METROLOGY for DRUG DELIVERY

MEDD II

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Gravimetric calibration method for microflow

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EMPIR

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Microflow sizes

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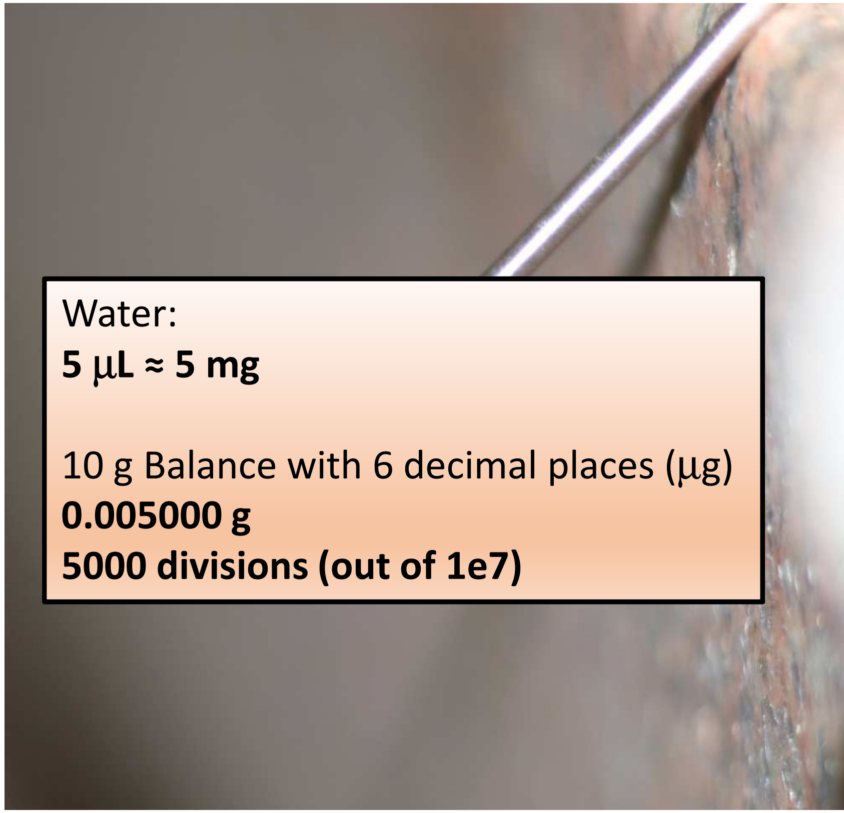
- **Flow rates from 100 nL/min and down to 15 nL/min => 6 mL/h to 0.9 µL/h**

Flow rate **100 nL/min**,
time to get the droplet: **50 min**

Flow rate **15 nL/min**,
time to get the droplet: **5.6 hours**



Gravimetric calibration method

Steady flow:

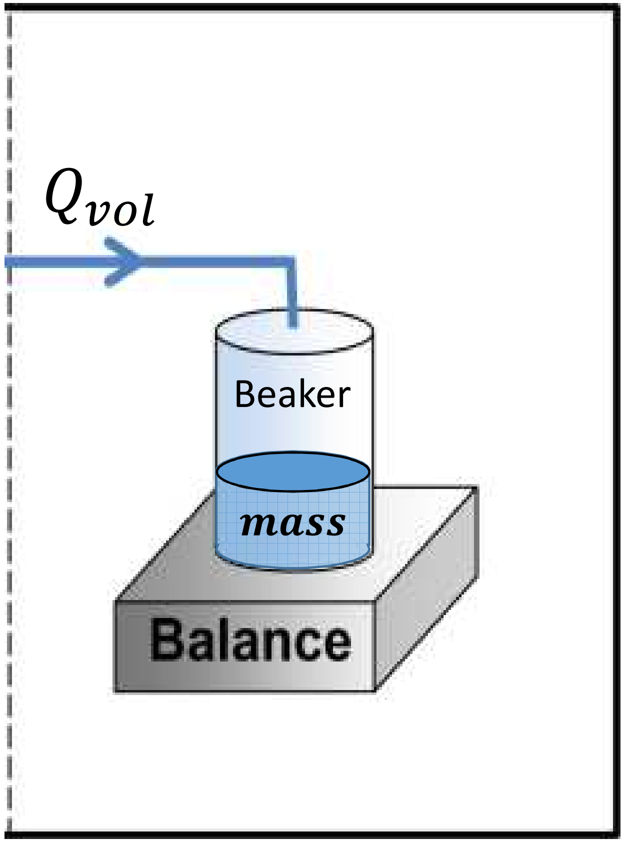
$$Q_{vol} = \frac{V_{delivered}}{\Delta time}$$

$$V_{delivered} = V_{finish} - V_{start}$$

$$\Delta time = t_{finish} - t_{start}$$

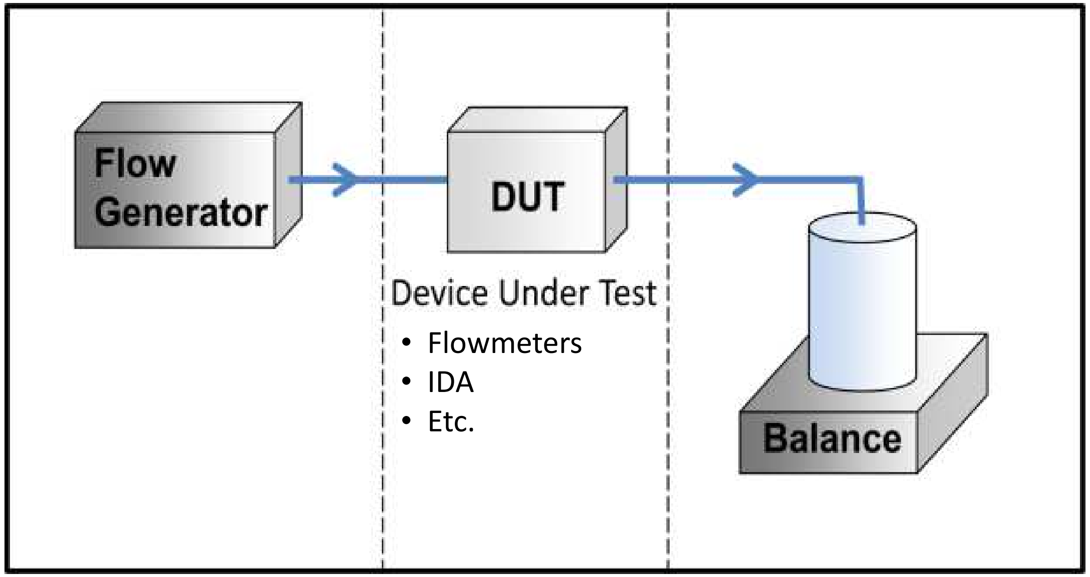
$$V = \frac{mass}{density}$$

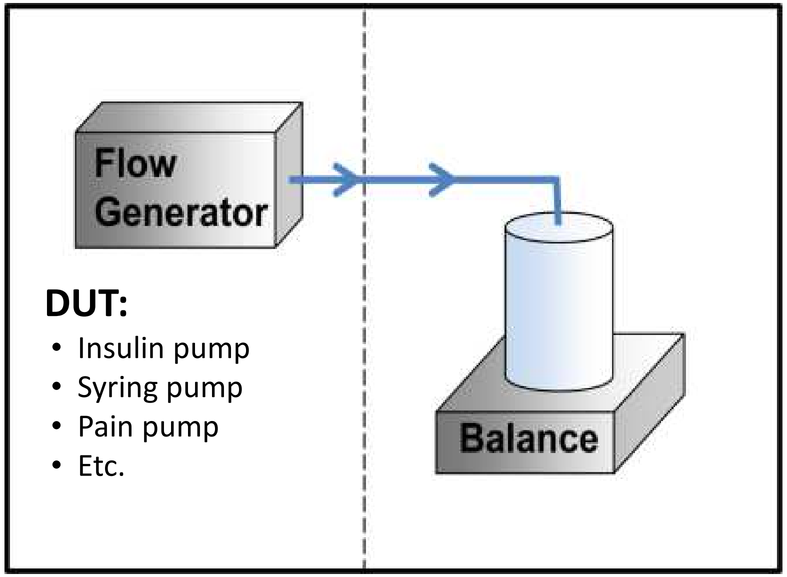
Density is a function of temperature and is different from fluid to fluid



Gravimetric method

- The gravimetric method relies on weighing the mass of the working fluid delivered by or flowed through the DUT (Device Under Test) for a set time.
  - Steady flow (down to ≈ 15 nL/min)
  - Dynamic flow (down to ≈ 83 nL/min)





Parameters influencing the measurements

- Evaporation
- Water degassing
- Priming the tubing and the flow meter under test
- Flow rate stability
- Timing/measurement of time
- Temperature stability
- Buoyancy correction of the delivered liquid
- Buoyancy correction due to the immersed tube into the liquid
- Jet force out of the immersion tube
- Stick/slip of needle and liquid
- Drift and Linearity of the balance

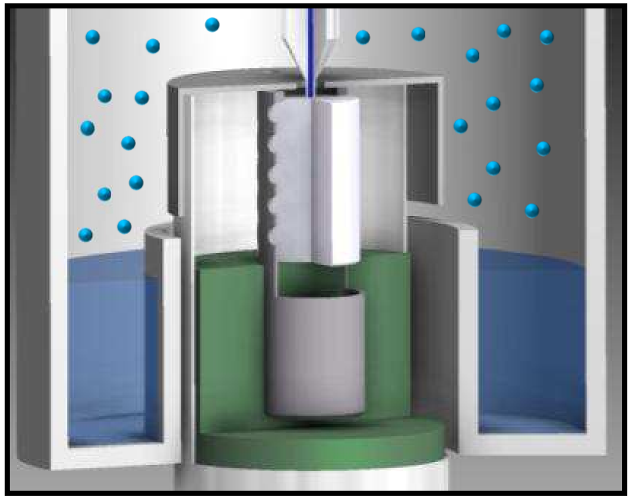
Evaporation traps

Evaporation rate from uncovered beaker is in the range of 40 nL/min which is more than the double of the lowest target flowrate of 15 nL/min.

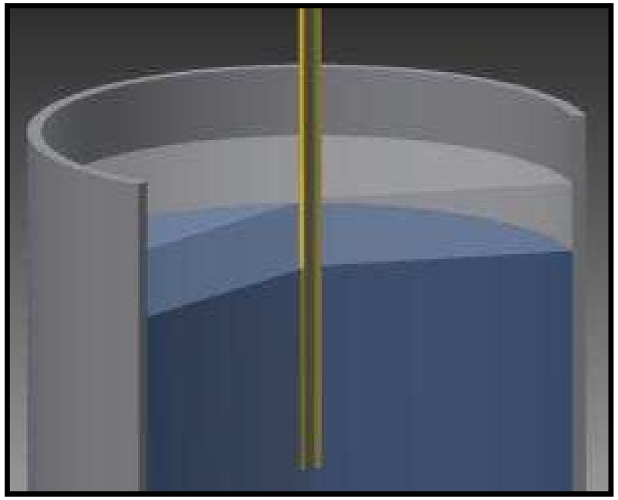
→ dependent on ambient condition as humidity, temperature etc.

→ With oil cover it can be lowered to 2-3 nL/min (must be adjusted for)

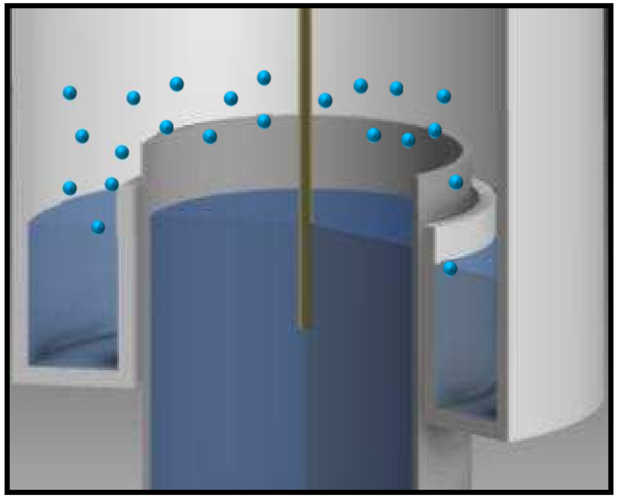
Water Bridge to water-absorbing materials in saturated air



Needle immersed into water with oil cover

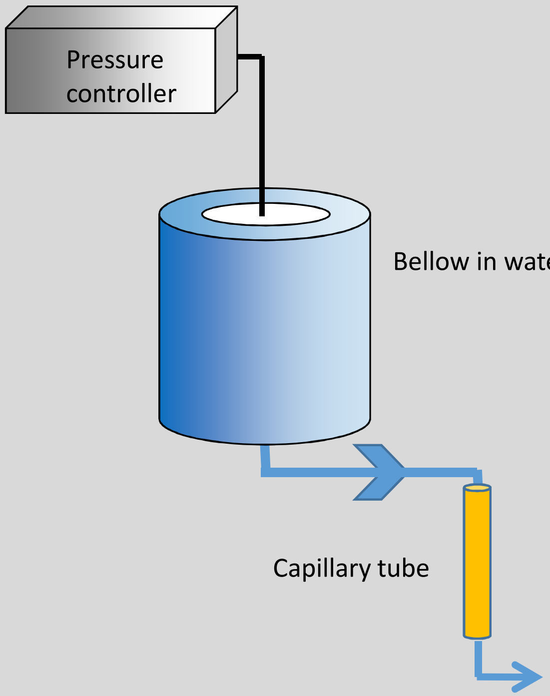


Needle immersed into water with saturated air around



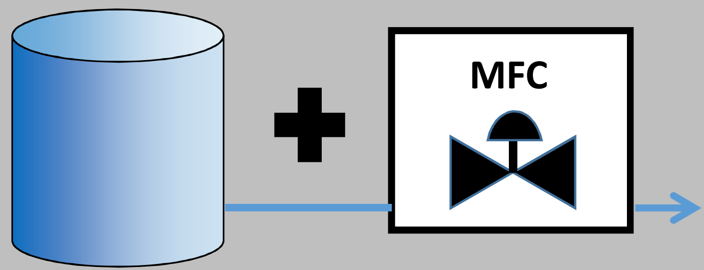
Flow stability
- Generating flow

Constant pressure drop over capillary tube setting the flow rate

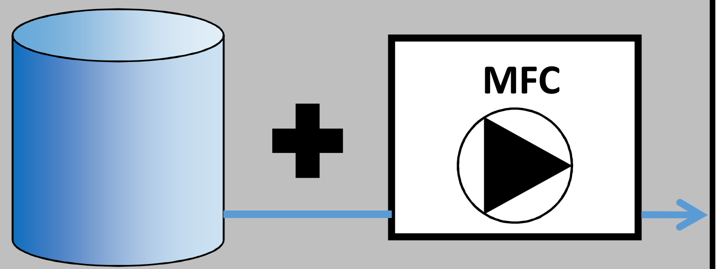


Syringe pump setting the flow rate

MFC setting the flow rate



MFC setting the flow rate

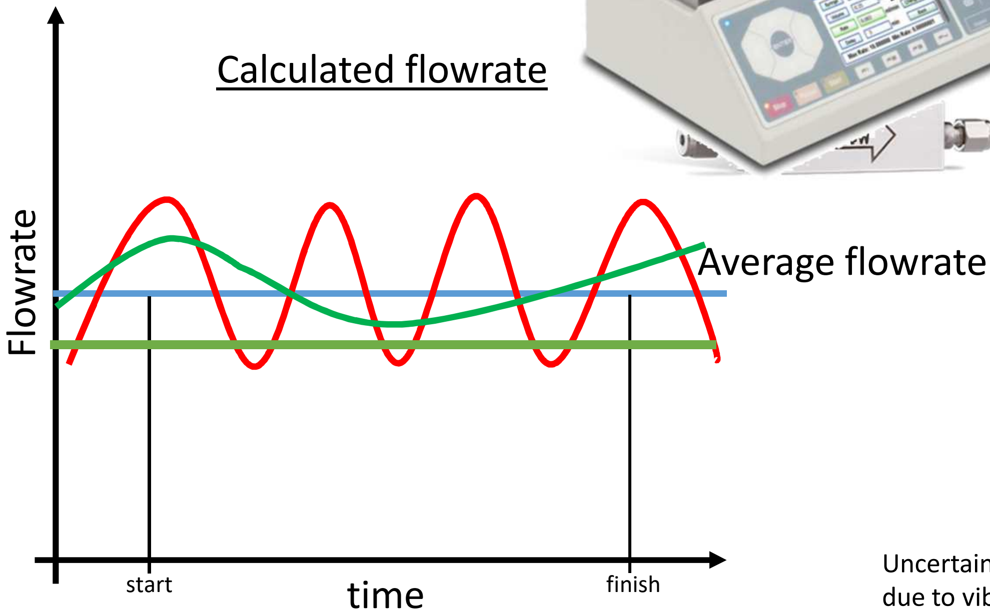


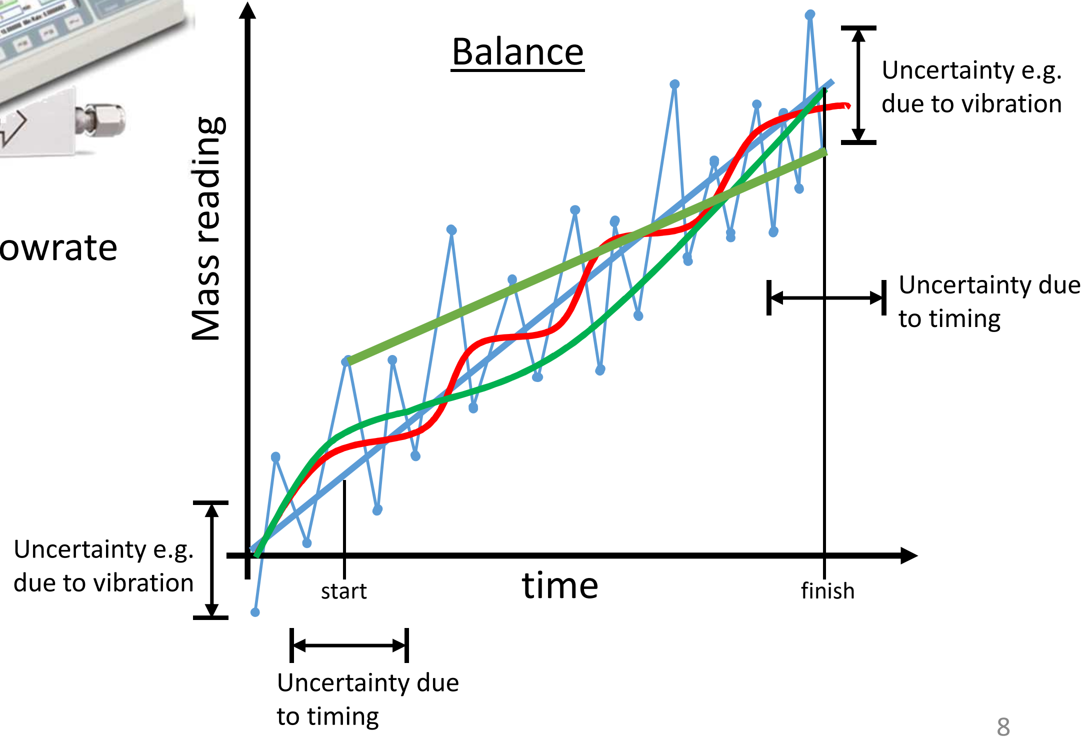
MFC = Mass Flow Controller

Flow and balance stability

$$\Delta mass = m_{finish} - m_{start}$$

$$Q_{average} = \frac{\Delta mass}{\Delta time}$$





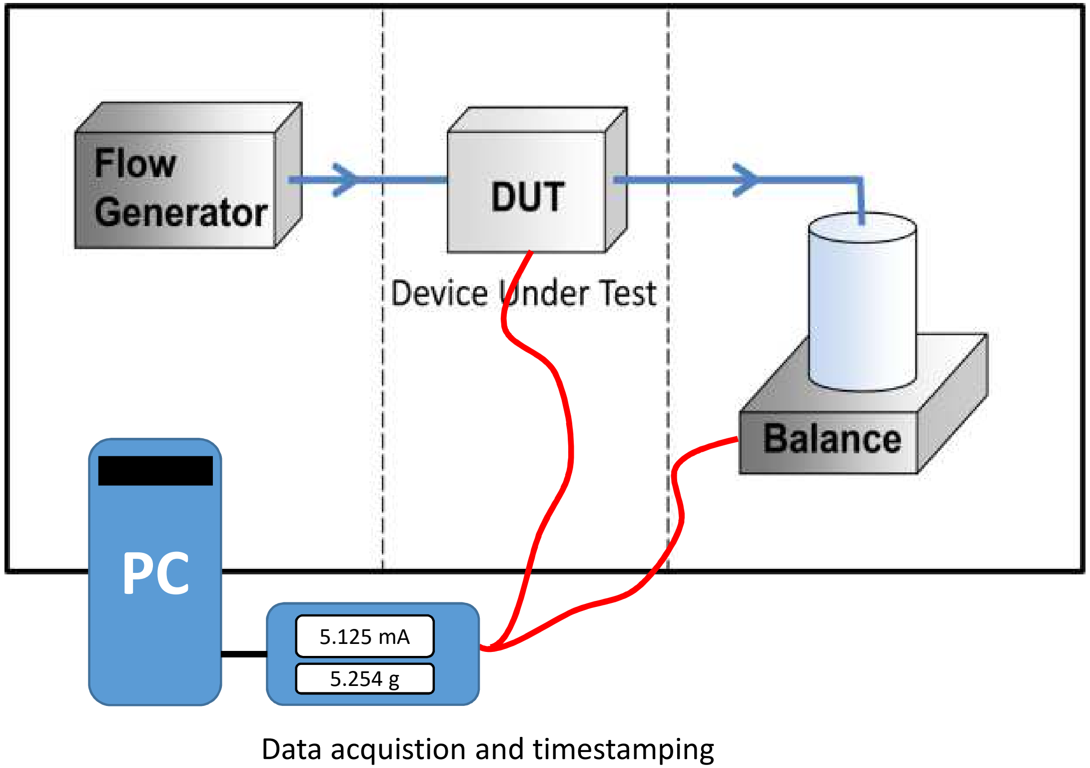
Weighing
- stability

- Stable support – minimize vibration
  - (Granite table on flex support –rubber feet)
- Temperature stability
- Shielding against convection
- Avoid static electricity

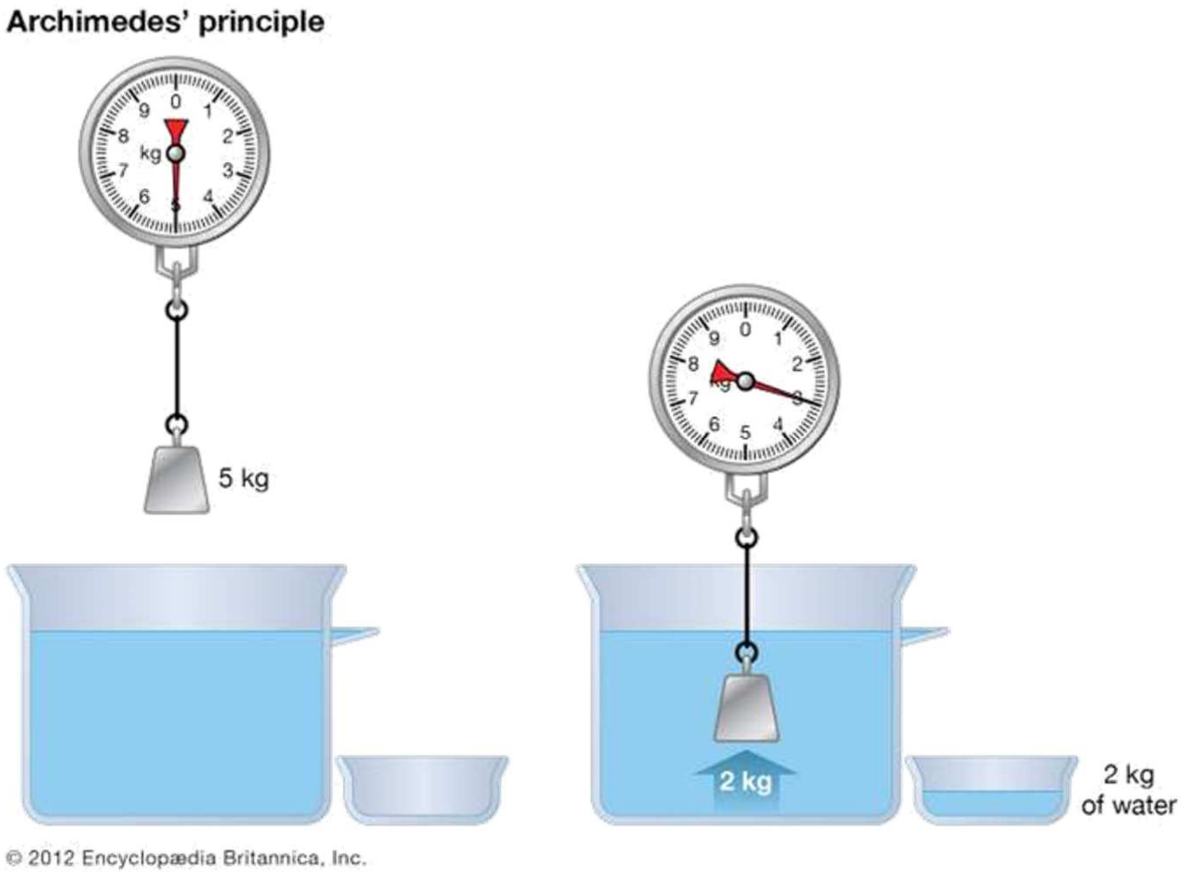
Timing

- ***Traceability***

- Steady flow
  - $Q_v = \frac{\Delta V}{\Delta t} = \frac{\Delta(m/\rho)}{\Delta t}$
- Example:
  - $\Delta t = 100\ \mathrm{s}$
  - $u_t = 0.1\ \mathrm{s}$
  - $\Rightarrow \frac{u_t}{\Delta t} = 0.1\ \%$
- Dynamic flow profile
  - $dQ_v = \frac{d(m/\rho)}{dt}$



Buoyancy correction

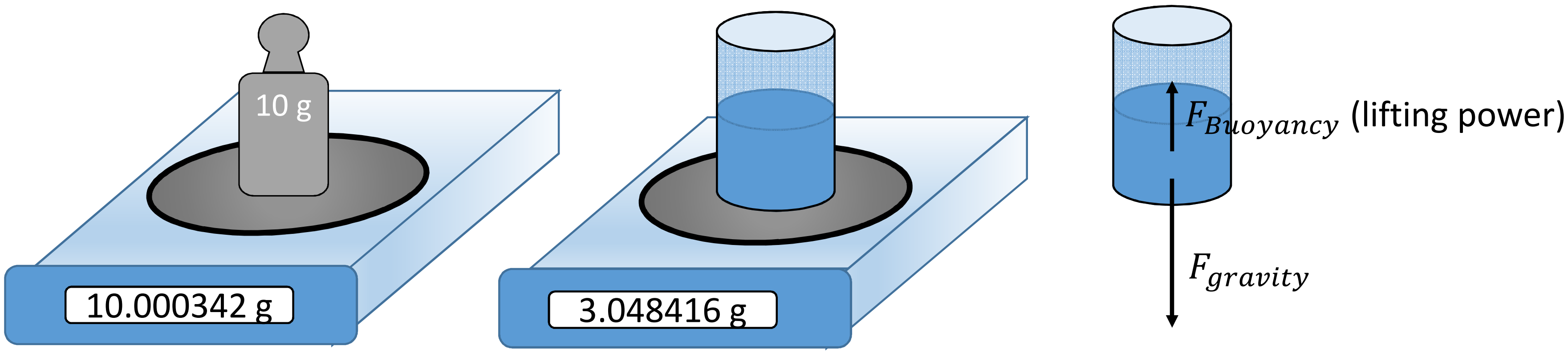


Buoyancy correction
- Buoyancy of the delivered liquid

$$m_{corr} = m_{uncorr} \cdot \frac{1 - \frac{\rho_{air}}{\rho_{weight}}}{1 - \frac{\rho_{air}}{\rho_{liquid}}}$$

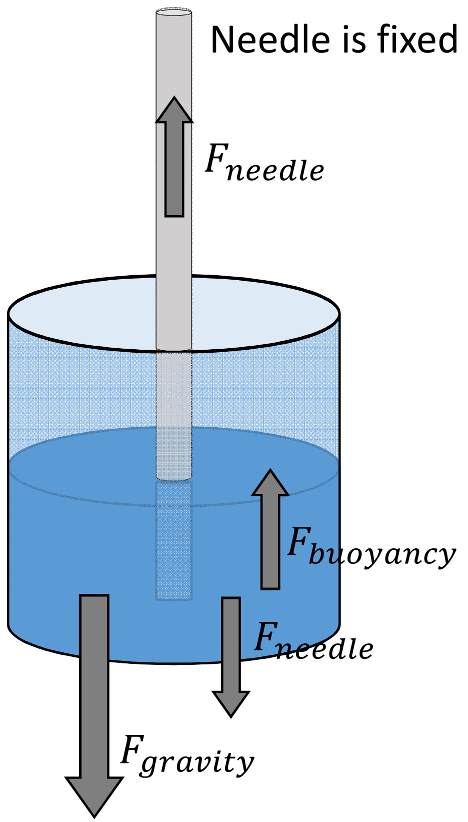
ρ_{air} is a function of air temperature, barometric pressure and humidity

ρ_{liquid} is a function of temperature



Buoyancy correction

- Immersion of tube into the liquid

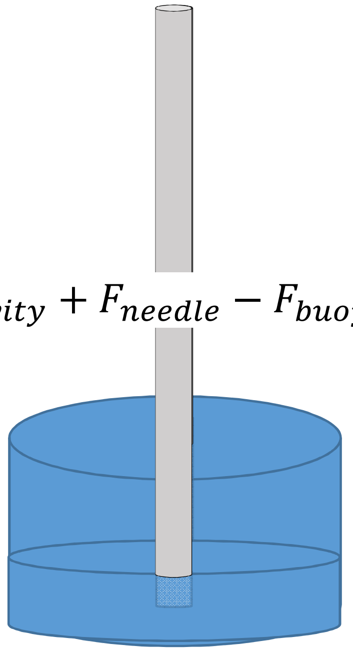


It's only necessary to calculate buoyancy corrections for Δmass

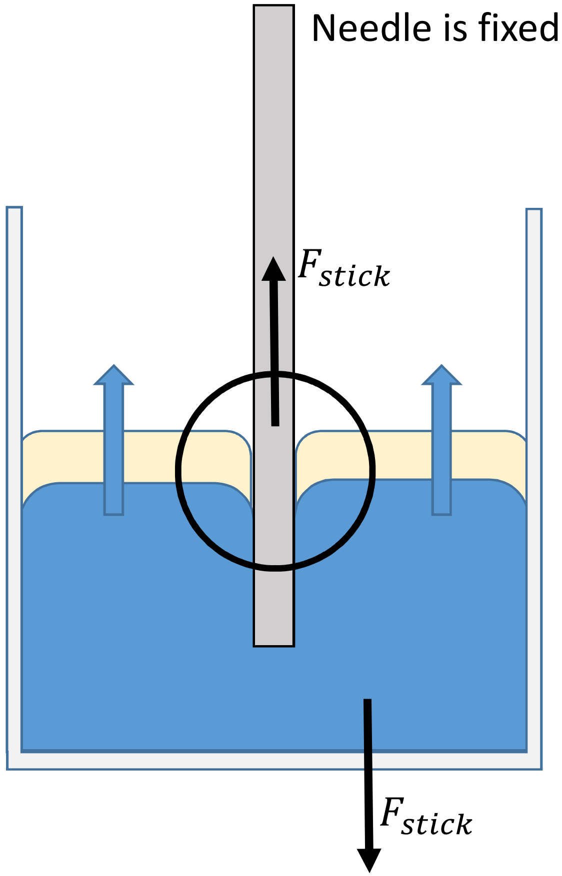
$$F_{total} = F_{gravity} + F_{needle} - F_{buoyancy}$$

Buoyancy correction

- Immersion of tube into the liquid



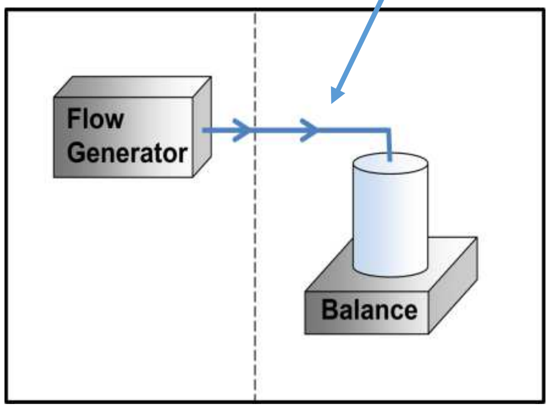
$$F_{total} = F_{gravity} + F_{needle} - F_{buoyancy} + F_{stick}$$



Temperature stability I

Effects of changing temperature:

- Weighing/balance
- Flow-meter reading
- Mass flow vs. Volume flow
- Flow generated by expansion

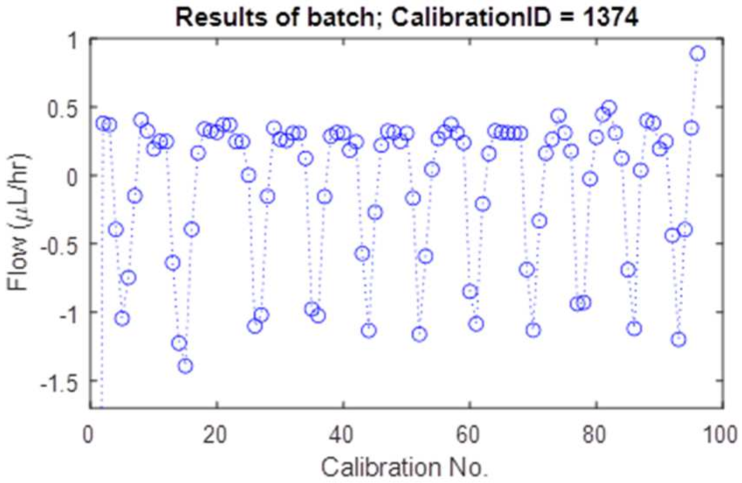


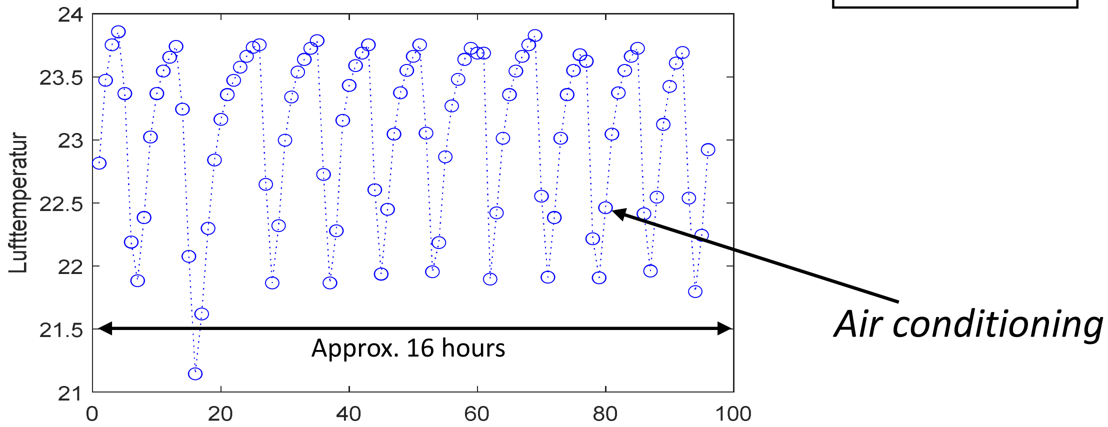
Flow generated by expansion

- Example: 1 m SS tube, ID = 1 mm
- Temperature: $23\ °\mathrm{C} \rightarrow 24\ °\mathrm{C}$
  - Water: $\Delta V = 121\ \mathrm{nl}$
  - Tube: $\Delta V = -12\ \mathrm{nl}$
  - Sum: $\Delta V = 109\ \mathrm{nl}$
  - If $\Delta t = 6\ \mathrm{min} \rightarrow \mathrm{flow} \approx 17\ \mathrm{nL/min}$

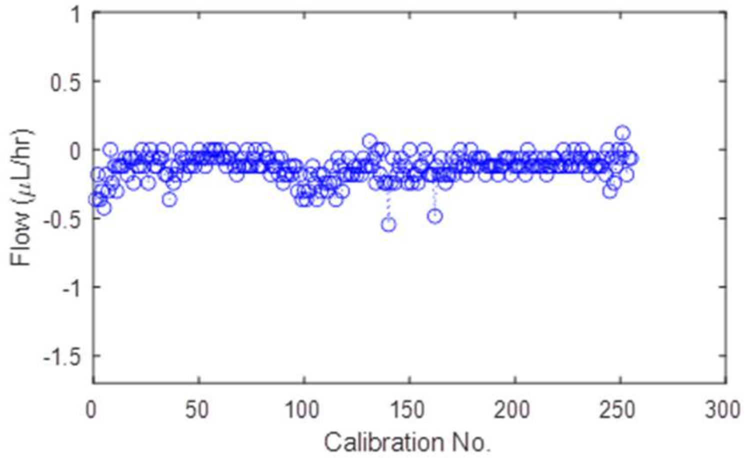
Temperature stability II

(before insulation) ← → ***(after insulation)***





Pump stopped!



Resolution (for 10 min measurement):

$$\frac{1\ \mu g}{10\ \text{min}} \sim 0.001\,\frac{3600}{600} = 0.06\ \mu\text{l/hr}$$

Temperature stability III

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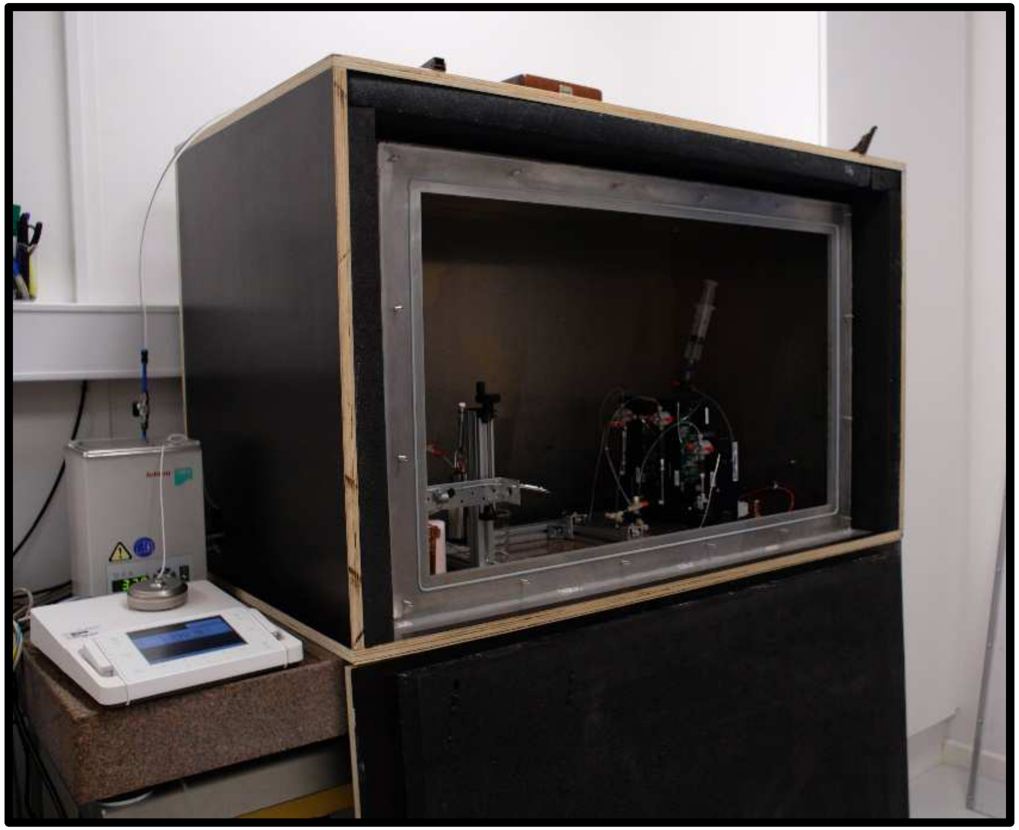


Temperature stability IV:
- What can we do?

✓Stabilize lab temperature

✓Large heat capacity

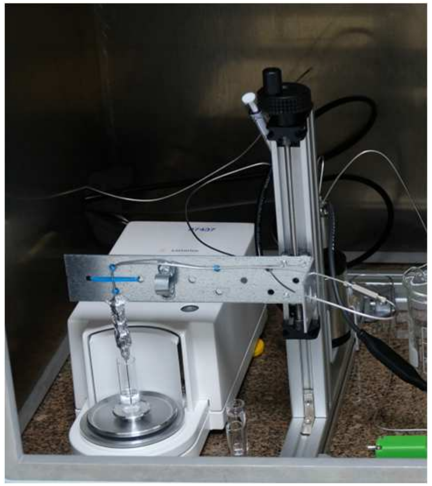
✓Heat conducting shield (→ isotherm)

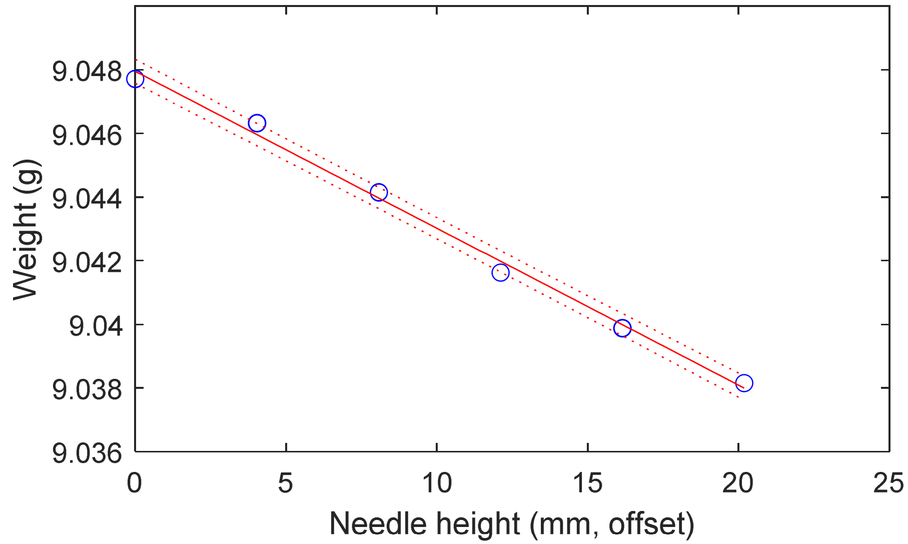
✓Isolating screen

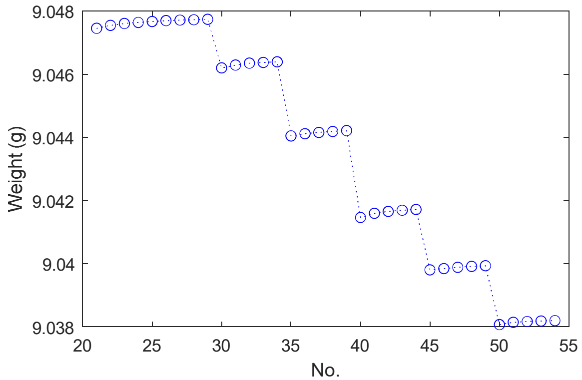
- Short tubes with small ID (Inner Diameter)
- Stabilization of setup by water cooling/heating

Displacement by needle

Check: Weight vs needle height





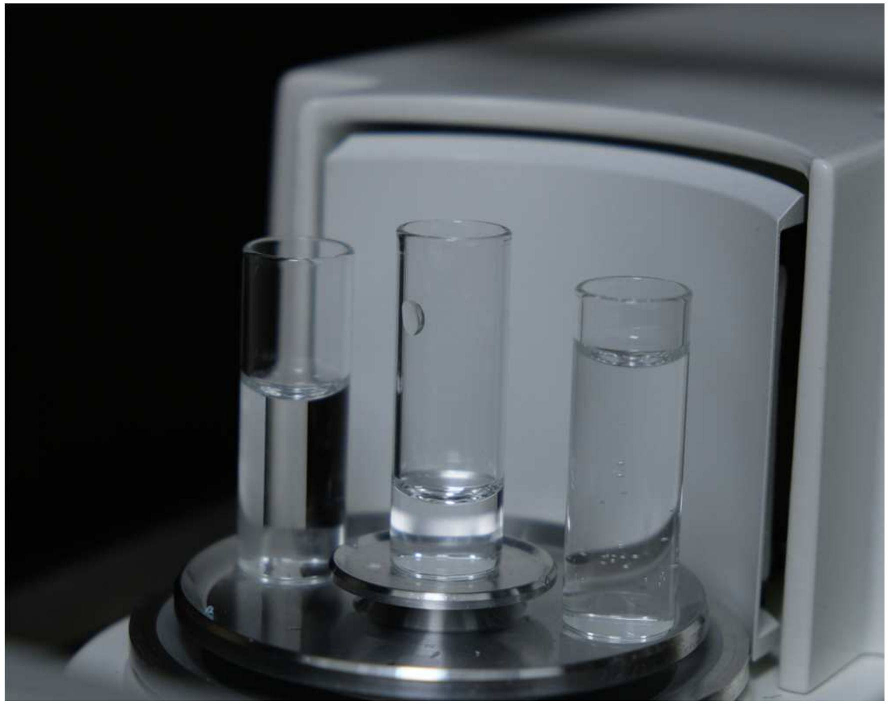


Emptying the beaker I:
- What do we do when the beaker is full?

- Option 1: Replace with a new
  - Manual process
  - Thermal pertubation
  - in practice: only small flows

- Option 2: Pump out
  - Automatic process
  - Thermal steady state
  - Increased flow rate

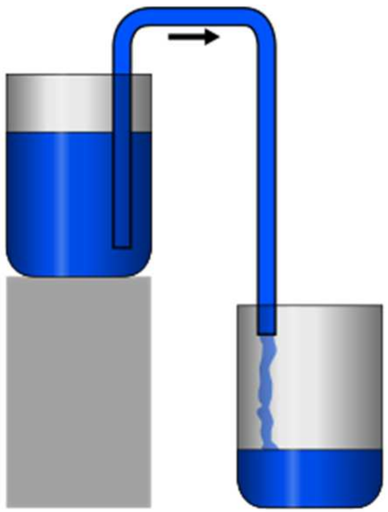
DTI → $\Delta m \approx 4\ g \Rightarrow Flow_{max} \approx 1\ \mathrm{ml/min}$

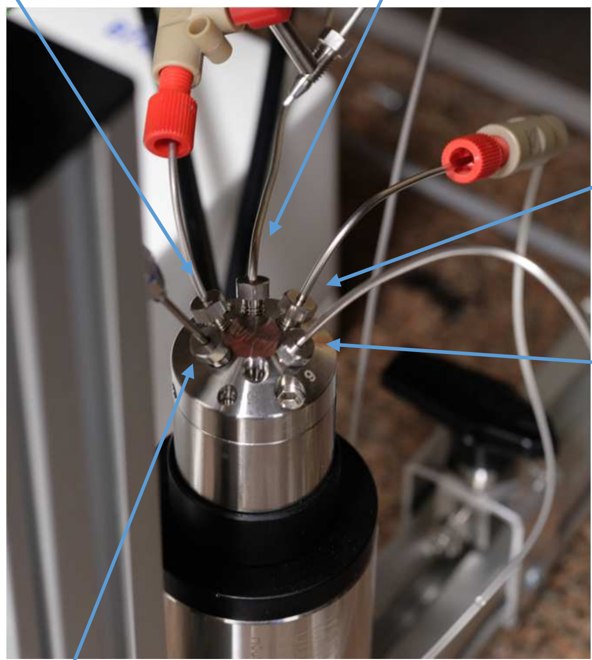


Emptying the beaker II:
- Example of beaker pumping system

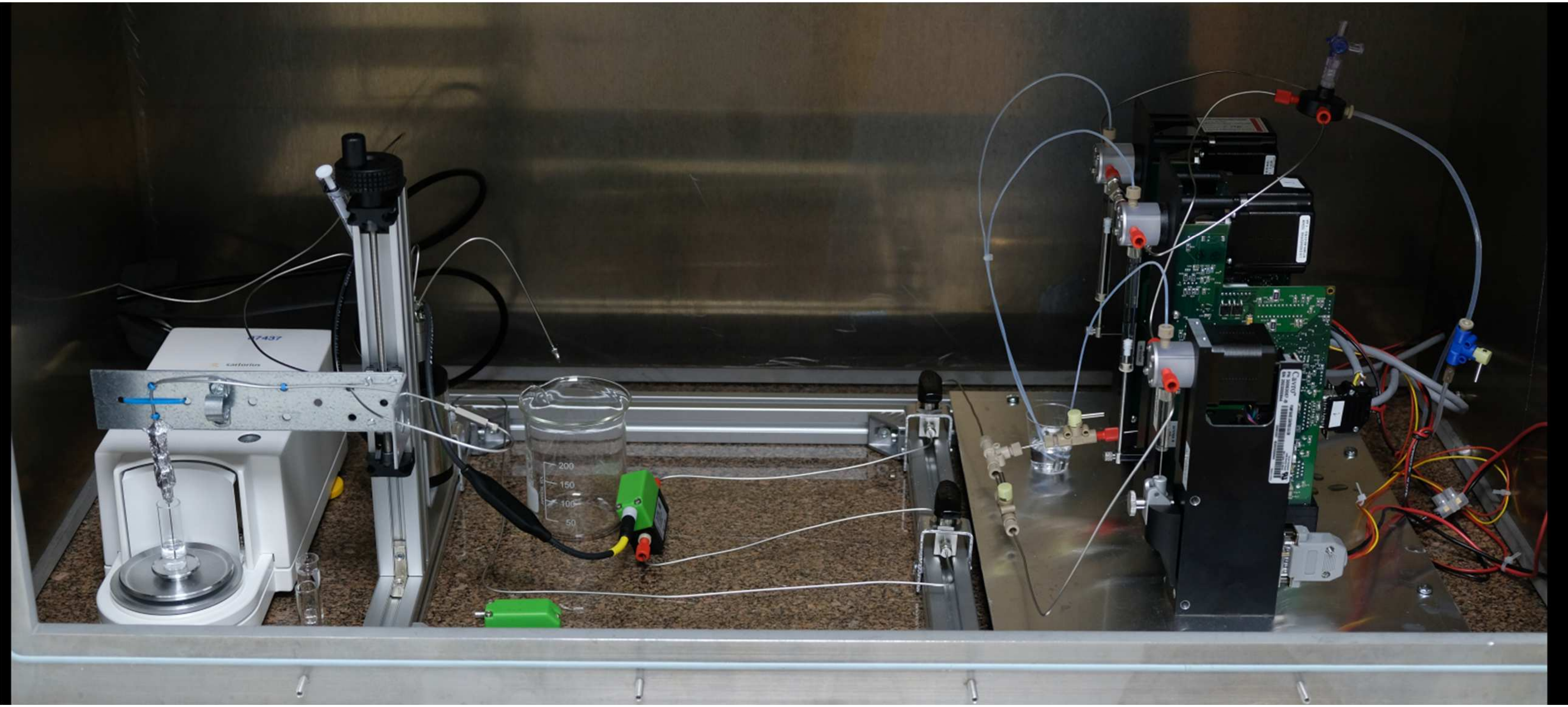
- Siphon
- Control: 6-port valve
- Control signal: Weight
  - 9.5 g → Empty
  - 5.5 g → Fill

Alternative: Insert separate needle / syringe (-pump)





Example of setup (DTI)



Project Team

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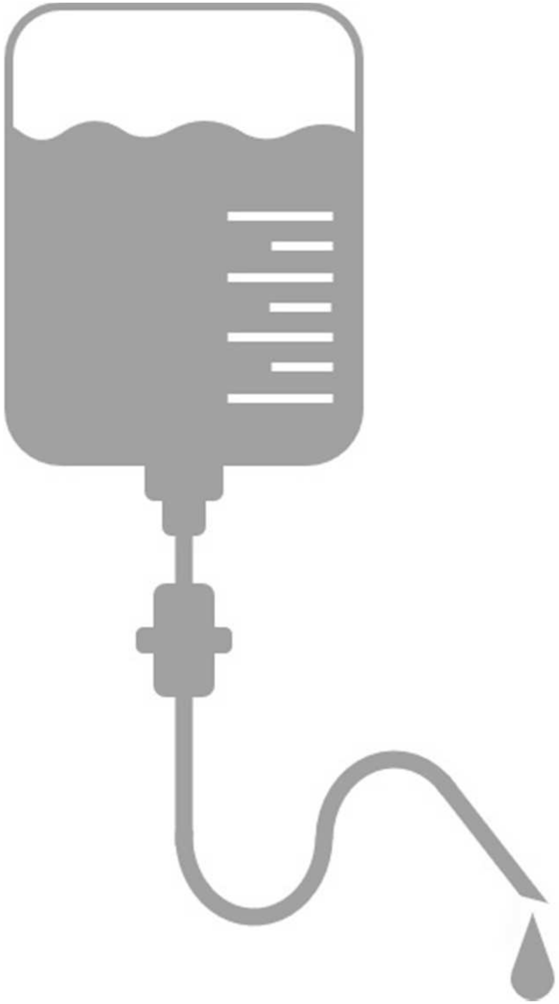

THANK YOU