PATENT NO. 11,035,707 | REFERENCE NO. 18-017

LICENSING OPPORTUNITY: OPTICAL FLOW METER

DESCRIPTION

Invention

NIST scientists have developed an optical flow meter that can continuously measure flow in the nanoliter per minute range. Over the instrument's dynamic range, the relative uncertainty in flow rate remains constant and can be controlled to within 5% or better. No existing technology can simultaneously achieve these performance metrics. Moreover, for applications such as leak detection, the instrument can be operated in a secondary mode that detects changes on the order of tens of picoliters per minute about zero flow.

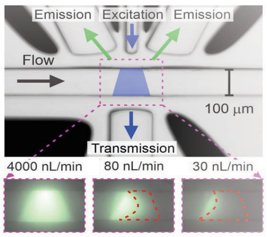
BENEFITS

Potential Commercial Applications

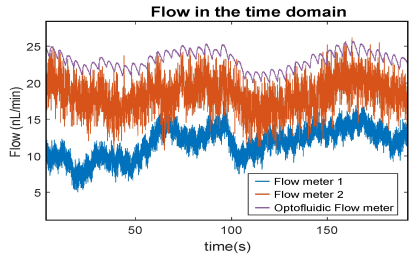
The invention can be integrated into existing microfluidic technologies as an in situ meter and thus become part of existing microfluidic devices. It could function, for example, as part of a flow control, chemical analysis, or particle/cell measurement system.

Competitive Advantage

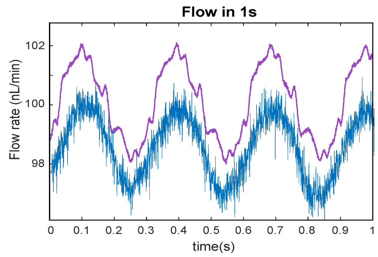
- World's most accurate continuous flow meter in the nanoliter per minute range
- Dynamic range can be adjusted across many decades of flow rates
- Secondary zero-flow mode's calibration data can be used to increase the dynamic range and decrease uncertainty in other instrumentation
- Zero-flow mode also provides a first-of-its-kind, high-sensitivity method for leak detection in the picoliter-per-minute range
- Adaptable to other applications such as flow cytometry, mass spectrometry, and drug delivery
- Response time is faster than traditional flowmeters at the nanoliter/min scale. Moreover, response time is independent of flow rate in typical operating modes



The optofluidic flowmeter determines flow rate by measuring the amount of photobleaching in a dye such as fluorescein.



Comparison of NIST flow meter with commercial meters using a 25 nL/min pump (note fine detail of individual motor clicks in the pump mechanism).



Comparison of extreme dynamic sensitivity of NIST flow meter with mechanically perturbed flow set nominal flow rate of 100 nL/min.

Contact: licensing@nist.gov

NIST TECHNOLOGY PARTNERSHIPS OFFICE

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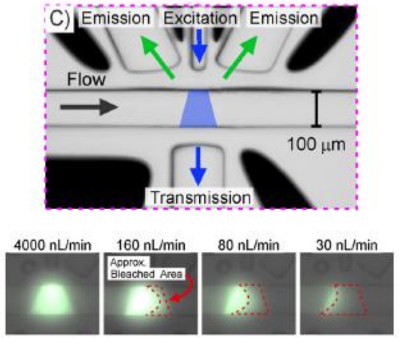
Optical Flowmeter and Serial Cytometer

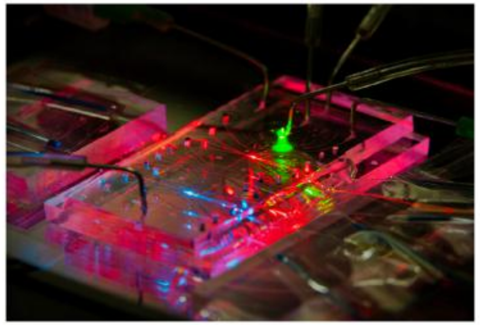
Meet **Greg Cooksey, Ph.D.,**

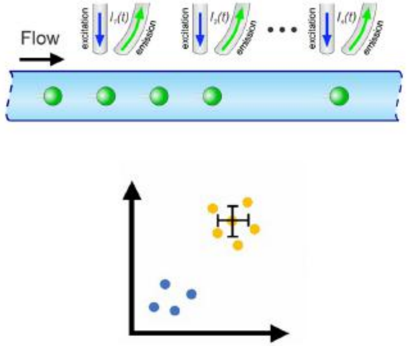
Biomedical Engineer , National Institute of Standards and Technology

Meet **Paul Patrone Ph.D.,**

Staff Scientist , National Institute of Standards and Technology







5% uncertainty at 1 nL/min

Per-particle imprecision <1%

Why Care About Really Slow Flow Measurements?

- **Validating performance of research and clinical instruments**
  - Support calibration of medical devices, e.g. drug pumps (to as low as 10's of nL/min)
  - Resolving power of separation technology is inversely related to flow rate.State of the art for HPLC is based on a few nL/min
- **Maintaining stable chemical processes**
  - Consistency in manufacturing using continuous or injected flows
  - Low volume reagent delivery and partitioning (e.g. in microchambers or microdroplets)
- **Flow cytometry, separations, and fundamental physics**
  - Characterization and control of measurements based on mixing (e.g. convection vs. diffusion)
  - Validating flow phenomena and physical properties of liquids

www.microchip.com
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Microflow Measurement – State of the Art

- **Mass flow – Gravimetric standard (Traceable)**
- **Heat Transfer Method (e.g. Sensirion, Bronkhorst)**
- **Front Tracking (Traceable)**
- **Particle Velocimetry (Traceable-Lite)**

Considerations

- Accuracy
- Dynamic Range
- Response Time
- Deployability

NIST Gravimetric Standard

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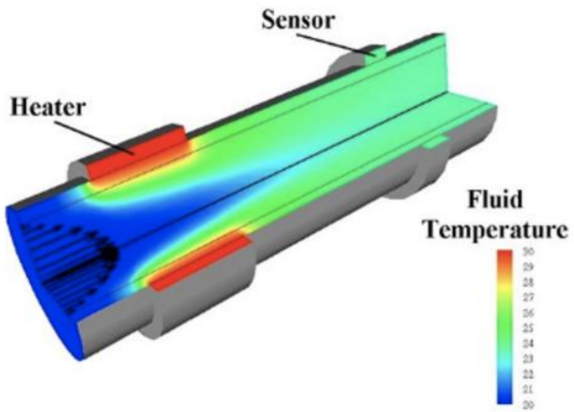
Heat Transfer Method



Front Tracking

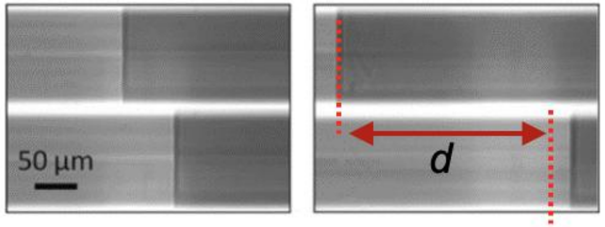


Figure 2. Meniscus appearance at 10 nL min^{-1} (left) and 50 nL min^{-1} (right). Time interval between the top and bottom frames is 10 s. Motion of the meniscus is from left to right. Liquid is on the left side.

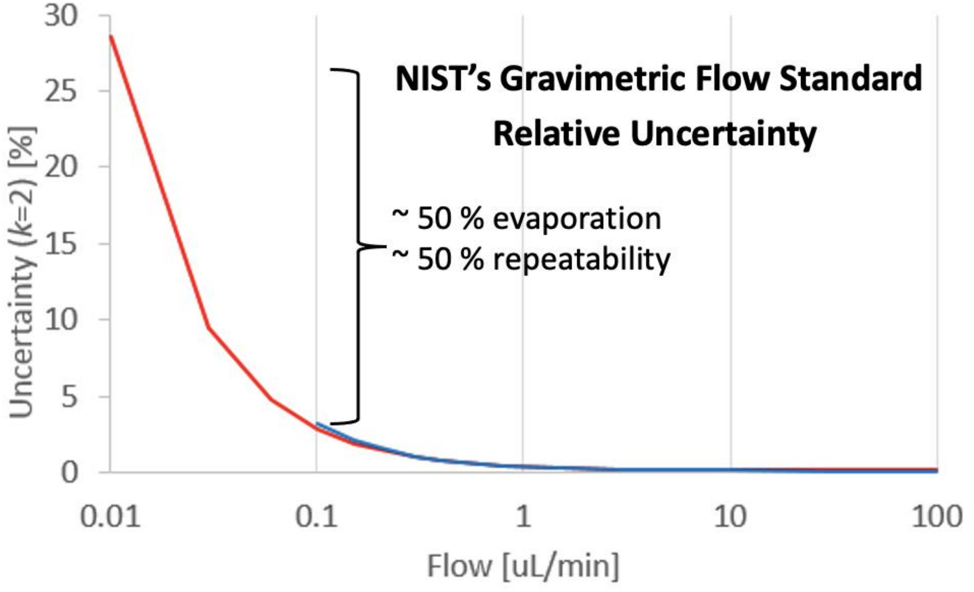
Ahrens et al., *Meas Sci Technol* 2014

Flow Metrology's Brick Wall

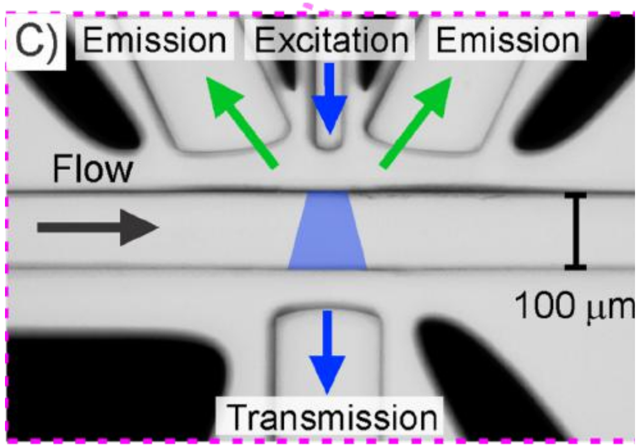
How Can We Overcome These Limitations

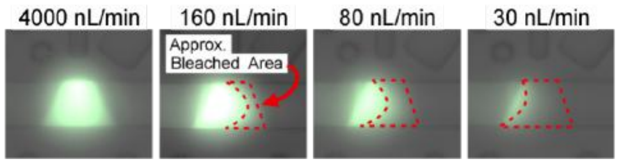
- **Improvements in sensitivity at low flow largely rely on miniaturization of existing (benchtop) technologies**

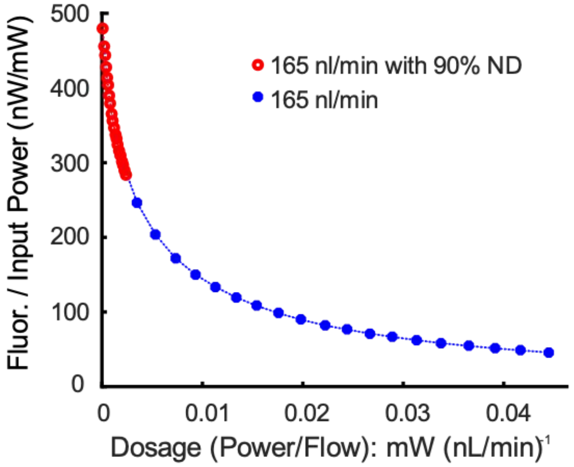
- **With smaller measurements, relative uncertainties become increasingly large due to:**
  - evaporation
  - surface forces
  - geometric factors
  - instrument noise



Dosage-based Flow Measurements



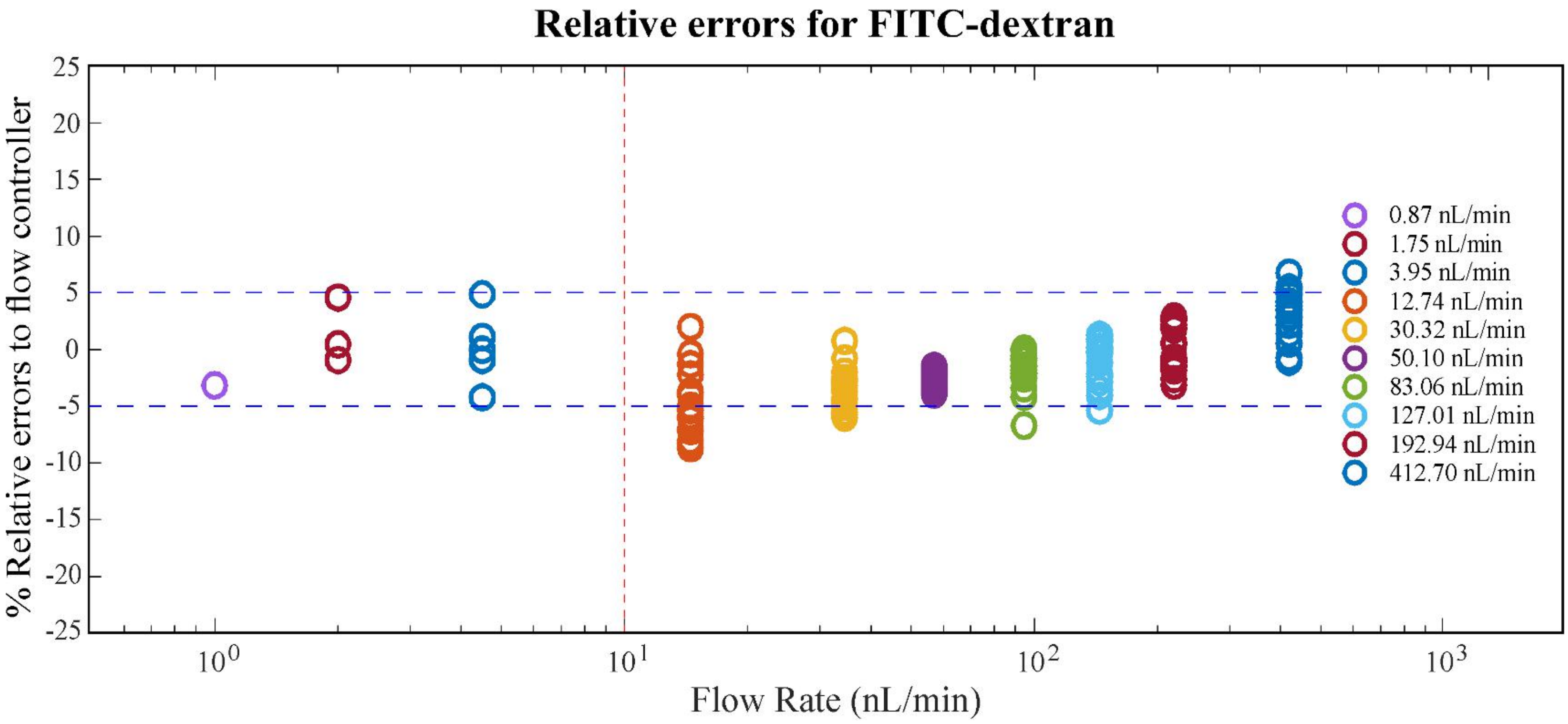




- Fluorophores receive a dosage related to laser power and flow rate-1
- Fluorophores bleach after average # of excitations
- Emission follows a fixed relationship with dosage
- Independent of channel geometry, laser pattern, and flow profile *(Patrone et al. Phys Lett Appl 2019)*
    - Calibrate the relationship at one flow, determine unknown flows from dosage

Recent Advances

Molecules with lower diffusion coeff. enable flow measurements to < 1 nL/min



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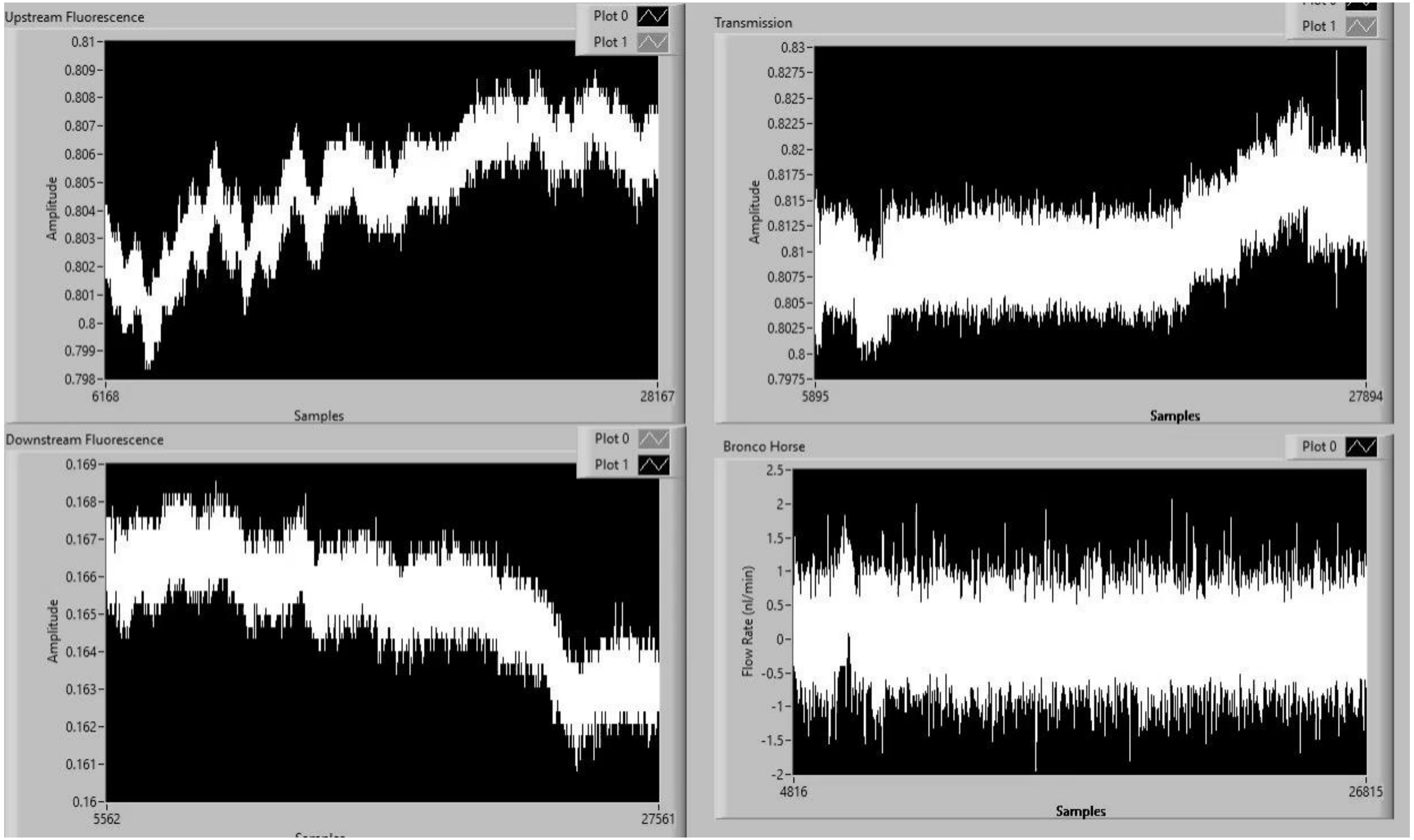
Recent Advances

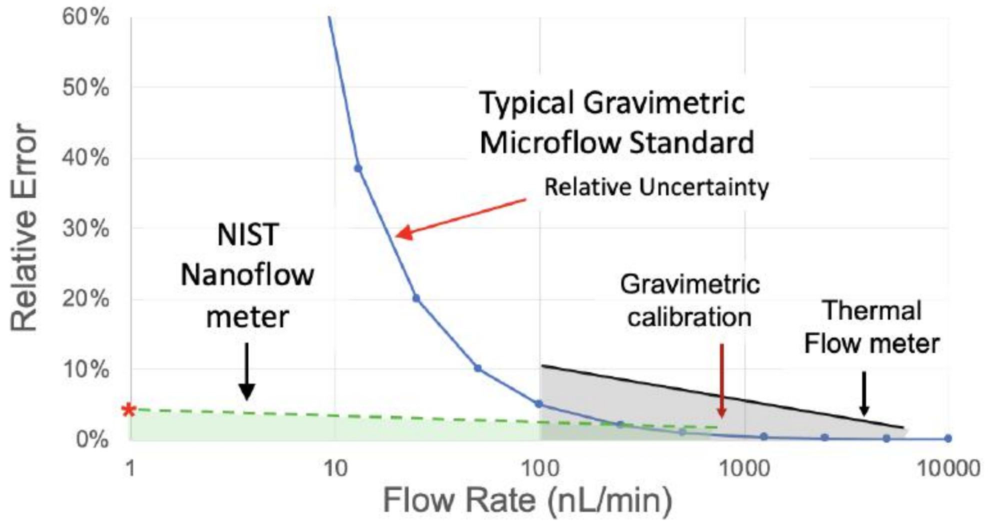
Real-time, dynamic measurements of 50 µm height changes (approx. 40 pL/min)



Nanoflow Metrology

Project Summary

- Create calibration curve of the relationship at known flow rates (e.g. at 1 μL/min)
- Translate uncertainty from calibration into lower regime through dosage using light intensity
- Dynamic flow measurement to 1 nL/min with approx 5% uncertainty
- < 20 pL/min uncertainty resolving advection from diffusion (e.g. zero flow)



Independent of channel geometry, laser pattern, and flow profile

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