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Characterisation of medical microfluidic systems regarding fast changing flow rates using optical front tracking methods

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ABSTRACT

The presented optical flow metering methods are appropriate to characterise the dynamic properties of microfluidic systems. The dynamic behaviour of clinical or medical devices, micro pumps and flow sensors based on thermal methods were investigated. The Camera-System covers a flow range from 50 nl/min to 500 µl/min. The uncertainty is less than 4%, sample rates up to 5 kS/s. The Displacement-Sensor-System covers a flow range between 100 µl/min and 50 ml/min. The uncertainty is less than 3% at sample rates up to 49 kS/s. It was shown that measuring pulsating flow rates with thermal flow sensors is possible, but the signal is low pass filtered. The low pass behaviour is determined by the thermal properties, thermal resistance and heat capacity, of the flow channel. But the mean flow rate was always measured properly. The fluidic properties of two different types of micro pumps were examined and characterised exemplary.

1. Introduction

In medical applications of liquid flows, fast changing flow rates are common. Flow adjustments during infusion therapy lead to significant flow deviations. In complex flow systems, flow rates and concentrations of drugs are often different from expected values [1–4]. To control microfluidic devices or intelligent systems, suitable actuators [5] and corresponding sensors are required. To investigate and furthermore control complex flow systems, a measuring technique to characterise the dynamic limitations of conventional flow meters is required. Thermal flow meters were delivered with high sample rates of about 1 kS/s [6]. But the thermal transfer properties and the inertia of the sensor channel influence the dynamic response to a flow change. In addition, the fluidic resistance of the flow sensors often dominates a micro fluidic system. Further challenges are measurements of high dynamic flow changes with accurately defined volumes. These are generated e.g. by valves or the pulsatile portion of micro pumps. For this purpose sensors with sample rates in the range of milliseconds are needed to measure the required volumes. Common applied gravimetric methods using high precision balances [7] are not suitable for such high sample rates.

For manufacturers of micro flow sensors and systems such as micro dosing units, analysis units (e.g. lab on chip systems) and infusion devices (drug delivery) a measurement technique will be provided, to qualify these products. The optical method should cover a wide range of clinical relevant flow rates (50 nl/min to 2 ml/min) and change rates up to 15 ml/s^2.

2. Methods

Thermal flow measuring methods have to be calibrated for every measured liquid and its properties specifically (i.e. heat conductivity, heat capacity, viscosity etc.). Differential pressure sensors are inappropriate for flow measurements of liquids with different viscosities. On the other hand, optical methods are independent of physical properties of the liquid. Front-tracking is a method developed to measure very low flow rates down to 5 nl/min [8]. The volumetric change inside a cylindrical geometry is measured with high precision by monitoring the displacement of the liquid front and the related time. The volumetric flow rate Q is determined by the displacement Δx of the liquid front during a time interval Δt and the radius R of the capillary or of the syringe.

$$Q = (\Delta x/\Delta t)\pi R^2 \tag{1}$$

This method was developed being part of the *Metrology for Drug Delivery* project, funded by the EMRP (European Metrology Research Programme), 2012–2015 [9–10]. In this work two optical front tracking methods have been applied:

(1) *Camera-System (CS)*: A high speed camera (SpeedCam MiniVis, Weinberger, Germany) combined with a magnifying telecentric lens (Vision & Control, Germany) was used to examine low flow rates between 50 nl/min and 500 µl/min at sampling rates up

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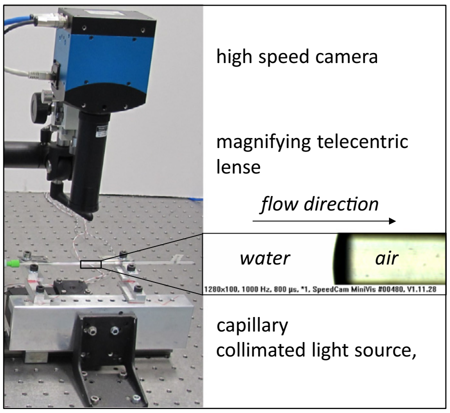

Fig. 1. *Camera-Front-Tracking-System*. High precision capillary in combination with telecentric lenses, a collimated LED light source and a high speed camera.

to 5 kS/s (5000 fps) (Fig. 1). The high speed camera was placed vertically above the horizontally mounted glass capillary (Hilgenfeld GmbH, Germany). To fix the camera and for fine adjustments, a microscope x–y–z stage was used. A ball bearing boom stand in line to the capillary was used to follow the region of interest (ROI). Below the capillary a white light emitting device (LED) and a collimating lens was installed on a linear stage in line with the capillary. Because of the capillaryś cylindrical geometry, an optical arrangement, in which the capillary was located between the light source and the telecentric lens was selected, to allow transmitted light measurement. The nearly parallel light bundle exceeds the limiting angle for total reflection at the boundary layer between air and water. This boundary layer was detected by image processing software. The light entering the water through the glass wall of the capillary was therefore totally reflected at the boundary layer (water/air). However, the light entering the air was refracted into the water at the boundary layer (air / water). Therefore, the phase boundary, the so-called front, could be clearly noticed as a transition from light (water) to dark (air) (Fig. 1). Since between 100 and 5000 frames per second are recorded, the pictures can no longer be transmitted and analysed in real-time. The images must be stored in the camera memory and have to be transferred to the PC after the measurement for analysis. The software package “Vision” (National Instruments) suits very well for this task. A program module called Virtual Instrument (VI) has been created in LabView for evaluating the camera pictures. Only one single image from the hard drive is uploaded into the memory, evaluated, and then removed again from the memory. As a consequence, the software was remarkably fast and stable. To detect the boundary between water and air, the *edge detection* function was used. After starting the measurement, the displacement of the front is determined image by image and the volume change is calculated thereof. To calculate the dosed volume, the capillary diameter must be known precisely. The manufacturer Hilgenberg GmbH produce capillaries with constant inner diameter. They specify the variability of the inner diameter with +/− 2 µm relatively in terms of the length of the capillary. The absolute value of the internal diameters of the cylindrical precision capillaries no. 1 (1000 μm +/− 30 μm), no. 6 (600 μm +/− 20 μm), no. 18 (300 μm +/− 10 μm) and no. 2 (150 µm +/− 4 µm) were measured with a digital microscope (Keyence VHX 600) at both ends to decrease the uncertainty. The microscope was calibrated especially for this measurement with a magnifying glass measure (Leica no.: 1031 0345) for the respective magnification. The imaging scale of the SpeedCam MiniVis with the corresponding telecentric lenses (T45/2.0L, 4.0L and 5.0L) on the CCD were also determined with the mentioned glass measure. The last parameter, the sample rate in frames per second, was set before the recording during the parameterization of the camera and stored with the images. The highest resolution was achieved using a 150 µm capillary in combination with T45/5.0L - lenses. The field of view, 3 mm x 3 mm, imaged to the CCD (charge coupled device) of 1280 pixels (px) resulted in a maximum resolution of 0.04 nl/px (Table 1).

Table 1
Resolutions of the individual combinations of the different capillaries and telecentric lenses.

Capillary ID in µm	T45/5.0L resolution in nl/px	T45/4.0L resolution in nl/px	T45/2.0L resolution in nl/px
150	0.04	0.05	0.10
300	0.17	0.21	0.42
600	0.66	0.84	1.68
1000	1.84	2.33	4.66

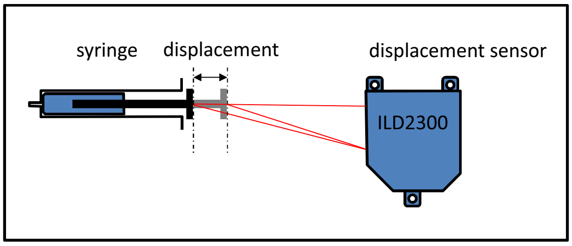

Fig. 2. *Displacement-Sensor-System*. The setup for larger flows consisted of a glass syringe and a laser displacement sensor.

Acquisition times between 2 and 60 s were possible. Uncertainty calculations and traceable calibrations of the key components are described elsewhere [8,11]. Evaporation can be neglected considering short acquisition times. To reduce stick slip effect and meniscus deviation the capillaries were carefully cleaned and then tempered for one hour at 500 °C. All measurements were performed with distilled and degassed water. Measurements presented in this paper were done with 1000 µm capillary and telecentric lens T45/4.0L. The uncertainty of this combination is < 4%.

(2) *Displacement-Sensor-System (DSS)*: The setup for larger flow rates consisted of a glass syringe (Fortuna Optima, 1 ml) and a laser displacement sensor (Micro Epsilon, OptoNCDT ILD2300) (Fig. 2). The flow into the syringe is pushing the plunger out of the syringe body. This setup allowed measuring the displacement of the liquid front (plunger) directly. The glass plunger and syringe body were paired exactly. The required force to move the plunger is extremely low. Therefore the surface tension is enough to prevent leakage. To reduce stick slip effect the part of the plunger outside the syringe body was cut and replaced by a less heavy plastic stick. Regarding the low signal to noise ratio (SNR), which was magnified by differentiation of the volume to calculate the flow rate Q of Eq. (1), Diadem (National Instruments) was used to filter the signal. An example in Fig. 3 demonstrates a raw signal (grey curve, 10 kS/s) versus a filtered signal (red curve, smoothed +/− 25 pts). The event started without flow. After one second the valve opened for nearly nine seconds and closed again. It is significant that the amplitude of the noise is decreasing with reducing the distance of the plunger to the displacement sensor. If the plunger is moving or not seemed to have no influence to the amplitude of noise. Therefore the sensor signal itself was examined using fixed steel blocks relatively to the displacement sensor. The optical properties of the surface were modified from dull to glossy and different colours but signal to noise ratio could not be improved significantly. The DSS was used to examine flow rates between 100 µl/min and 50 ml/min at sampling rates up to 49.02 kS/s. The uncertainty of DSS <3%.