How to Optimise Process Quality of Liquid Tube Systems

Optimisation of liquid tube systems can be achieved in single-use bioprocessing applications by means of ultrasonic technologies

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Process monitoring is the systematic recording or measurement of an operation or process by means of technical aids (1). The repeated, regular execution of this process is a central element of its definition. Statistical process control and management enables processes to be optimised and stabilised, and guarantees threshold values to be monitored (2-3).

Ultrasound-based technologies provide ideal measuring methods for this purpose. In particular, the non-invasive character of the measurement, and thus the option of gathering data without having to intervene in the actual process, makes contactless flow meters ideally suited for both permanent and occasional measurements. Additionally, non-contact flow sensors excel in high precision and ease of use. Modern ultrasonic flow sensors enable the non-contact flow measurement of a wide variety of liquids in flexible tubes with an accuracy of up to ± 2% of the measured value over a wide flow range. Even under varying media properties and over a wide temperature range, an accuracy of ± 5% of the measured value can be accomplished. With the help of inline flow meters, absolute accuracies in a single-digit µl/s range can be easily achieved – even at very low flow rates.

Moreover, the continuous flow monitoring on critical points in up and downstream bioprocesses is an essential element to fulfilling regulatory goals of the Process Analytical Technology (PAT) framework. PAT has been defined as a mechanism to design, analyse, and control biotechnical and pharmaceutical manufacturing processes through the measurement of critical process parameters. Constant flow monitoring can fundamentally support its overall targets to:

- Reduce production cycling time
- Prevent rejection of batches
- Enable real time release
- Increase automation and control
- Improve energy and material use
- Facilitate continuous processing (4)

Clamp-On Ultrasonic Flow Meter – An Essential Tool to Measure Flow Rates Accurately Without Any Liquid Contact

One of the main advantages in applying ultrasonic technology for flow measurement is the fact that constant liquid flows can be measured independently of their charge, density, or viscosity (5). A specific method of utilising ultrasonic liquid flow measurement is its non-invasive application. Non-contact flow meters are able to directly measure through the walls of flexible, but also rigid, plastic tubes or pipes without interfering with the circuit or coming into contact with the flowing medium. As long as the liquids are acoustically transparent, the ultrasonic wave propagates. Sound waves react sensitively to changes or certain properties of the matter permeated by the beam. This effect is exploited in the transit time difference method (6-8). The ultrasonic wave can be carried along or slowed down by the flowing medium. This so-called entrainment effect ensures that the flow velocity of the medium – and indirectly the volume flow – can be measured.

According to equation 2 from **Figure 1a, Figure 2** shows the transit time difference as a function of the flow velocity in the case of water at a medium temperature of T = 23˚C for an ultrasonic clamp-on flow sensor (red line), applying an ideally circular tube with an inner diameter (ID) of 4.0mm. In comparison, the blue line represents an inline flow sensor with an equally circular channel and an ID of 4.0mm. Absolute time differences – especially when applying non-contact clamp-on flow meters – can be in the range of a few picoseconds. Inline flow sensors, in turn, can process

(1) $\Delta t = t_{AB} - t_{BA}$ with $\Delta t = \frac{2 \cdot L \cdot \cos(\beta)}{c^2}$ [AB=BA=L]

(2) $v = \frac{c^2 \cdot \Delta t}{2 \cdot L \cdot \cos(\beta)}$

(3) $Q = A * v$

Transit time difference of the ultrasound signal with the flow (t_{AB}) and against (t_{BA}) flow direction as a measure for the flow velocity

c: speed of sound in the medium
v: flow velocity
A: cross-sectional area of the tube
Q: volume flow

Figure 1a: Mathematical-physical derivation of the transit time calculation

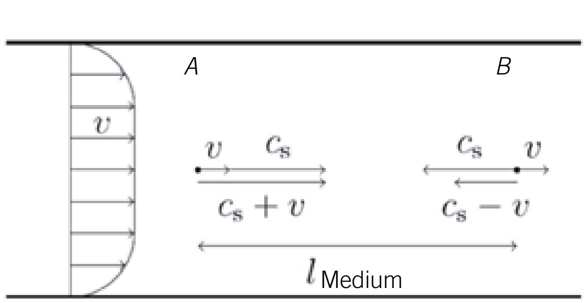

Figure 1b: Schematic representation of the transit time principle used for invasive flow measurement along the flow direction (inline flow sensor)

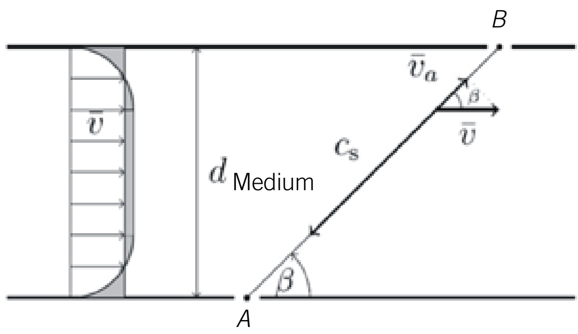

Figure 1c: Schematic representation of the transit time principle used for non-invasive flow measurement at an angle β (clamp-on flow sensor)

significantly higher time differences at the same flow velocity to calculate for exact flow rates.

The exact flow measurement requires a highly precise time measurement. Especially for non-invasive clamp-on flow measurement, a high time resolution and low-noise measurement is indispensable. Modern electronic circuits with high-precision timing components enable a time measurement with a resolution in the single-digit picosecond range. This allows clamp-on flow sensors to stably detect even low-flow velocities while maintaining high measuring speed. The fast measuring speed qualifies flow meters to precisely manage even very fast pumping and dosing processes.

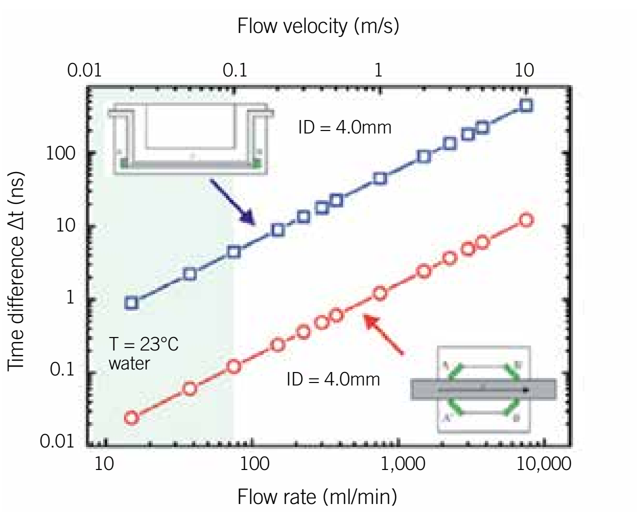

Figure 2: Time difference according to equation 2 (see Figure 1a) for water at a medium temperature T = 23°C of an inline sensor (blue) and a clamp-on sensor (red), with the measurement along the flowing medium with an inner diameter of ID = 4.0mm. The measuring range with a flow velocity of v ≤ 0.1 m/s is highlighted in green

A major challenge for signal evaluation is to ensure a maximum possible signal-to-noise ratio.

Geometric Tube Properties – An Important Measurement Criterion When Using Clamp-On Flow Meters

Ultrasonic flow measurement is a time measurement enabling calculation of the velocity of the flowing liquid. A main challenge in getting an exact volume flow lies in determining the cross-sectional area of the flexible tubing. The cross-sectional area inside the flexible tube is not clearly defined and can hardly be predicted precisely in theory. A variation of the cross-sectional area directly affects the flow rate measurement. The resulting error is added one-to-one to the overall error value. Despite having nominally the same measuring section (see red arrows in **Figure 3**), the cross-sectional area and thus the calculated flow rate may vary considerably. When a flexible tube is inserted into the channel of the sensor, the cross-sectional area is formed depending on the ratio of inner to outer diameter and the shore hardness of the tube. These effects underline the need for a careful, empirical reconciliation of the geometric factors when calculating the volume flow to a specific tube. This finally leads to a considerable increase in the accuracy of the flow measurement.

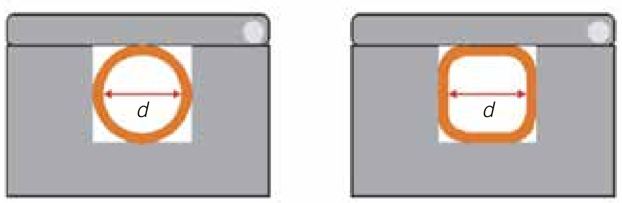

Figure 3: Modification of the cross-sectional area for the same measuring section (red arrow) by clinging to the channel wall

A study executed to evaluate how accuracy shifts when tubes of different materials, durometers, manufacturers, or inner/outer diameter relations are applied after the company's clamp-on flow meter has been calibrated to a certain tube, demonstrated shifts ranging from one-digit percentage rates (different manufactures of the same tube material) up to 50% for differing tube inner diameters (9). To ensure an accurate measurement, a sensor adjustment to specific tubes is, therefore, necessary.

Non-Contact Bubble Sensors – Clamp-On Systems for Precise Bubble Detection in Liquid Tubes

Ultrasonic air bubble detection is based on non-invasive measurement through the walls of flexible and rigid plastic tubes by means of transmission technology (10). The clamp-on-architecture of the sensors enables non-contact measurement straight on the tubing. For that, the tube has to be simply inserted into the measuring channel of the sensor. Two transducers – which are placed on opposite sides of the liquid-filled tube – act as transmitter and receiver. The transmitter generates an ultrasonic wave that moves through the tube perpendicularly to the liquid and reaches the receiver on the opposite side of the tube. Since air has an acoustic impedance that is about 3,500 times lower than water, the reflection co-efficient at the water-air-interface is accordingly high and most of the acoustic energy is reflected. Additionally, ultrasonic waves are much more attenuated when propagating in air, compared to water. Both phenomena cause the amplitude of the receiver signal to decrease.

Non-Contact Flow Meters	Non-Contact Bubble Detectors
Buffer/media prep: replacing scales for volume measurement	**Bioreactors/fermentators**: detection of excessive foaming in feed/harvest lines
Chromatography: balancing acid/base delivery to the system	**Chromatography**: prevention of air being pumped into columns and diversion of air infused liquids around the columns
Tangential flow filtration: measuring flow rates on feed, permeate, or retentate lines	**Tangential flow filtration**: prevent air from entering TFF filter cassettes
Inoculation: injecting cell lines into the reactor	**Feed stream**: continuous monitoring for air bubbles in the feed to prevent from air entry into the filter
Bioreactor (continuous/perfusion): feeding media/nutrients, control flow into and out of the bioreactor and ATF filters	**Pump protection**: detection of air bubbles caused by cavitation and protection from dry running
Centrifugation: determining flow/no flow	**Transfer lines**: notification when transfer reservoirs run dry
Fill/finish: measuring volume of fluid dispensed into containers	**Fill/finish**: detection of undesired air entering vessels to be filled

Table 1: Ultrasonic non-contact flow and bubble sensors and their use in bioprocessing applications

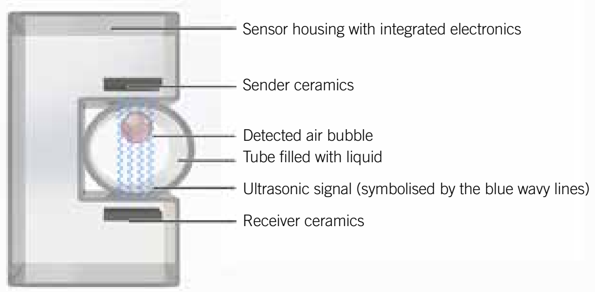

Figure 4: Exemplary presentation of the design and transmission technology of an air bubble detector

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Fernando Rangel is International Sales Manager for Non-invasive Fluid Monitoring at **SONOTEC.** For over six years, he has been working in biological, medical, and industrial applications where non-contact measurement is the technology driver. Prior to that he held various sales positions in chemical and automotive companies in Germany, the US, and Mexico. Fernando graduated as a Mechanical/Electrical Engineer from Tecnológico de Monterrey, Mexico, has a degree in Marketing, and holds an Executive Master of Business Administration title from the University of Applied Sciences, Furtwangen, Germany.

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