processing as well as data interface that are provides a variety of options including the default

I²C and Bluetooth LE. Customers can request most of the common interfaces such as RB485, IO-Link and voltage output. The meter provides a default 100:1 dynamic range and the product is also available for customization.

The moulded flow channel is completely separated from the control electronics and other parts of the meter making the disposable option is possibility from the material cost of view. However, to ensure the accuracy of the performance, each of the meter is currently required to be calibrated. The selection of a calibration process is dependent on the required dynamic range and accuracy which could be quite time consuming. The calibration process contributes the major cost of the product. Hence for a high volume but cost-effective microfluidic flow sensing product, optimization of the calibration process is critical.

3. Calibration approaches and setups

For the calibration of a microfluidic sensing products, there are a few approaches are currently available and those can be readily applied. Among these approaches, precision syringe pumps and balances are commonly are accepted as the reference standards. Using a high precision Coriolis mass flow meter is also justified as the Coriolis has the needed precisions for a calibration.

3.1 Calibration with syringe pump and balance

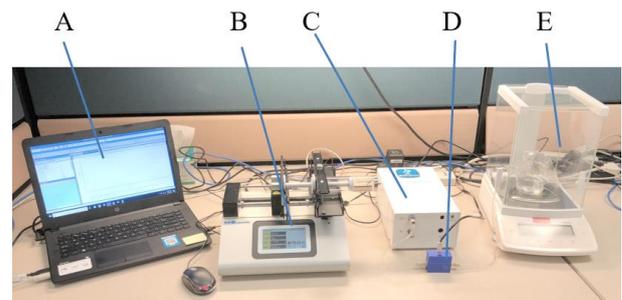


Figure 2: The calibration setup with a precise syringe pump and a precise balance. A – the calibration control system with software and connections to all references; B – reference syringe pump; C – degasser; D – the flow meter to be calibrated and E – the precise balance.

Figure 2 is a simple yet conventional calibration setup for microfluidic flow meters. The reference meter shown in the picture is a precise syringe pump by KD Scientific, Legato 210 dual syringe infusion/withdraw pump. It has an accuracy of $\pm 0.35\%$ for a volume of 0.5 μ L to 140mL providing a capability of measuring 3.06 μ L/min to 215.8mL/min. It also has a maximum step rate of 26 μ sec/ μ step which allows a smooth delivery of the fluid. Another reference is to utilize the precise balance system

that can weight the fluid at the exit assuming a continuous and no dead volume in the flow path. The balance shown in the setup is a Sartorius CPA225D that can measure up to 220g (220mL for water). It has a precision of 0.01mg or 0.01 μ L for water as well. Both these two reference meters are equipped with digital interfaces that are readily connected to a computer in which a software developed in house can simultaneously read the data from the two references as well as from the meters to be calibrated.

It is critical to ensure the flow path is air bubble free during the calibration as the compression or expansion of the air would create unexpected uncertainties which would prevent the measurement from establishing the repeatability which is the base for an accurate calibration. In the system shown in Figure 2, a degasser made by Biotech, DEGASI PREP+ is placed in the calibration ring to ensure the air bubbles are not present during calibration. This model of degasser has multiple channels and each channel has a capability of handling 70mL/min with the degassing efficiency about 85% at about 10ml/min. It also has a very low pressure drop of 0.0226 kPa/ml/min.

3.2 Calibration with Coriolis flow meters

The precise syringe pumps have been widely used as a reference for microfluidic system, but it is not the ideal one for manufacture of a flow sensor as the syringe volume is limited and continuation of operation would have been frequent interrupted. For example, a full syringe in above system could only calibrate about 5 flow sensors with a full scale of 50mL/min. Therefore, alternative approaches shall be preferred.

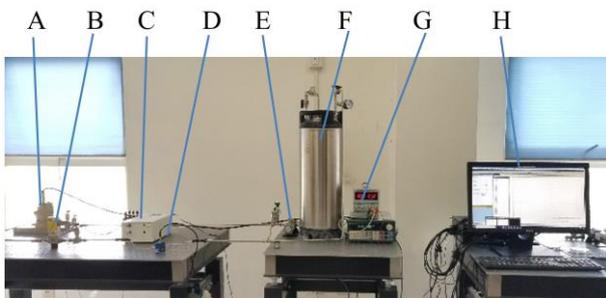


Figure 3: The calibration setup using a standard flow meter as a reference. A – the reference Coriolis mass flow meter by Bronkhorst; B – line pressure gauge; C – degasser; D – the flow meter to be calibrated; E – system pump; F – pressurized water tank; G – power sources and H – the data acquisition system.

Figure 3 shows the calibration system using a Coriolis mass flow meter as the reference standard. In this system, the reference Coriolis mass flow meter was manufactured by Bronkhorst, model

M14V14I. This meter has a nominal uncertainty of $\pm(0.2\% \text{Reading} + 6\text{g/hr})$ but the actual uncertainty per calibration was $\pm 0.06\%$ at 5.3 bar gauge pressure at 20°C with water when the ambient was at 101.6kPa. The calibration water density was 998.5 kg/m³. The cycling of the water was supplied by a magnetically coupled gear pump that delivers a maximum flow rate of 3kg/hr. As the Coriolis mass flow meter is sensitive to the vibration, an optical table was used to support the system as shown in the figure. The line pressure before the product to be calibrated was about 0.05 bar, which was monitored during the calibration by a pressure gauge that is also made by Bronkhorst, the model is P520C with a rated accuracy of $\pm 0.5\%$ FS.

The degasser is the same as that used in the syringe pump calibration system as discussed earlier, and the water tank has a volume of 18.9L with a water filter.

The advantage of the Coriolis mass flow meter system is that the calibration medium is cycled continuously without the needs of change the supply as it does in the syringe pump calibration system. Hence it is more efficient for the volume manufacture.

3.3 Calibration procedures

Calibration of a microfluidic sensor is nontrivial as the susceptibility of various components of the system with respect to the variation in system pressure. Several discussions about the calibration procedures [5.6] have addressed the system stability and proximity of the sensor performance. One of the key issues is to ensure the flow path is free of obstacles since the channel size is very much limited in size. To ensure the performance, the system is normally flushing with the fluid medium to be calibrated until a stable condition is reached and air bubble degasser was working for a reasonable time frame. Then start the actual initiation of the calibration process.

For the calibration with the syringe plus the precise balance system, as the product with the full scale flow ranges of a few 10s of millilitre per minute are the ranges for most of the calibration discussed in this paper, the evaporation would not contribute to any measurement uncertainties, therefore the enclosure protection for evaporation would not be necessary for the current discussed flow range. However, for reducing the droplet impact to the balance, the water cup set on the balance was pre-loaded with water that allows the pipe exit to be immersed into the water in the cup.

The thermal time-of-flight sensor products to be calibrated were dried with nitrogen before connected to the system. This is to ensure that there would not be any residues which could create wetted separations or interfaces inside the small flow channels. The computer with the software, which is digitally connected to both the syringe pump and the balance, is controlling the calibration process via the data recording sequences. When the products to be calibrated is connected and no leakage is registered in the whole microfluidic line system, the calibration is then ready to start. For the syringe pump plus balance calibration system, the calibration will start by running the syringe pump at the full-scale flowrate in order to establish a completely filled flow path which is further confirmed after the data were received from the output of the balance, the calibration data acquisition shall start after waiting for about 30 sec for system to be stabilized. For the same reason, the same waiting time applied to the Coriolis mass flow meter calibration system.

4. Calibration and verification

In the one-dimensional proximity, the change of the temperature T with time t in the flow direction x can be expressed as below,

$$\frac{\partial T}{\partial t} = D \left(\frac{\partial^2 T}{\partial x^2} \right) - V_x \left(\frac{\partial T}{\partial x} \right) \quad (1)$$

where D represents the fluid properties and V_x is the fluid velocity. Therefore, in the current one sensor approach, the measurement shall be flow medium dependent. Since the medium properties will not be changing within the interested working conditions, the calibration in theory can be converted to different medium with water calibration. To completely make the measurement independent on flow medium, at least two sensors will be required on the same sensor chip.

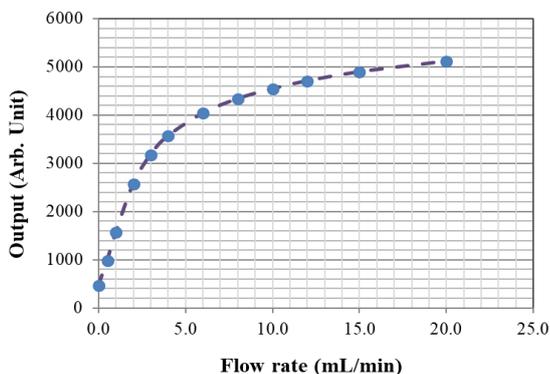


Figure 4: The calibration curve using the phase shift (time lag) sensing with the syringe pump calibration system.

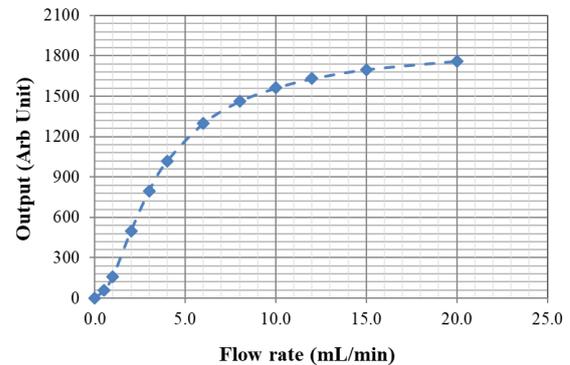


Figure 5: The calibration curve using the amplitude (calorimetric) sensing with the syringe pump calibration system.

Figure 4 and 5 show the calibration curves from the phase shift (time lag) and the amplitude (calorimetric) that were acquired simultaneously from the thermal time-of-flight microfluidic sensing product LF6000. The data shown in the figures were both taken from the syringe pump system where the balance and syringe data were correlated to each other with excellent linearity ($R^2=1$) and a deviation within $\pm 0.25\%$. During the calibration, the reference flow rates were from the set points of the syringe pump and the corresponding voltages were acquired from the product. The time lag (Figure 4) can be fitted with a polynomial while the calorimetric output is hardly fitted with the same approach. The amplitude curve then fitted with a sampling function and converted into a lookup table (LUT).

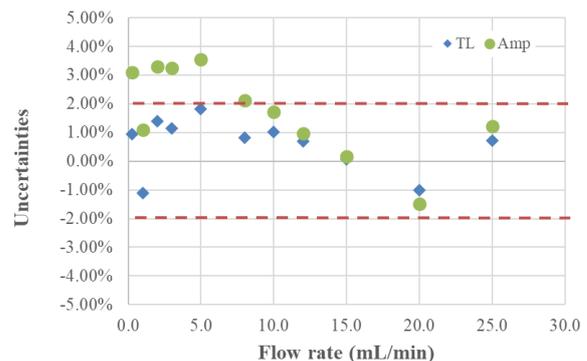


Figure 6: The verification data using the syringe pump system showing that the time lag measurement yielded a higher accuracy as compared to those with amplitude data.

Figure 6 compares the performance of the calibration based on the time lag and amplitude, respectively. The verification data were acquired again from the syringe pump system. The performance using the time lag data calibration is clearly better over those with the amplitude data, in particular at the low flow rate regime. In the dynamic range of 100:1 (25 to 0.25mL/min), a $\pm 2.0\%$ reading accuracy can be achieved based on

the verification. The linearity is not as desired but there could be some additional data acquisition procedure improvement including the data sampling and average algorithm.

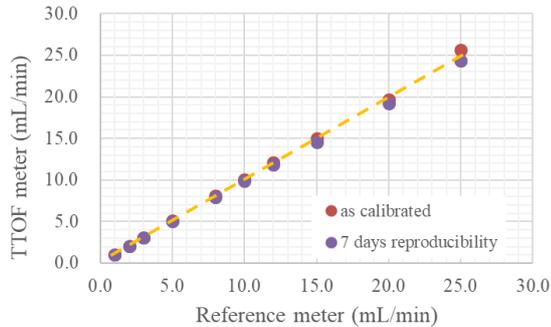


Figure 7: The reproducibility data using the syringe pump system with the time lag measurement.

Figure 7 shows the reproducibility tests where it was found that unlike the traditional thermal mass flow performance, the reproducibility of this tested meter was better at the low flowrate. The deviations observed at the high flow could be due to the fact that the calibration curve reached its flatness where instability would be more likely. Therefore, in this particular flow channel design, the flow rate specifications would be better moving to a lower flowrate regime.

5. System correlations

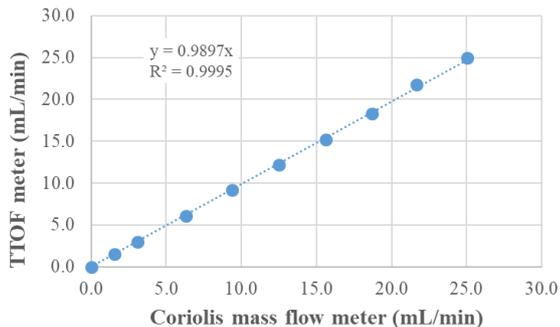


Figure 8: The reproducibility data using the syringe pump system with the time lag measurement.

As discussed above, the syringe-balance system could be accurate and easier for a larger dynamic range test, but it is not suitable for a volume production. The Coriolis mass flow meter system will be much more efficient for the production. As the pressure drop is very low for the products as well as the calibration system discussed (not including the pressure drop across the Coriolis mass flow meter), the Coriolis mass flow meter calibration system can achieve multiple sensor calibration while for the syringe pump it is difficult. It was estimated the

efficiency would be about 10x with the current configurations. Figure 8 shows the verification data for a thermal time-of-flight LF6000 meter that was first calibrated with the syringe-balance system and then verified with the Coriolis mass flow meter system. The results show an excellent linearity with a deviation of -2.1% with the regression. This value is marginally larger than that for the achieved product accuracy, but can be easily corrected once the true value is established. Additional work to identify the sources for the system deviations were in process as of this report is completed.

7. Concluding remarks

This paper discussed the two calibration systems for microfluidic flow metering products. The syringe-balance calibration system could be accurate and easy to adjust the calibration dynamic range but it is not efficient for volume manufacture. The Coriolis mass flow meter calibration system has the necessary accuracy and is much more efficient for the volume manufacture. Correlations of these two systems were well established and further work for eliminating the system deviations is in progress.

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