VSL

Primary standard for nanoflow rates

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Primary standard nanoflow rates

Overview of this presentation

MEDD Drugmetrology.com

- Motivation
- Design and working principles
- Traceability
- Results - intercomparison
- Conclusions and future work

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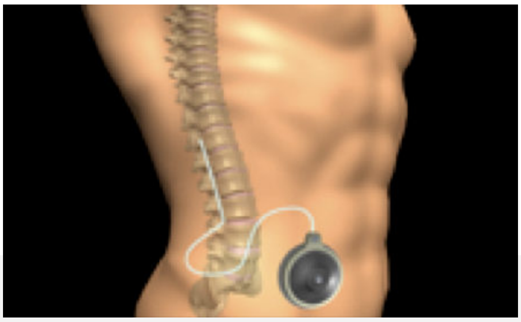
Motivation

Low to ultra-low flow rates

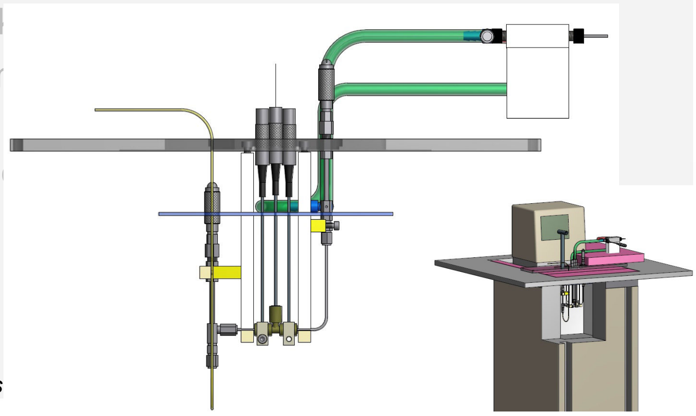


- Applications
  - Drug delivery by means of implanted infusion pumps (e.g. Tricumed IP 2000V down to 0.01 mL/h)
  - Drug delivery for patients with fluid restrictions (down to 0.1 mL/h)
  - Critical drug delivery, e.g. anesthetics and vasoactive drugs (down to 0.1 mL/h)
- Difficult to control flow rate
  - Technology not applicable (e.g. 50 mL syringe for 0.1 mL/h)
  - Technology not fully matured (e.g. implanted infusion pumps)
  - Metrological infrastructure not in place, no traceable calibrations possible
    - No calibration facilities available flow rates < 0.5 mL/h
    - Calibration facilities below 100 mL/h not validated
    - Current commercial devices not validated/ not applicable

Presenting the results of MeDD

Today's program Part I and II

- Clinical relevance (Annemoon Timmerman - UMC)
- Calibration facilities based on the gravimetric principle (Hugo Bissig - METAS)
- Calibration facilities based on volumetric expansion (Peter Lucas - VSL)
- Calibration facilities based on front tracking in a capillary (Martin Ahrens – FH Lübeck
- Preliminary results assessm
(Elsa Batista - IPQ)
- Dosing errors in multi-infusi



Primary standard nanoflow rates

Goal

Standard (calibration facility) for nanoflow rates

- flow rate 10 nl/min ~ 10 µl/min
- liquid flow rates at ambient pressure and temperature
- target uncertainty ≤ 0.5% (required drug delivery uncertainty ≈ 5%)
- based on volumetric expansion
- calibration facility **generates** a flow rates

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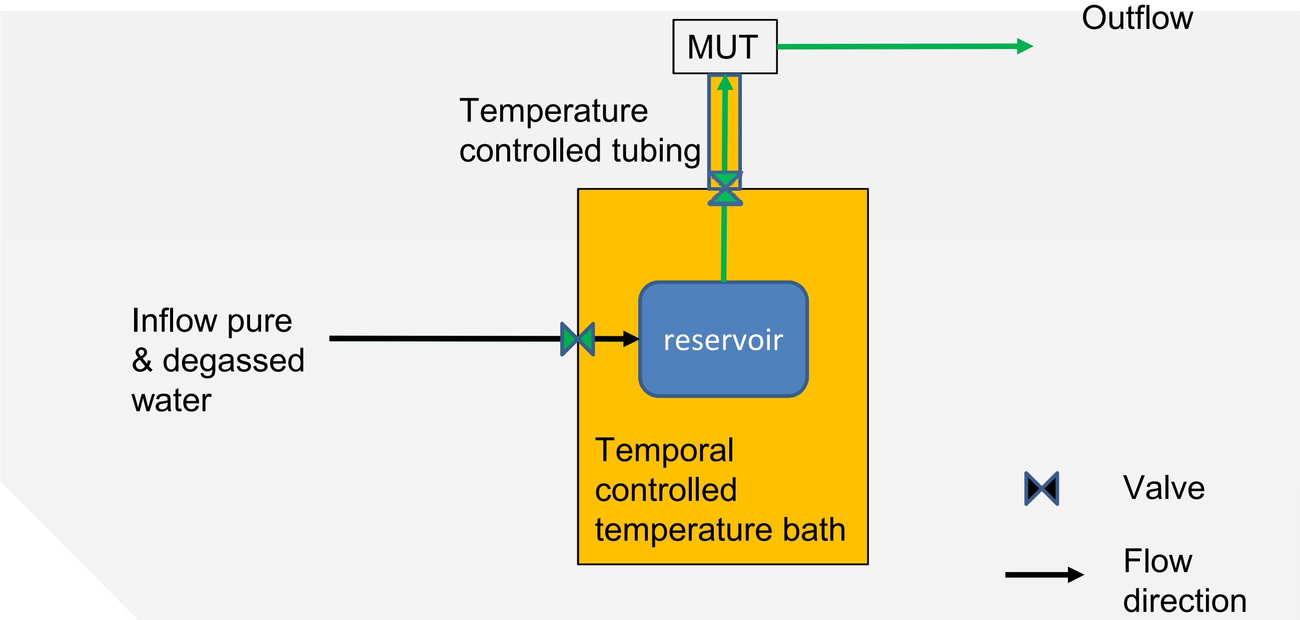
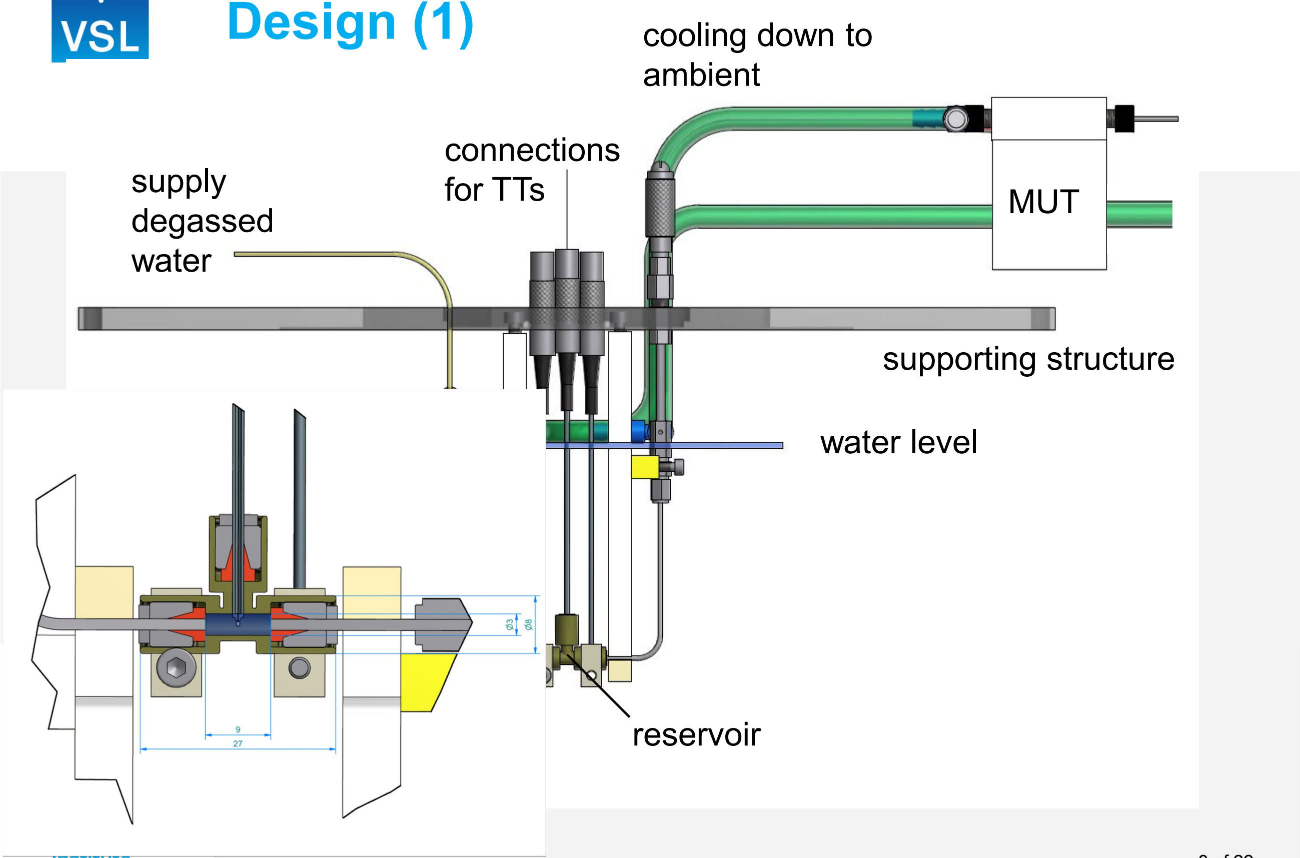
Working principle

Calibration



Design (1)



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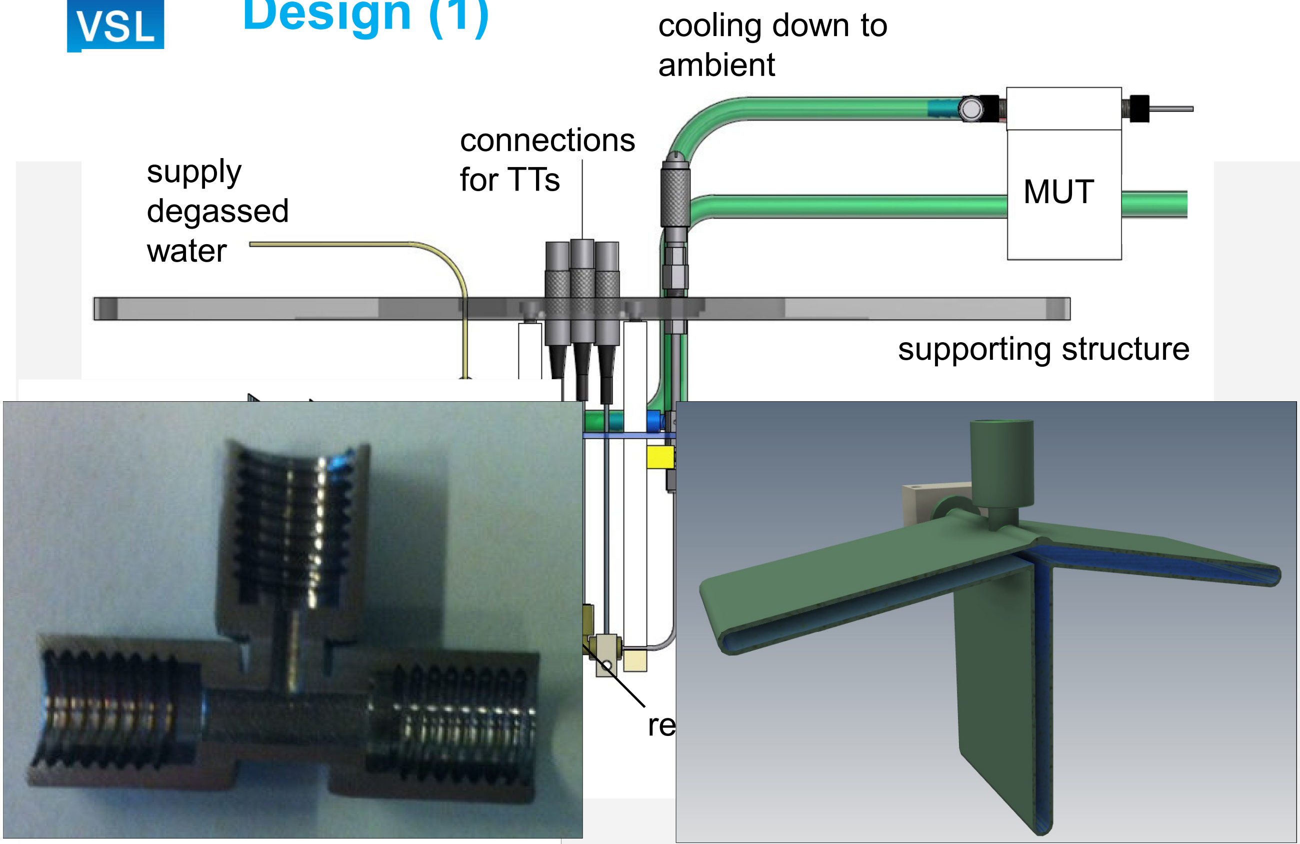
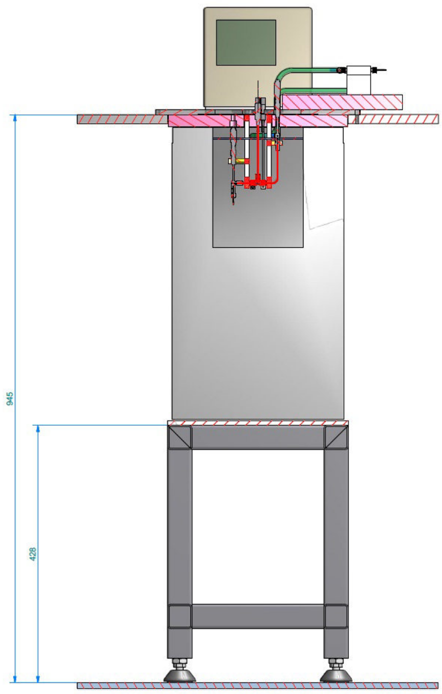


Design (2)



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Theoretical model

Basics

Volume flow due to volume expansion: $Q = -\frac{1}{\rho_{MUT}} \frac{\partial m}{\partial t}$

Working out the equations: $Q = -\frac{mk}{\rho^2} \left(\frac{\partial \rho}{\partial T} \right)_p$

Traceability through empty and full measurement

Traceability through temperature measurements

Traceability through the Tanaka equation for density (for pure water as function of temperature)

m mass, function of time

k temperature gradient (constant)

ρ density, function of temperature

$\left(\frac{\partial \rho}{\partial T} \right)_p$ partial derivative density w.r.t. temperature at constant pressure

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Theoretical model

Corrections

Flow rate at the **exit of the reservoir**: $Q = -\frac{mk}{\rho^2}\left(\frac{\partial \rho}{\partial T}\right)_p$

Required corrections:

- Cooling down fluid elements (<1.5%)
- Spatial variation in temperature (<1.5%)
- Spatial variation in temperature gradient (<1%, ↓0)
- Reservoir expansion (7 -13%, for T_{start} 40 – 20 °C)

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Theoretical model

Full model

Volume flow through MUT:

$$Q = -\frac{V_{H_0}}{\rho(T_{MUT})}\left[\left(1 + \beta\left(T_R(t) - T_0\right)\right)\left\{\frac{\partial \rho(T_M)}{\partial T}\left(\frac{dT_M}{dt} + \frac{dc(t)}{dt}\right) + \frac{\partial^2 \rho(T_M)}{\partial T^2}\frac{dT_M}{dt}c(t)\right\} + \rho(T_R)\,\beta\frac{dT_R}{dt}\right]$$

Main term: volume expansion due to temporal temperature gradients

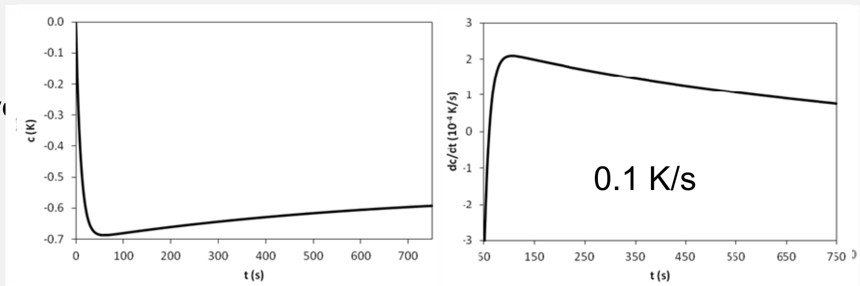
Correction for spatial temperature gradients

$$c(t) = T_A(t) - T_M(t)$$

A: average, M: measured (in reservoir)

Reference conditions

Correction for expansion reserv



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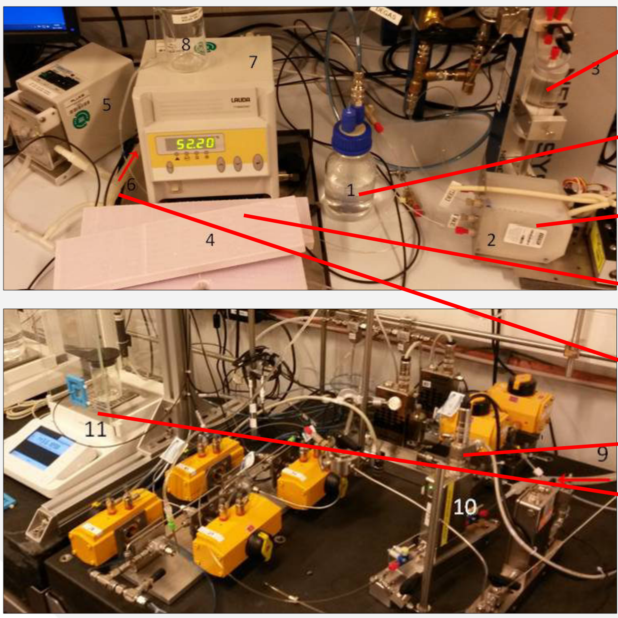
Intercomparison

nFlow – chip-based CMF – gravimetric standard



Syringe pump to purge system

Supply reservoir (double distilled water)

Inline degasser

Temperature controlled bath

Cooled fluid line to CMF

Chip-based CMF

Balance

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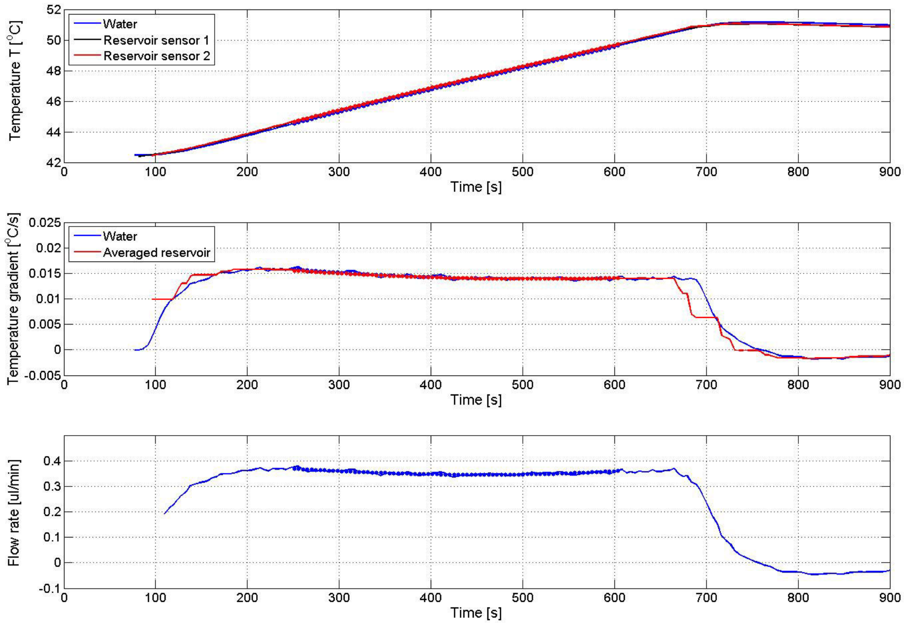
Results 333 nL/min

Temperature, - gradient, flow rate



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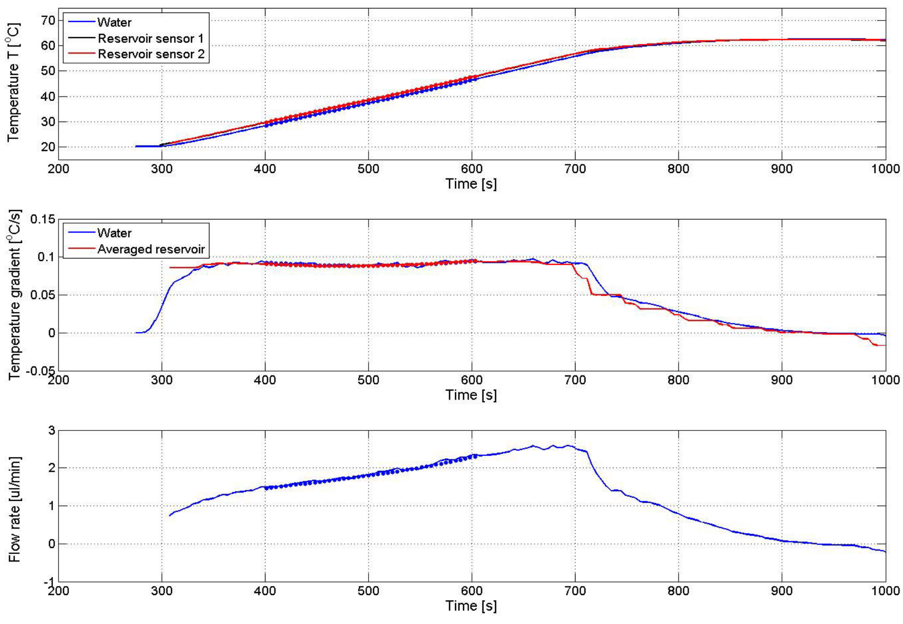
Results 2000 nL/min

Temperature, - gradient, flow rate



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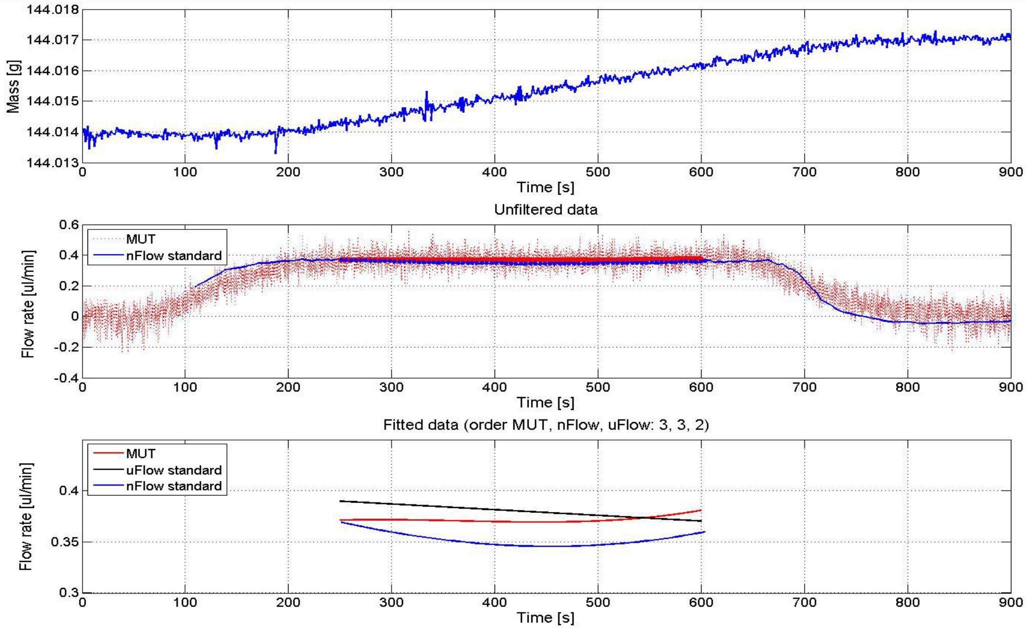
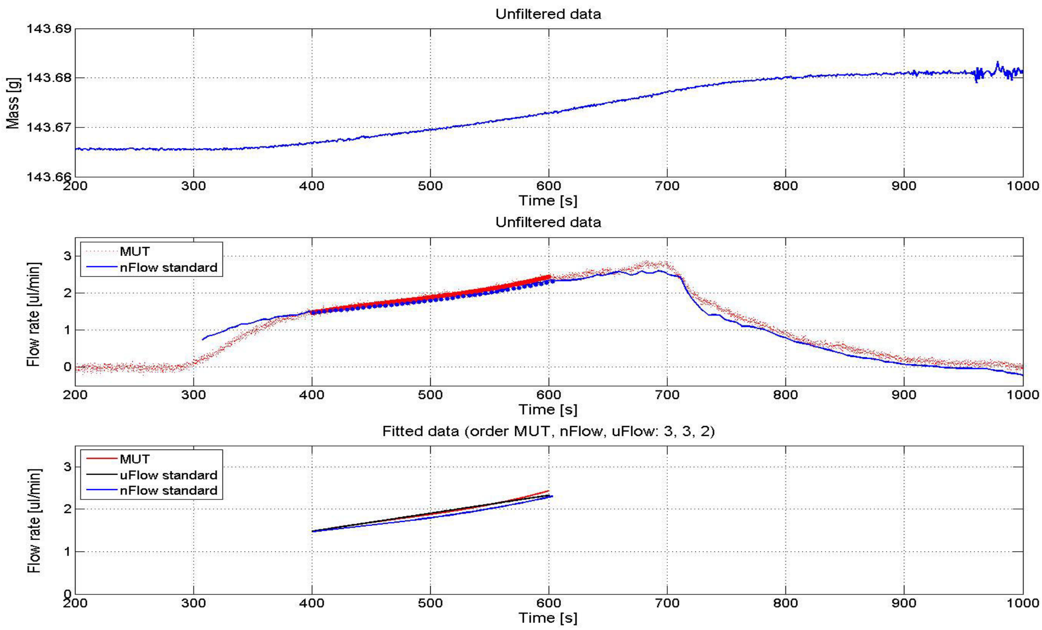
Results 333 nL/min

Balance, flow rates balance, CMF and nanoflow



Results 2000 nL/min

Balance, flow rates balance, CMF and nFlow



Results

Consistency balance, CMF and nanoflow standard

	Mean flow rate (nL/min)			Relative error (%)			Standard deviation error (%)		
Target [nL/min]	nFlow	grav. stand.	Coriolis	Coriolis/ grav. st.	Coriolis/ nFlow	grav. st. / nFlow	Coriolis/ grav. st.	Coriolis/ nFlow	grav. st. / nFlow
100	113	110	134	28	21	5.7	24	14	18
333	353	378	369	-2.3	4.5	-6.5	0.2	1.6	1.3
2000	1776	1816	1796	-1.1	1.2	-2.2	0.8	1.2	0.7

Target flow rate (nL/min)	Indicated flow rate nFlow (nL/min)	Indicated flow rate grav. std. (nL/min)	Zero stability CMF (%)	Calibration uncertainty nFlow standard (%)	Calibration uncertainty uFlow standard (%)	Deviation (%)	E_n (-)
100	113	110	33	21.3	> 100	5.7	< 1
333	353	378	10	6.3	> 100	-6.4	< 1
2000	1776	1816	2	3.1	11.2	-2.2	0.2

Conclusions and outlook

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Conclusions

- Primary standard for nanoflow rates based on volumetric expansion
- CFD to complete model and uncertainty budget
- Validated uncertainty budget
- Calibrate flow meters or facilitate cross checks

Outlook

- Simple coil rather than 3D printed reservoir

Thank you for your attention!

Questions or remarks?

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