# User Manual

# Measuring Flow Resistivity in Microfluidics-Based Medical Devices

## Tool Reference

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## Calculating Experimental and Theoretical Flow Resistivities

In the medical device field, flow resistivity measurements can serve two primary purposes for early-stage device developers. Firstly, developers can use flow resistivity measurements to ensure the device has low flow resistivity, as higher flow resistivity can lead to higher pressures and an increased risk of mechanical integrity issues. High flow resistivity may also induce higher shear stress on the biological molecules and materials, which can compromise their viability and functionality. Secondly, the flow resistivity of a new design can also be compared to validated benchmark models to confirm that the new system under investigation, along with its flow and pressure controllers and sensors, is adequate over its entire intended operating range. The protocol provided below demonstrates how to measure the resistivity in a commercially available design, as well as the additional considerations that are important when developing the methodology for this measurement.

Testing Parameters

- A straight microfluidic channel with a square cross section.
- Pressure difference measured across the microfluidic channel ($\Delta$p) using a single pressure sensor at the inlet of the chip with the outlet at the atmospheric pressure.
- Volumetric flow rate (Q) measured using a flow sensor (flow pre-calibrated by provider using water) and represents the flow rate in the absence of any failure modes (e.g., leakage, bubbles).

Flow resistivity can then be measured using the following equation (1)[1]:

$$R_{fluidic} = \frac{\Delta P}{Q} \qquad (1)$$

In addition, the standard deviation ($\sigma_{R_{fluidic}}$) should be measured at least in triplicate on a single chip by a single user, and the $\varepsilon_{R_{fluidic}}$ is the absolute error determined using the following equation:

$$\varepsilon_R = \left| \frac{R_{fluidic} - R_{theoretical}}{R_{theoretical}} \right| \times 100 \qquad (2)$$

where,

$$R_{theoretical} = \frac{12\,\mu L}{1 - 0.63 \times \left(\frac{H}{W}\right)} \left(\frac{1}{H^3 W}\right) \qquad (3)$$

And the $L$, $W$, and $H$ are the length, width, and height of the microchannel, respectively.[2,3] The $\mu$ is the dynamic viscosity estimated to be 0.001 Pa·s for water at 23 °C. Using the known values used for the experimental set up, the theoretical flow resistivity is calculated to be $4.97 \times 10^{12}$ Pa·s/m$^3$.

Tool Output

If the test results of companies indicate that the flow resistivity and absolute errors are in reasonable agreement with Table 1 using the standardized microchannel geometry over the entire operating range of the medical device as specified by the manufacturer to effectively achieve the intended application, then the sensors and the methodology for assessing flow performance can be considered validated. Manufacturers should strive to obtain values that are equal to or lower than the values reported in Table 1.[3] Rather than relying on the sensor performance data provided by the third party, manufacturers may consider conducting their own assessment of the sensor accuracy for their application.

**Table 1. Selected values of flow resistivity, standard deviation, and absolute error from theoretical flow resistivity for various flow rates. The flow resistivities do not scale with the flow rates as the values reported are consolidated for the minimum $\varepsilon_{R_{fluidic}}$ based on three models of sensors used (and includes a few cases where sensors were used beyond their rated operational range).**

| Flow Rates $(\frac{\mu L}{min})$ | $R_{fluidic}$ $(\frac{Pa.s}{m^3})$ | $\sigma_{R_{fluidic}}$ $(\frac{Pa.s}{m^3})$ | $\varepsilon_{R_{fluidic}}$ (%) |
|---|---|---|---|
| 43.5 | 5.83E+12 | 2.32E+11 | 17.3 |
| 60 | 5.66E+12 | 2.66E+11 | 13.8 |
| 80 | 5.30E+12 | 2.48E+11 | 6.6 |
| 100 | 5.09E+12 | 3.26E+11 | 2.5 |
| 200 | 5.22E+12 | 8.83E+10 | 5.0 |
| 300 | 4.88E+12 | 9.93E+10 | 1.8 |
| 400 | 4.80E+12 | 6.12E+10 | 3.4 |
| 510 | 4.59E+12 | 6.72E+10 | 7.7 |
| 750 | 4.41E+12 | 7.70E+10 | 11.3 |
| 1000 | 4.43E+12 | 3.53E+10 | 10.9 |
| 2045 | 4.32E+12 | 7.19E+09 | 13.0 |
| 2420 | 4.27E+12 | 1.01E+10 | 14.0 |

Following the proposed validation method, manufacturers can then proceed to quantify their device's system flow resistivity using the validated sensors and methods specifically for their flow rates and devices of interest. Additionally, after determining their device flow resistivity and confirming adequate fluid pump capabilities of the system, they can subsequently assess the effects of failure modes (e.g., bubbles or leaks) by characterizing changes in the system flow resistivity in the presence of these failure modes.

Technical Limitations

The calculations used here assume that the flow is incompressible, laminar, and is at steady state. The findings reported here are only limited to a straight channel (square cross-sectional area of 100 µm x 100 µm with the area remaining constant throughout the length) and for flow rates ≥ 43.5 µL/min and ≤ 2420 µL/min using water at 23 °C with dynamic viscosity of 0.001 Pa·s which is a Newtonian fluid.

## Additional Information on Calculating Theoretical Flow Resistivity

- The Hagen-Poiseuille equation describes the relationship between the pressure drop and the flow rate for a laminar steady-state flow in a pipe with constant circular cross-section with length of much higher than its diameter where the fluid is incompressible, and Newtonian (e.g., water). For using the non-Newtonian fluids (e.g., blood) as the fluid, this equation may need extra modifications. It is also assumed that flow resistivity is independent of the flow rates. When rearranged, equation (1) in the tool can be used to calculate the experimental flow resistivity in a microfluidic channel using the pressure differential across the inlet and outlet of the microfluidic device and the flow rate. In this tool, the pressure at the inlet of the microfluidic device was measured using the pressure sensor and the outlet was atmospheric.
- The user can apply the theoretical value of flow resistivity as a reference value for calculating experimental error (absolute error). The theoretical value of the flow resistivity for a straight microchannel with a rectangular cross-section is provided in equation (3) of the tool. This equation has the same assumptions as the Hagen- Poiseuille equation except it uses a rectangular cross-section instead of a circular cross-section.
- The flow resistivity of the tubing and connectors between the pressure sensor and the device was determined to be negligible compared to the flow resistivity of the microfluidic device. For example, tubing internal diameter used was equal to 1/32" (794 µm) and its length is 10 cm. Therefore, the flow resistivity of the tube, $R_{Hc} = \frac{8\mu L}{\pi r^4} = \frac{8*0.001*0.1}{\pi(0.00079375)^4} \cong 6.41 * 10^8 \text{ Pa.s/m}^3$, which is four orders of magnitude smaller than the flow resistivity caused by the microchannel. Thus, the value that the pressure sensors read is a good measure of the pressure at the inlet of the microfluidic device.

## Preparation of Experimental Set up for Measuring Flow Resistivity

The measurement of flow resistivity of a microfluidic-based medical device required a pressure source, a pressure controller to stabilize and control the air pressure levels in the pressurized tank and generate fluid flow, flow and pressure sensors to facilitate accurate measurements, and analysis of flow rate and pressure drop across the device under investigation (e.g., microfluidic device) as shown in Figure S1(a).

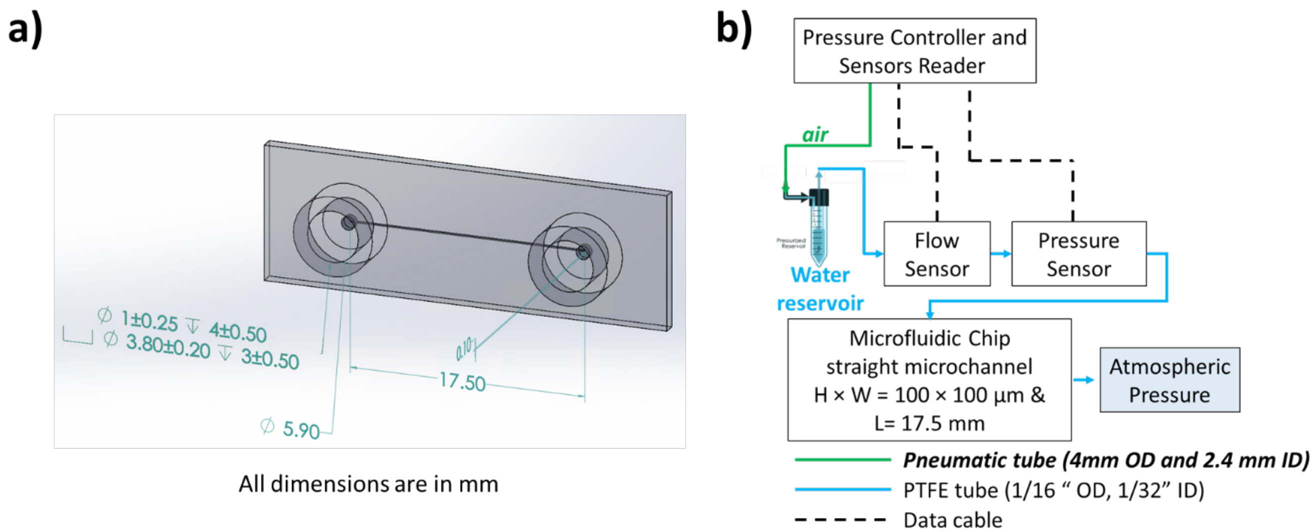


*Figure S1. (a)CAD design of the chip used for determining flow resistivity (b) Schematic of the flow resistivity measurement setup.*

## Specifications of the Microfluidic Device

- The microfluidic channel (not a medical device) under test was made of Cyclic Olefin Copolymer (COC).
- The device consisted of a straight microchannel with a 100 µm x 100 µm square cross-section and a length of 17.5 mm.

## Specifications of the Tubing and Fittings

- The 1/16" O.D. x 1/32" I.D. PTFE tubing were connected to the pressurized reservoir and sensors via ¼-28 Swivel compression fittings. It was connected to the microfluidic device via mini-Luer connectors.
- The gas tubing from the pressure controller to the reservoir was reinforced tubing with dimensions of 4 mm O.D. and 2.4 mm I.D. It was connected to the tank via a ¼-28 Swivel to barbed 3/32" I.D. Adapter.
- The tubing containing water was positioned in a downward orientation. This arrangement simplifies the process of preventing and removing (purging) any potential air bubbles downstream within the test setup.

## Pressure Controller Specifications

- The pressure controller was connected to a line of 2.5 bar compressed air using an in-line pressure regulator, dehumidifier (humid trap), and a 5 um particle filter in series.
- The operational output pressure range was 0 to 2 bar. The actual maximum pressure of the system was 1925 mbar.

- To maintain effective pressure control and stability, a minimum pressure of approximately 100 mbar was maintained at the pressure controller outlet.
- The claimed stability was 0.005% of the Full Scale (F.S.) value, which equals 0.1 mbar.
- The pressure controller response time and settling time were down to 10 ms and 50 ms, respectively, as per the manufacturer.
- The pressure controller position was at a higher elevation than the pressurized tank and microfluidic device to reduce the potential of liquid backflow into the pressure controller.
- A hydrophobic disk filter was used at the pressure controller outlet.
- The pressure controller had an initial calibration and subsequent onsite recalibration every three months.
- After each replicate test run, the pressure source was deactivated or shut down.
- The pressure controller was operated within a clean and dry setting, maintaining a humidity level of no more than 60% and ensuring proper ventilation in the room.

Pressure Sensor Specifications

- The pressure sensor selected was able to measure 0 to 1 bar with max overpressure of 3.1 bar.
- Its accuracy was up to the ± 0.2 of max range.
- The typical and max linearity % spans of the pressure sensor were 0.25 and 0.5, respectively. Its repeatability and hysteresis % spanned ± 0.2.
- The pressure sensor was at the same altitude as the microfluidic device.
- The internal wetted material of pressure sensor was polyetherimide, silicon, and a fluorosilicone seal.

Flow Sensor Specifications

- Three different flow sensors of A, B and C with the corresponding flow rate range of the 500-5000, 100-1000 and 8-80 µL/min, respectively, were used.
- The flow sensor accuracy was 5% of m.v. (measured value).
- The internal diameters were 430 µm (sensor-C), 1000 µm (sensor-B), and 1800 µm (sensor-A).
- The max pressures were 100 bar (sensor-C), 15 bar (sensor-B), and 15 bar (sensor-A).
- Their wetted materials are PEEK and Borosilicate.

Pre-Test Procedure

a. The flow resistivity measurements should be conducted in a controlled environment with regulated temperature and humidity. The environmental conditions were a temperature of 23±2 $^{0}$Celsius and a relative humidity of 55±5 %.

b. All setup components, including the pressure controller, measurement sensors, test media (water), and microfluidic device, were placed in the room where the testing was conducted for several hours before testing to ensure thermal equilibrium.

c. Ultrapure deionized water was introduced into the flow circuit.

d. Electrically powered components, such as the pressure controller and flow/pressure sensors, were powered on for at least 30 minutes before commencing any measurements. The pressure controller required filling a reservoir (i.e., pressure pump) at least 30 minutes before initiating measurements.

e. Before starting any measurements, the entire fluidic system underwent purging/wetting.

f. Purging/wetting was executed using water at the maximum allowable pressure of the pressure controller, pressure sensor, flow sensor, or microfluidic device, whichever had the lower maximum allowable pressure.

Test Procedure

a. All components were assembled, ensuring secure and tight connections of all fittings.

b. The pressure controller reservoir was filled at least 30 minutes prior to initiating measurements.

c. Connections for all necessary electrical power sources to the pressure controller and pressure/flow sensor were established and power on for at least 30 minutes before initiating any measurements.

d. Purging/wetting the setup was done using water at the maximum allowable pressure (2 bar), considering the limitation of the pressure controller, pressure/flow sensor, or microfluidic channel.

e. Both the pressure and flow sensors were zeroed to minimize potential measurement offsets.

f. A target pressure (up to 2000 mbar) was set on the pressure controller and then the pressure was monitored over time using the in-line pressure sensor.

g. Flow rate was read using the flow sensor once a stable pressure was achieved without any significant upward or downward drift.

h. Steps f and g were then repeated for all required pressures.

i. Flow resistivity for each measurement was calculated based on equation (1).

j. Figure S2 presents a selection of the test results along with the corresponding relative errors relative to the values from equation (2) (i.e., theoretical value).

k. In some limited cases the flow sensors were operated beyond their rated operational ranges to assess the impact of flow resistivity measurement accuracy for this situation. The accuracy varied sensor to sensor and no general trends could be derived.

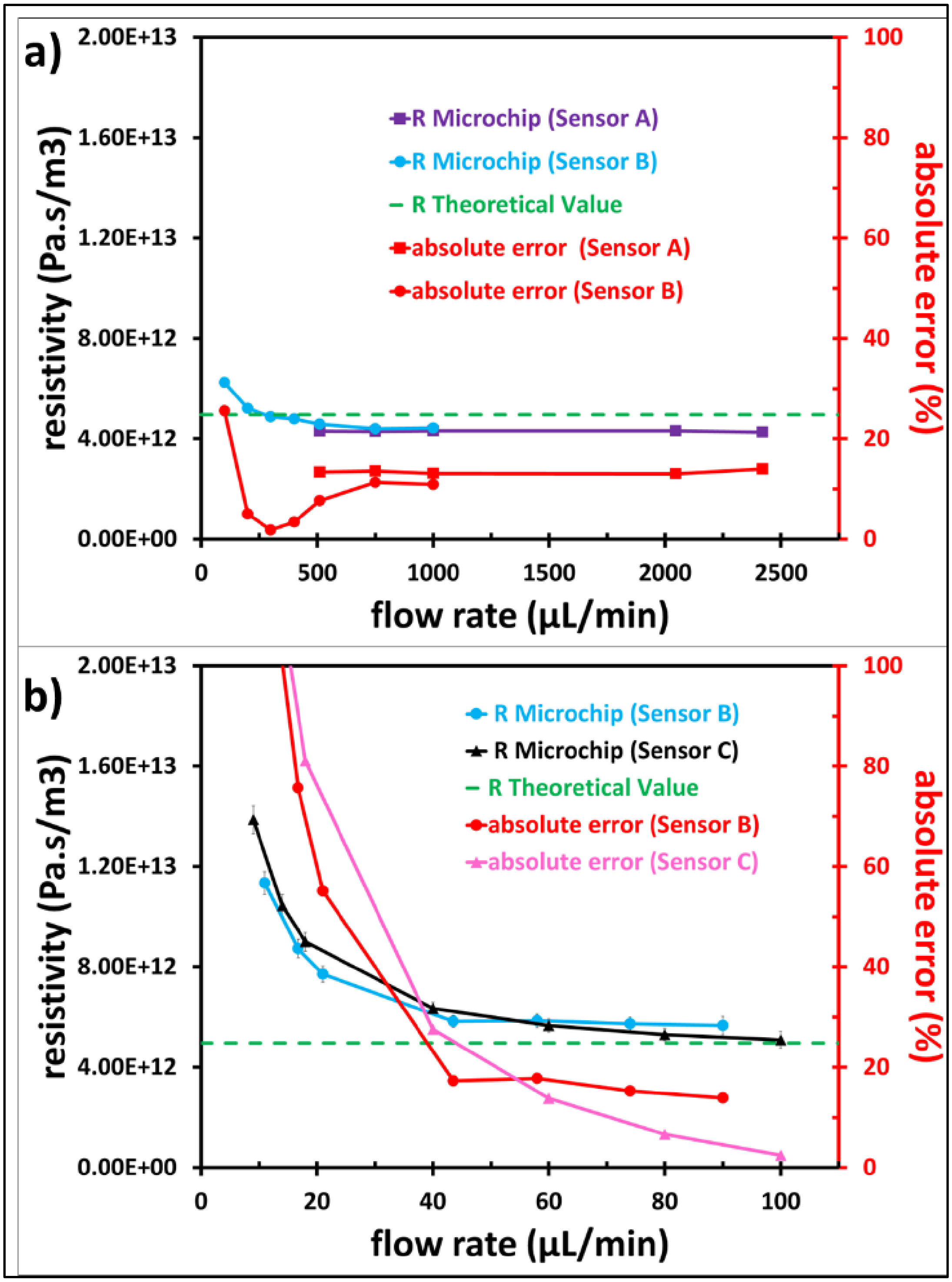


*Figure S2. Flow resistivity and absolute error over a range of flow rates for (a) Sensors A and B (≥ 100 µL/min) and (b) Sensors B and C (≥ 8 µL/min).*

Additional Considerations

- The system stability may be compromised by the compliance (elasticity) of the entire setup and dead volumes, which can potentially trap air, especially when using a liquid (i.e., water) as the test medium. Stability may be improved by considering using PEEK, PEEKSil, or steel tubing options.
- The selection of the pressure controller, pressure sensor and flow sensor should align with the allowable pressure and flow range within the microfluidic channel. It is advisable to employ these elements operating within 10% to 100% of their maximum pressure and flow rate capacity.
- Tubing and Fittings:
  - When selecting and configuring fittings and connectors, it is important to consider that any potential leakage can lead to measurement errors and a reduction in the accuracy of flow resistivity measurements.
  - Opting for fittings and connectors with minimal dead volume to enhance performance may be beneficial. To reduce the likelihood of bubble formation, it may be beneficial to use low displacement plugs and fittings/connectors, whenever feasible, instead of the standard connectors.
- Pressure Controller:
  - The stability of the pressure controller can be commensurate with the accuracy needed for measuring pressure drop or flow resistivity.
  - It is essential to ensure that the pressure source (compressed air at the inlet) of the pressure controller is supplied with an adequate pressure level to operate effectively. The same principle applies to the necessary electrical power supply. Use only the manufacturer-supplied voltage source.
  - For installing the particle/humidity filter between the pressure source and the pressure controller, please consult ISO 8573-1, clause 3.
  - The pressure controller can be employed solely with gases (air) that are neutral, dry, and free from dust and oil. Under no circumstances should the pressure controller be utilized with pure oxygen or in any situation presenting a fire risk.
- Pressure Sensor:
  - The precision of the pressure sensor should align with the accuracy required for the pressure drop or flow resistivity measurement.
  - To reduce compliance, use a sensor with internal wetted materials characterized by low elasticity, such as polyetherimide, silicon, and fluorosilicone.

- Before conducting any pressure measurements, each pressure sensor should be calibrated.

- Flow Sensor:
  - The precision of the flow sensor should match the required accuracy for measuring pressure drop or flow resistivity.
  - All flow sensors must undergo calibration before any pressure measurements are conducted.

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