Primary standard for nanoflow rates

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Overview of this presentation

- Motivation
- Design and working principles
- Traceability
- Results - intercomparison
- Conclusions and future work
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 assessment drug delivery devices (Elsa Batista - IPQ)
• Dosing errors in multi-infusion (Roland Snijder – UMC)
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

Primary standard nanoflow rates

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Working principle

Calibration

MUT

Outflow

Temperature controlled tubing

Inflow pure & degassed water

reservoir

Temporal controlled temperature bath

Valve

Flow direction

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Design (1)

cooling down to ambient

supply degassed water

connections for TTs

supporting structure

water level

reservoir

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Design (1)

- Supply degassed water
- Connections for TTs
- Cooling down to ambient
- Supporting structure

Design (2)
Primary standard nanoflow rates

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Theoretical model

Basics

Volume flow due to volume expansion:

\[ Q = -\frac{1}{\rho_{\text{RT}}} \frac{\partial m}{\partial t} \]

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)

\[ \rho, \frac{\partial \rho}{\partial T}_p \]

mass, function of time

temperature gradient (constant)
density, function of temperature

Partial derivative density w.r.t. temperature at constant pressure

Dutch Metrology Institute
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 \( T_{\text{start}} \) 40 – 20 °C)

Theoretical model

Full model

Volume flow through MUT:

\[ Q = \frac{V_{\text{in}}}{\rho(T_{\text{MUT}})} \left( 1 + \beta(T_R(t) - T_0) \right) \left( \frac{\partial \rho(T_M)}{\partial T} \frac{dT_M}{dt} + \frac{dc(t)}{dt} \right) + \frac{\partial^2 \rho(T_M)}{\partial T^2} \frac{dT_M}{dt} \frac{dc(t)}{dt} + \beta \rho(T_R) \frac{dx_s}{dt} \]

Main term: volume expansion due to temporal temperature gradients

Correction for spatial temperature gradients

\[ c(t) = T_A(t) - T_M(t) \]

Reference conditions

Correction for expansion reservoir

A: average, M: measured (in reservoir)

0.1 K/s
Primary standard nanoflow rates

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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
Results 333 nL/min

Temperature, gradient, flow rate

Results 2000 nL/min

Temperature, gradient, flow rate
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

<table>
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<th>Mean flow rate (nL/min)</th>
<th>Relative error (%)</th>
<th>Standard deviation error (%)</th>
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Conclusions and outlook

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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