

Measuring arrangement and method for analyzing a fluidic sample

5 The present invention relates to a measuring arrangement for analyzing a fluidic sample by means of optical spectroscopy and a method for analyzing a fluidic sample by means of a measuring arrangement. Analytical methods employing spectroscopy are in particular used for studying chemical or biopharmaceutical substances.

10 Samples can be determined and/or analyzed with the aid of such measuring arrangements. For the measurements, the samples are irradiated with electromagnetic radiation, in particular light. The interaction between the electromagnetic radiation and the investigated sample can be observed and absorption and/or scattering and/or emission of radiation can be analyzed, in particular in a spectral analysis. In particular, spectra obtained by IR-spectroscopy, UV spectroscopy or Raman spectroscopy
15 can provide information on the molecular structure of a sample. Therein, frequencies of absorbed radiation or frequency shifts of part of scattered/emitted radiation can be observed - later on also referred to as spectroscopic response. The material and/or at least one property/characteristic of the material can be determined from this material-specific frequencies or frequency shifts. In this way, specific structures of molecules can be identified or the spectroscopic response of specific structures of molecules to the irradiation can be used in modelling/predicting the presence, in particular the concentration, of corresponding substances. In particular Raman Spectroscopy shows a high potential in characterizing even macromolecules like proteins or bioactive molecules and enables an acquisition of biochemical and structural information of a sample, for instance in biopharmaceutical development or process analytical technology.
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In biopharmaceutical development, rigorous testing and/or characterization of product quality attributes are necessary to ensure the final product meets the required
30 standards. Common product quality attributes monitored during the development of a new biologic entity may include protein concentration, aggregation levels, glycosylation patterns, and biological activity. Such tests help to confirm that the product remains stable and effective throughout its shelf life and/or complies with regulatory requirements.

35 Optical spectroscopy offers strong tools for instance in Process Analytical Technology for biopharmaceutical downstream processing, enabling real-time, non-invasive

monitoring of critical quality attributes. The integration of the techniques into manufacturing workflows may enhance process control and product quality, although challenges in data interpretation and calibration have to be overcome. Often these techniques comprise the use of prediction models (data interpretation schemes wherein the sought after attributes like concentration values are computationally derived from data of spectroscopic measurements) wherein calibration is necessary for instance for quantifying composition of components and correcting systematic errors in the measurement equipment, using analytical references for components of interest.

WO 2020/086635 A1 discloses a method for monitoring a biopharmaceutical process by a spectroscopy system, wherein training data are selected from observational data sets and used to calibrate a local model specific to the biopharmaceutical process. By way of example algorithms methods are outlined for creating local training data sets, training a process model using that training set and making predictions using the trained model.

Typically, the accuracy of such prediction models depends on the quality and quantity of training data. Therefore, there is a need to develop a method for a generation/acquisition of good quality spectral data, in particular wherein the method is suitable for a high-throughput of samples and/or automation to provide a measurement arrangement for such a method.

The measurement can be conducted statically using a single sample or multiple individual samples, in particular associated to steps in a purification process and/or chromatography run, for example samples from a bioreactor. The measurement can also be carried out using a flow cell to enable in-situ measurements of flowing fluids in downstream processing.

Flow cells can also be used for instance for monitoring concentrations in chromatography with optical spectroscopy, preferably Raman spectroscopy. Due to the inherent correlation of, in particular Raman, spectra with the chemical bonds present within a molecule, the spectra can be correlated to the concentration of the respective molecules and therefore, in particular by using data processing with machine learning models, concentrations for instance of proteins can be monitored.

It is particularly important that the fluidic sample is not damaged and/or contaminated. In particular, irradiating the sample with high-energy radiation can damage

the fluidic sample and/or cause unwanted reactions. Further, air bubbles, dirt or other foreign objects must be prevented from accumulating or from being trapped in the flow cell. Damages of the fluidic sample and/or accumulated gas bubbles and/or dirt in the flow cell can distort the measurement and lead to inaccurate or incorrect analysis. Corresponding measurements have to be repeated, which is costly and time-consuming.

It is therefore an object of the present invention to provide a measuring arrangement and a method which enable a particularly accurate measurement of the fluid sample and/or comprise a particularly low susceptibility to errors in the measurement.

The present object is solved by a measuring arrangement for analyzing a fluidic sample by means of spectroscopy according to claim 1 and by a method for analyzing a fluidic sample by means of a measuring arrangement according to claim 12.

The measuring arrangement comprises a flow cell, through which the fluidic sample flows. The measurement is carried out by means of the flow cell. The measuring arrangement further comprises a pumping device to pump the fluidic sample through the flow cell.

According to an aspect of the present invention, the flow cell comprises a measuring section, wherein the measuring section is at least essentially disc-shaped or designed as a hollow cylinder. The flow cell is arranged such that the fluidic sample flows through the flow cell from bottom to top to prevent or reduce gas bubbles in the flow cell, in particular related to and/or against the direction of gravity. The flow from bottom to top through the flow cell can reduce or prevent gas bubbles in the flow cell. In this way it is possible to reduce or prevent a negative influence of gas bubbles contained in the sample and/or the flow cell. By arranging the flow cell accordingly, gas bubbles can accumulate in the area of the flow cell output or in an area of an output of the measuring section of the flow cell. The gas bubbles can be removed from the flow cell in a particularly simple manner due to the flow of the fluidic sample through the flow cell. The measurement can thus be carried out particularly quickly and easily.

According to a further aspect of the present invention, which can also be realized independently, the residence time in which the fluidic sample is pumped and/or flows,

in particular in a fluidic entry of the measuring arrangement or the flow cell is greater than 1 second.

5 Within the residence time, an optimum flow of the sample can be achieved within the measuring arrangement and in particular the flow cell. A corresponding residence time results in a particularly accurate and reliable measurement. Furthermore, air bubbles can be effectively prevented from being introduced into the flow cell, whereby a particularly accurate measurement with no or very little negative influences is achieved.

10 According to a further aspect of the present invention, which can also be realized independently, the inlet of the flow cell is fluidly connected to an adapter for receiving the fluidic sample. In particular, the adapter forms a fluidic entry port into the measurement arrangement and/or serves as an interface between an injection needle and the flow cell. The pumping device comprises an injection needle for injecting the fluidic sample into the adapter. In particular, the pumping device with the injection needle is adapted to aspirate (in particular suck in) and dispense fluidic sample. Further, the measuring arrangement comprises a detection device which is configured and/or designed to detect when the injection needle is fluidly coupled to the adapter and when not. With the aid of the injection needle and the adapter, the sample can be dosed and fed to the flow cell in a particularly precise and easy manner. By recognizing when the needle is connected to the adapter, the data obtained using spectroscopy can be superimposed or linked with the data on when a sample was injected using the time data. Based on the time at which the needle was connected to the adapter, it can thus be recognized that a new and/or different sample has been injected and thus analyzed using spectroscopy. In this way, a spectrum obtained by spectroscopy can be assigned to each sample in a particularly simple and reliable manner.

30 Preferably, the detection device comprises a light barrier. Detection can be carried out without contact and in a particularly simple and reliable manner by means of a light barrier. It is also possible that the detection device comprises a pressure sensor, a contact sensor or the like.

35 In particular, the detection device can automatically recognize that a new sample is being filled into the adapter and thus a new sample is fed into the flow cell. Preferably, the date-time when the fluidic sample is injected into the flow cell is then recorded.

In particular, the recorded date-time information is used to link individual data sets or spectra to individual samples, in particular for associating data sets or spectra to the respective samples, in particular by using data processing and/or code programs. It is then possible – even for continuous measurements – to automatically differentiate
5 between data associated to different successive fluidic samples. By this a serial measurement of multiple fluidic samples can be conducted in an efficient manner.

When the needle is fluidically connected to the adapter, the needle and the adapter preferably form a fluid-tight connection. In this way, the penetration and/or mixing of
10 air into the fluidic sample can be prevented, whereby the measurement is particularly error-free.

If the needle is not fluidically connected to the adapter and/or the needle is disconnected from the adapter, the adapter is preferably hermetically sealed from the environment. In this way, air can be prevented from entering or mixing into the liquid
15 sample in the adapter and/or from entering or mixing into the adapter. This is a particularly effective way of preventing air from entering the flow cell.

In particular, the pumping device is designed to fluidly connect the injection needle to the adapter and/or to disconnect a fluidic connection between the injection needle and the adapter. In this way, samples can be automatically pumped into the adapter, whereby a particularly high degree of automation of the measurement can be
20 achieved.

The flow cell can be arranged in such a way that the fluidic sample flows through the flow cell at an angle to the vertical. The angle is preferably less than 33° . In particular, the angle is less than 20° , more preferably less than 15° . In particular, the fluidic sample flows at least essentially vertically through the flow cell. The flow cell is preferably arranged at least essentially vertically. The angle is preferably greater than or
25 30 equal to 0° .

Preferably, the measuring arrangement is adapted to pump the fluidic sample forwards and backwards through the flow cell during measurement of the fluidic sample. In particular or alternatively, the measuring arrangement comprises a computer
35 which is configured to control the pumping device in such a way that the fluidic sample is pumped forwards and backwards through the flow cell during the measurement of the fluidic sample. Preferably the pumping device can be controlled to pump the

fluidic sample forwards and backwards through the flow cell while the measurement/analysis is conducted. The fluidic sample can then be measured and/or analyzed at a flow rate and/or in motion, in particular aligned to purification and/or downstream processes.

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By moving the fluidic sample forwards and backwards, the energy input from the source of the electromagnetic radiation, in particular from the light source, in particular a laser, can be reduced. In this way, heating of the fluidic sample can be reduced and/or prevented. In particular, damage to the fluidic sample can be prevented even at high light source power levels.

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Preferably, the forward and backward pumping involves flushing back a portion of an initial injection volume with a predefined number of backward and forward pumping steps. Since the identical sample volume is at least in parts pumped backwards and forwards and thus the same part or part after part of the sample is measured/analyzed several times, only a small sample volume is required. The required sample volume can thus be reduced compared to a measurement that is only performed during the forward flow of the fluidic sample. The measurement can therefore be carried out easily and reliably even with small sample volumes. Due to the small sample volumes required, cost savings can be achieved, especially with regard to expensive fluidic samples.

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The possibility to carry out measurements with small or smaller sample volumes and/or, in particular mere, fractions of a larger sample can also enable a higher accuracy in the analysis of a sample, in particular if different fractions of a sample can be analyzed independently of each other.

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In particular, the measuring arrangement is used for measuring fluidic samples which are fractions of a fluidic sample of a larger volume which has undergone a chromatographic process, in particular wherein the individual fluidic sample is a fraction collected from a chromatography run or corresponds to a chromatography step. Due to the smallness of the sample volume which can be measured with the measuring arrangement, the overall sample processed in a chromatography run can be split into more fractions, in particular corresponding to successive chromatography steps, of volumes of sufficient size for the spectroscopic measurements or the fractions corresponding to successive chromatography steps can be divided again into multiple samples for spectroscopic measurement.

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Preferably, fractions taken from a chromatography run of an overall sample can be re-mixed by different ratios to generate a set of individual samples. For modelling purposes these individual samples generated by re-mixing are set to correspond to finer successive steps of the chromatography run, in particular by measuring additional samples generated by remixing more data points can be generated, for instance for modeling effects (for example, the concentration of different substances in successive chromatography steps). All the fractions plus mixed samples were off-line measured by Raman spectroscopy using the pumping system described in this application.

At the same time, the measuring duration and thus the accuracy can be increased or adjusted as required. For example, the number of forward and backward movements can be easily adjusted to ensure sufficient or improved measurement.

Preferably, the residence time in which the fluidic sample is pumped and/or flows is greater than 1 second, preferably greater than 1,5 second, more preferably greater than 2 seconds, and/or less than 5 seconds, preferably less than 4 seconds, preferably at least essentially 3 seconds. Corresponding residence times of the fluidic sample result in a particularly accurate and reliable measurement. Furthermore, air bubbles can be effectively prevented from being introduced into the flow cell.

Preferably, the, in particular internal, volume of the flow cell is smaller than the volume of an individual fluid sample, in particular the volume of the fluidic sample is at least slightly larger than the volume of the flow cell. In particular, the volume of the fluidic sample corresponds to at least 2 times, preferably at least 2,5 times, the volume of the flow cell. The volume of the fluidic sample can be less than 25 times, preferably less than 20 times, more preferably less than 15 times, more preferably less than 10 times, the volume of the flow cell.

The volume of the fluidic sample corresponds to at least 2 times, preferably at least 2,5 times, the dead volume of the measuring arrangement.

In the context of the invention, the term "dead volume" is to be understood as the, preferably internal, volume of the measuring arrangement that relates from the location of the sample feeding up to and including the flow cell.

Preferably, the measuring arrangement comprises an emitter for emitting electromagnetic radiation and a receiver unit for receiving and/or collecting electromagnetic radiation. The emitter and/or the receiver unit is/are arranged and/or designed in such a way that the electromagnetic radiation emitted by the emitter and/or received
5 and/or collected by the receiver unit is aligned transversely to the flow of the fluidic sample through the flow cell. In particular, the electromagnetic radiation emitted by the emitter and/or received and/or collected by the receiver unit is aligned perpendicularly to the flow of the fluidic sample through the flow cell. In this way, a particularly accurate and reliable measurement can be achieved.

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Depending on the spectroscopic method used with the measurement arrangement, the optical set-up for the irradiation of the fluid sample and the collection of light from the fluidic sample preferably forms a confocal arrangement, in particular for Raman spectroscopy, or an in line arrangement, wherein the receiving unit is arranged opposite to the light source or collects radiation emitted on the other side of the fluidic
15 sample – an arrangement particularly used for absorption spectroscopy. Particularly preferably, the emitter and/or the receiver unit are configured as a probe. In this way, quick changes or adaptations of the measurement arrangement are feasible.

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The measuring arrangement preferably comprises a spectrometer, in particular a Raman spectrometer, or can be designed as a spectrometer, in particular a Raman spectrometer. Raman spectroscopy can be used to provide a structural fingerprint by which specific molecular structures can be identified in a cost-effective way.

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In particular, the measuring arrangement comprises a probe which is connected to the Raman spectrometer and/or the light source, in particular a laser or laser light source, by a light guide, in particular an optical fiber. Preferably this probe comprises a lens, in particular a sapphire lens, by which the light from the light source, in particular the laser light, is focused and, in particular preferably, by which also the light
30 backscattered from the sample is collected. It is in particular preferable that the light guide used for the transmission of the laser light is also used for the transmission of the electromagnetic radiation collected from the sample. In this way, a particularly accurate optical measurement set-up can be achieved. At or within the spectrometer various optics, in particular including a beam splitter, can be used to guide the light
35 collected from the sample or from the site of the sample to a detector of the spectrometer.

According to an aspect of the invention, the pumping device is a fluent liquid handling system, in particular a pipettor and/or an automatic pipetting device. Additionally or alternatively, it is also possible that the pumping device is or comprises a reciprocating piston system or a gear pump.

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The invention also relates to a method for analyzing a fluidic sample by means of a, in particular proposed, measuring arrangement. The measuring arrangement comprises a flow cell.

10 In this respect, reference is made to all explanations on the proposed measuring arrangement. In particular, corresponding advantages can be achieved.

According to an aspect of the invention the flow cell comprises a measuring section, wherein the measuring section is at least essentially disc-shaped or designed as a
15 hollow cylinder. The fluidic sample flows through the flow cell from bottom to top, in particular against the force of gravity, in order to prevent and/or reduce gas bubbles in the flow cell. In this way it is possible to reduce or prevent a negative influence of gas bubbles contained in the sample and/or the flow cell.

20 According to a further aspect of the present invention, which can also be realized independently, the residence time, in which the fluidic sample is pumped is greater than 1 second. Within the residence time, an optimum flow of the sample can be achieved within the measuring arrangement and in particular the flow cell. A corresponding residence time result in a particularly accurate and reliable measurement.

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According to a further aspect of the present invention, which can also be realized independently, the measuring arrangement injects the fluidic sample via a needle into an adapter which is connected to the flow cell, wherein it is detected when the injection needle is fluidly coupled to the adapter and when not. Preferably, the measurement continues to be running until all the samples are injected into the flow cell,
30 and the measurement data can further be automatically analyzed and matched to each sample depending on the recorded data-time information.

According to a further aspect of the present invention, which can also be realized
35 independently, the flow cell is purged and/or cleaned, in particular after the sample has been analyzed. Gas bubbles can be removed from the flow cell by purging and/or

cleaning. At the same time, the flow cell can be prepared and prefilled with purified water to keep the flow cell free of gas bubbles until the next measurement.

5 The purging/cleaning of the flow cell comprises at least three steps. In a first step, a cleaning fluid (for instance purified water) can be passed through the flow cell with a first flow rate to expel large gas bubbles from the flow cell. In a subsequent, second step the cleaning fluid can be passed through the flow cell with a second flow rate to expel small gas bubbles from the flow cell. In a further subsequent, third step, step
10 the cleaning fluid is passed through the flow cell with a third flow rate to keep the flow cell free of gas bubbles.

In particular, the second flow rate is greater than the first flow rate. The different flow rates allow gas bubbles of different sizes to be effectively removed from the flow cell.

15 In particular, the first flow rate is greater than the third flow rate and/or the second flow rate is greater than the third flow rate. In the third step, the flow cell can be prefilled with purified water. Preferably, gas bubbles are prevented from entering the flow cell. In this way, the flow cell can be kept free of gas bubbles until the next measurement is carried out.

20 According to another aspect of the invention, the fluidic sample is pumped forwards and backwards through the flow cell during the measurement of the fluidic sample. In this way, the amount of liquid sample used for the measurement and/or analysis can be reduced. The fluidic sample can then be measured and/or analyzed at a flow
25 rate and/or in motion.

The required energy input from the laser source into the fluidic sample can be reduced, whereby damage to the fluidic sample can be reduced and/or prevented. Furthermore, the individual sample volume can thus be reduced as explained above. In
30 this way, cost savings can be achieved. At the same time, the measuring duration and thus the spectra quality can be increased or adjusted as required.

Preferably, the fluidic sample or a part of the fluidic sample is pumped forwards and backwards more than 10 times, preferably more than 20 times, preferably more than
35 30 times. Additionally and/or alternatively the fluidic sample or a part of the fluidic sample is pumped forwards and backwards less than 200 times, preferably less than 150 times, preferably less than 110 times. In particular, the fluidic sample or a part

of the fluidic sample can be pumped forwards and backwards between 40 and 100 times during the measurement. In this way, a particularly accurate and reliable measurement can be made.

5 The aspects of the present invention mentioned above and described in the following specific description may also be implemented and advantageous individually and in various combinations.

10 Further details, advantages and properties of the present invention will become apparent from the claims and from the following description of preferred embodiments with reference to the drawings, in which:

15 Fig. 1 shows a schematical view of a proposed measuring arrangement according to a first embodiment;

 Fig. 2 shows a schematical view of the interaction of electromagnetic radiation with a liquid sample in the flow cell;

20 Fig. 2a shows a schematical, detailed view of the flow cell in a measuring arrangement according to or at least principally similar to the first embodiment;

 Fig. 2b shows a schematical, detailed view of the flow cell in a measuring arrangement according to a second embodiment;

25 Fig. 3 is a schematical cross section of an adapter of the measuring arrangement;

 Fig. 4 shows a schematical view of a proposed measuring arrangement according to a third embodiment;

30 Fig. 5 shows a perspective view of a proposed measuring arrangement according to a fourth embodiment;

 Fig. 6 is a perspective view of a flow cell for the measuring arrangement;

35 Fig. 7 is a perspective view of the flow cell filled with a fluidic sample, wherein the sample is pumped forwards through the flow cell;

- Fig. 8 is a perspective view of the flow cell, wherein a part of the fluidic sample is pumped backwards through the flow cell;
- 5 Fig. 9 shows two Raman spectra of a flow cell filled with water and air respectively, in which the Raman counts or the intensities of Raman scattering signal are shown over the frequency shifts or Raman shift;
- 10 Fig. 10 a diagram showing the Raman response in a section of a continuous measurement of a flow cell which is purged with water, wherein the Raman counts or the intensity of the Raman scattering signal at the frequency shift of 418 cm^{-1} over a period of time is shown;
- 15 Fig. 11 is a diagram showing the Raman response of a plurality of successively measured fluidic samples (extracted from a chromatography run with a sample containing proteins), wherein averaged Raman count or intensity over all frequency shifts is shown over a run time corresponding to the number of samples measured, wherein the detection has been carried out with the proposed measuring arrangement; and
- 20 Fig. 12 a Raman detection of the identical samples as in Fig. 11, wherein the detection has been carried out with a measuring arrangement according to a previous set-up.
- 25 In the following description of preferred embodiments by reference to the drawings, the same or corresponding reference signs have been used for the same or similar components or parts, where similar or identical advantages and properties may be achieved even if the associated description has not been repeated.
- 30 In a schematic manner, Fig. 1 shows a measuring arrangement 1 according to a first embodiment. The measuring arrangement 1 according to the first embodiment is designed to analyze different fluidic samples 2 one after the other, as will be explained in detail below.
- 35 The measuring arrangement 1 comprises a flow cell 3, in which the fluidic sample 2 can be illuminated with a source of monochromatic light or a laser 4. As shown in

Fig. 1, the flow cell 3 is preferably fluidly connected to a conveying device 5 for conveying fluid to be analyzed, in particular in at least one direction.

5 The flow cell 3 preferably comprises an input/inlet 6 and an output/outlet 7. In particular, the input 6 is fluidly/fluidically connected to the conveying device 5. Further, the outlet 7 can be connected to the conveying device 5 downstream of the inlet 6.

10 Further, the flow cell 3 preferably comprises a measuring section 8. In particular, the measuring section 8 is arranged between the input 6 and the output 7. Preferably, the measuring section 8 is directly connected to the input 6 and/or the output 7.

15 The input 6 preferably comprises an at least essentially round cross section. The cross section can also be designed differently, for example polygonal. In particular, the input 6 extends along an input axis A.

The output 7 can also comprise an at least essentially round cross section. The cross section can also be designed differently, for example polygonal. In particular, the output 7 extends along an output axis B.

20 In particular, the input 6 and output 7, are arranged at least essentially coaxially to each other and/or the output axis B is arranged at least essentially coaxially to the input axis A as shown in Fig 1.

25 In particular, the input 6 and the output 7 comprise an at least essentially identical cross-section.

30 The measuring section 8 can be at least essentially disc-shaped or designed as a hollow cylinder that extends along a measuring axis C. In particular, the measuring axis C is arranged transversely, in particular perpendicular, to the input axis A and/or output axis B.

35 The flow cell 3, in particular the measuring section 8, can be made of metal. The metal construction allows the electromagnetic radiation 4 to be reflected in a particularly advantageous manner at the walls of the flow cell 3, in particular the measuring section 8.

Fig. 2 is a schematic view showing the interaction of electromagnetic radiation with the fluidic sample 2 in the flow cell 3.

5 The fluidic sample 2 within the measuring section 8 can be irradiated with electromagnetic radiation 4, in particular monochromatic light and/or laser light, as explained in detail below.

10 The measuring arrangement 1 can comprise a measuring device 9 for measuring and/or analyzing the fluidic sample 2 interacting with the electromagnetic radiation 4. The measuring device 9 and/or the measuring arrangement 1 preferably comprises a radiation unit/light source 10S or emitter 10E for emitting electromagnetic radiation 4 and a detector or receiver unit for detecting signals corresponding to the interaction with the electromagnetic radiation, for instance inelastically scattered light.

15 Fig. 2 shows schematically the interaction of electromagnetic radiation 4 and the fluidic sample 2 to be measured in the flow cell 3 by measuring device 9.

20 Fig. 2 shows the concept of the detection of electromagnetic radiation 4 scattered/emitted from the fluidic sample 2 in an abstract manner. The spatial arrangements for instance for the flow cell 3 in relation to the incoming radiation 4 or the collection/detection of radiation 4 emitted from the fluidic sample 2 typically varies in actual embodiments. Fig. 2 is only intended to show a rough sketch of the principle, in which, above all, the collection/detection of radiation 4 is shown. Fig. 2a and Fig. 2b, which are explained in detail below, show a more practical and/or detailed embodiment.

The electromagnetic radiation 4 is preferably emitted by the emitter 10e as a beam of light.

30 Preferably, monochromatic laser radiation can be used as the emitter 10E to provide emitted electromagnetic radiation 4.

In particular, a laser, especially a diode laser, can be used to generate the electromagnetic radiation 4.

35 The emitted electromagnetic radiation 4 can range in particular from 300 nm to 900 nm, preferably from 350 nm to 850 nm, preferably from 400 to 800 nm. In particular,

the wavelength of the emitted electromagnetic radiation 4 is in the near infrared range, preferably 785 nm. In particular when doing Raman spectroscopy on samples containing biological molecules like proteins, illuminating the sample with near-infrared light is preferable, as unwanted fluorescence effects are reduced, in particular in
5 comparison to working at lower wavelengths or with UV light.

Alternatively, it is also possible to use other electromagnetic radiation 4, such as X-ray radiation, IR radiation or the like.

10 For example, IR radiation with a wavelength from 800 nm to 1 mm can be used to conduct an analysis of the fluidic sample 2 by infrared spectroscopy/IR spectroscopy.

In particular, the emitter 10E defines a main emitting direction ME. Preferably, in the present case, the term "main emitting direction" refers to the direction in which, preferably the centre line, i.e the middle line of the focused beam, of the electromagnet
15 radiation 4 is emitted, in particular onto the flow cell 3 and/or into measuring section 8.

The electromagnetic radiation 4 can be emitted transversely, in particular perpendic-
20 ularly, or parallel to the measuring axis C.

Additionally or alternatively, the electromagnetic radiation 4 is preferably emitted transversely, in particular perpendicularly, to the input axis A and/or the output axis B of the flow cell 3.

25 Preferably, the main emitting direction ME is at least essentially transversely, in particular perpendicularly, to the input axis A and/or the output axis B.

The electromagnetic radiation 4 can interact with molecules 11 and/or atoms of the
30 sample 2. Thus, the radiation 4 can be scattered inelastically by the molecules 11 and/or atoms. The term "inelastically scattered" is to be understood in the context of the invention to mean that an energy transfer takes place between the radiation 4 and the molecule 11 and/or atom. The inelastically scattered electromagnetic radiation 4 can have more or less energy as the electromagnetic radiation 4 initially trans-
35 mitted into the flow cell 3. In Fig. 2 inelastic scattering is indicated by reference sign I.

In addition, the radiation 4 can be elastically scattered by the molecules 11 and/or atoms of the sample 2. In the present case, the term "elastically scattered" is to be understood as meaning that no transfer of energy takes place between the radiation 4 and the molecule 11 and/or atom. The elastically scattered radiation 4 has the
5 same energy as the electromagnetic radiation 4 initially transmitted into the flow cell 3. In Fig. 2 elastic scattering is indicated by reference sign E.

The measuring device 9 and/or the measuring arrangement 1 preferably comprises a detector and/or receiver unit 13 for receiving and/or detecting electromagnetic ra-
10 diation 4, in particular scattered electromagnetic radiation 4.

Generally, the detector and/or receiver unit 13 is preferably configured to detect electromagnetic radiation 4 coming from one direction, in particular a main measuring direction MM. Preferably, in the present case, the term "main measurement direction"
15 refers to the direction, preferably the center line, in particular the middle line, in which the electromagnetic radiation is detected and/or collected by the receiver unit 13.

The detector and/or receiver unit 13 is configured for detecting and/or analyzing the fluidic sample 2, in particular the molecules 11 of the fluidic sample 2, interacting with
20 the electromagnetic radiation 4. In particular frequencies of absorbed electromagnetic radiation 4 or frequency shifts of part of scattered/emitted electromagnetic radiation 4 can be observed.

The main measuring direction MM is preferably at least essentially parallel and/or identical or opposite to the electromagnetic radiation 4 emitted by the light source
25 10S, in particular the main emitting direction ME.

Preferably, the main measuring direction MM is transverse, in particular perpendicular, or parallel to the measuring axis C. Preferably, the main measuring direction MM
30 is transverse, in particular perpendicular, to the input axis A and/or the output axis B.

Fig. 2A shows a schematical, detailed view of the flow cell 3 in a measuring arrangement 1 according to a first embodiment, in particular a confocal arrangement. Fig. 2b shows a schematical, detailed view of the flow cell 3 in a measuring
35 arrangement 1 according to a second embodiment, in particular an in-line arrangement.

The flow cell 3 comprises a measuring section 8 which is preferably at least essentially disc-shaped or designed as a hollow cylinder, in particular a flat hollow cylinder, in particular a cylinder which has a diameter which is significantly larger than the height of the cylinder. Preferably, the measuring axis C is identical to the central axis of the disc or cylinder or extends through the center of the measuring section 8.
5 Preferably, the principal plane of the disc-shape measuring section 8 extends perpendicular to the main measuring direction MM.

In the embodiment as shown in Fig. 2A, the measuring arrangement 1 comprises a light source 10S for emitting electromagnetic radiation 4. The electromagnetic radiation 4 can be focused by a lens 10A1 and/or refracted by the lens 10A1 to form an axis-parallel beam. The electromagnetic radiation then preferably strikes a beam splitter BS and is deflected by the beam splitter BS. The electromagnetic radiation 4 can be guided into a light guide 10B, in particular an optical fiber.
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15 A further lens 10A2 can be arranged at the other end of the light guide 10B. The lens 10A2 can focus the electromagnetic radiation 4 into the preferably at least essentially cylindrical measuring section 8. In this case, the electromagnetic radiation 4 can be focused onto a partial area of the measuring section 8, in particular a point, preferably a focal point, and/or an area of the measuring section 8.
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The lens 10A2 preferably consists of sapphire. Sapphire has the advantage that the interaction of this material with the electromagnetic radiation 4 is at different frequencies and/or wave number ranges than the interaction of biological molecules with the electromagnetic radiation 4.
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As Fig. 2A also shows, the electromagnetic radiation 4 is preferably directed along, in particular parallel to, the measuring axis C into the measuring section 8.

30 The flow cell 3 preferably comprises a window for introducing and/or exiting electromagnetic radiation 4. The window is preferably arranged on an axial end face of the measuring section 8 with respect to the measuring axis C. The window can be made of sapphire. It is also possible for the window to be formed by the lens 10A2 made of sapphire.

35 The electromagnetic radiation 4 introduced into the measuring section 8 can at least partially interact with the fluidic sample 2, in particular be inelastically scattered. A

part of the electromagnetic radiation 4 introduced into the measuring section 8 does not interact with the fluidic sample 2 and is reflected at the walls of the flow cell 3, in particular elastically scattered.

5 Both, the elastically scattered and the inelastically scattered radiation is transmitted into the light guide 10B, in particular via the same Lens 10A2 through which the electromagnetic radiation 4 was introduced into the flow cell 3. The lens 10A2 is preferably configured to confocally collect the scattered electromagnetic radiation emerging from the measuring section 8.

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The scattered electromagnetic radiation 4 introduced into the light guide 10B is then composed of elastically scattered and inelastically scattered radiation and/or light.

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At the end of the light guide 10B, the scattered electromagnetic radiation 4 is preferably guided through the beam splitter BS. The scattered electromagnetic radiation 4 then preferably encounters a filter F.

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The filter F is preferably configured to block the elastically scattered electromagnetic radiation 4 and/or light of the laser wavelength. In this way, the elastically scattered electromagnetic radiation 4 is blocked. Preferably, only the remaining inelastically scattered electromagnetic radiation 4 passes through the filter F.

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The remaining scattered electromagnetic radiation 4 is then directed to the detector and/or receiver unit 13. In this case, the electromagnetic radiation 4 can be focused and/or diverted by a further lens 10A3.

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The light source 10S, the beam splitter BS, the filter F, the lens 10A1, the lens 10A2 and/or the lens 10A3 can belong to a spectrometer 15, in particular a Raman spectrometer.

The spectrometer 15 may be connected to a probe 10 via the light guide 10B, wherein the probe 10 may comprise the lens 10A2.

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The lens 10A3 can be part of the detector and/or receiver unit 13.

In alternative to Raman spectroscopy, the measuring arrangement 1 can be configured to analyze the fluidic sample 2 by any other spectroscopy, for example IR Spectroscopy or the like.

5 Fig. 2b shows a schematical, detailed view of the flow cell 3 in a measuring arrangement 1 according to a second embodiment. The measuring arrangement 1 according to the second embodiment differs from first embodiment in that the irradiation of the fluidic sample 2 with the electromagnetic radiation 4 takes place from one side of the flow cell 3 and the collection of the scattered radiation from the
10 opposite side of the flow cell 3, as will be explained in detail below.

The measuring arrangement 1, according to the second embodiment shown in Fig. 2B, comprises an emitter 10E for emitting electromagnetic radiation 4. The incoming electromagnetic radiation 4 is refracted by the lens 10A4 to form an axis-parallel beam.
15

The measuring section 8 of the flow cell 3 is preferably configured in the form of a cylinder. The measuring cell 3, in particular the measuring section 8, is preferably formed from metal. The measuring section 8 preferably comprises a first window for introducing electromagnetic radiation 4 at one of its end faces, relative to the measuring axis C. The first window can be formed by the lens 10A4.
20

The irradiation of the measuring cell 3 with electromagnetic radiation 4 can be done by means of a probe 10. The first lens 10A4 can then be part of the probe 10.
25

On the opposite axial end face, the measuring section 8 preferably comprises a second window for the emission of electromagnetic radiation 4, in particular of scattered electromagnetic radiation 4.

30 A second lens 10A5 is preferably provided to collect the scattered radiation. In particular, the second window can be formed by the second lens 10A5. The second lens 10A5 can also be made of sapphire.

The second lens 10A5 is preferably configured to collect the scattered electromagnetic radiation 4 arising in the measuring section 8 in a confocal manner and/or to focus and/or direct it to the detector and/or receiver unit 13.
35

The collection of the scattered electromagnetic radiation 4 can be done by means of another probe 10. The second lens 10A5 is then preferably part of the other probe 10.

5 The measuring device 9 preferably comprises a spectrometer 15, in particular a Raman spectrometer or can be designed as a Raman spectrometer.

The flow cell 3 can be configured and/or designed to be used in spectroscopic measurements, in particular for conducting Raman measurements on a fluidic sample 2.

10

In Fig. 1, the measuring device 9 preferably comprises a spectrometer 15, in particular a Raman spectrometer as described in Fig. 2a. The spectrometer 15 is preferably connected to a probe 10 for irradiating the flow cell 3 and/or collecting scattered electromagnetic radiation 4.

15

The probe 10 is preferably arranged, unlike as shown in Fig. 1 for reasons of illustration, in such a way that the flow cell 3 is irradiated with electromagnetic radiation 4 via an axial end face of the measuring section 8.

20

Preferably, the main measuring direction MM is arranged parallel to the main emitting direction ME. In particular, the main measuring direction MM and the main emitting direction ME are opposite to each other.

25

The main emitting direction ME and/or the main measuring direction MM is/are preferably parallel to the measuring axis C.

30

The measuring device 9 and/or the measuring arrangement 1 can comprise an analysis device, in particular a computer or analysis unit 14, as shown in Fig. 1. The analysis unit 14 is preferably designed to analyze the measurement carried out with the aid of the measuring device 9, in particular the probe 10 and the spectrometer 15, in particular Raman spectrometer.

35

The analysis unit 14 is preferably data connected to the measuring device 9, in particular the spectrometer 15, detector and/or receiver unit 13 and/or the emitter 10E. The connection between the analysis unit 14, the measuring device 9, spectrometer 15, detector and/or receiver unit 13 and/or the emitter 10E can be wired, in particular

realized by means of a cable. Alternatively, it is also possible that the connection is wireless, for example a Bluetooth and/or WIFI connection.

5 For example, it is possible to analyze the structure of the molecule 11 and/or correlate specific signals to the presence of specific molecules, in particular by use of respective calibration data sets for said specific molecules 11 which have been acquired beforehand preferably.

10 The analysis unit 14 can be part of a computer or can comprise a computer.

The measuring arrangement 1 can comprise a regulation and control unit 29 to control the measuring device 9, in particular the spectrometer 15, the emitter 10E and/or the detector and/or receiver unit 13. By means of the regulation and control unit 29, the emission of electromagnetic radiation 4 and/or the collection of scattered electromagnetic radiation 4 can be controlled and/or initiated.

As shown in Fig. 1 and Fig. 2, the flow cell 3 is preferably arranged in such a way that the fluidic sample 2 flows through the flow cell 3 from bottom to top.

20 In the context of the present invention, the term "from bottom to top" means that the fluidic sample 2 flows from the input 6 to the output 7 of the flow cell 3 from bottom to top in relation to the direction of gravity. In particular, the input 6 is arranged below the output 7 in relation to the direction of gravity. In particular, the fluidic sample 2 flows through the flow cell 3 against the direction of gravity.

25 The fluidic sample 2 can comprise or form a main flow direction MF when flowing through the flow cell 3, as shown in Fig. 2.

30 Preferably, in the context of the present invention, the term "main flow direction" is to be understood as the direction which is defined by a straight line that forms a direct connection between the input 6 and the output 7. The main flow direction MF preferably extends from the input 6 in the direction of the output 7.

35 Preferably, the flow cell 3 is arranged in such a way that the fluidic sample 2 flows through the flow cell 3 at an angle to the vertical, the angle being less than or equal to 33°, preferably less than 20°, more preferably less than 15°.

In the context of the present invention, the term "at an angle to the vertical" means that the sample's 2 main flow direction MF forms an acute angle to the vertical regarding the gravity.

5 In particular, the flow cell 3 is arranged/orientated such that the fluidic sample 2 flows through the flow cell 3 at least essentially vertically, preferably against the force of gravity.

10 Preferably, the main flow direction MF is arranged at least essentially vertically, in particular against the force of gravity.

The main flow direction MF is preferably arranged/orientated transversely, in particular perpendicularly, to the emitted electromagnetic radiation 4. The main flow direction MF is preferably arranged transversely, in particular perpendicularly, to the radiation emitted by the probe 10 or emitter 10E.

15

In particular, the main flow direction MF is orientated transversely, in particular perpendicularly, to the main measuring direction MM and/or the main emitting direction ME.

20

In particular, the output 7 can be positioned exactly above the input 6 in relation to the direction of gravity.

25 Gas bubbles contained in the fluidic sample 2 or the measuring section 8 can negatively influence the analysis/measurement or distort the result of the analysis/measurement.

When flowing through the measuring section 8, part of the sample 2 can form a flow transverse to the main flow direction MF. In particular, an at least essentially circular partial flow can be formed inside the measuring section 8.

30

The arrangement of the flow cell 3 allows gas bubbles that are contained in the fluidic sample 2 and/or the flow cell 3 to be removed from the measuring section 8 in an easy and effective way. Due to the arrangement of the flow cell 3, gas bubbles can accumulate in an area of the measuring section 8 near the output 7, even if there is a partial flow of the sample 2 transverse to the main flow direction MF in the measuring section 8. The flow of the fluidic sample 2 can guide the gas bubbles into the

35

output 7. In this way, the gas bubbles are removed from the measuring section 8. In particular, the dwell time of gas bubbles within the measuring section 8 can be reduced. Thus, a negative influence of gas bubbles on the measurement and/or analysis can be reduced and/or prevented.

5

The measuring arrangement 1 can comprise a pumping device 16 for conveying and/or pumping the fluidic sample 2 through the flow cell 3 as shown in Fig. 1. In particular, the pumping device 16 is designed to provide a defined volume flow of the fluidic sample 2 and/or a defined volume of the fluidic sample 2.

10

The measuring arrangement 1 is preferably adapted to pump the fluidic sample 2 forwards and backwards through the flow cell 3. In particular, the pumping device 16 is preferably configured to pump the fluidic sample 2 forwards and backwards through the flow cell 3 during a measurement.

15

The pumping device 16 is preferably fluidly and/or fluidically connected and/or connectable to the flow cell 3.

The pumping device 16 can comprise a reciprocating piston system 30, a gear pump or the like.

20

As shown in Fig. 1, the pumping device 16 is preferably designed as a fluent liquid handling system, in particular an automatic pipetting device 17. Alternatively, the pumping device 16 can be designed as a pipettor or the like. It is also possible that the pumping device 16 comprises a fluent liquid handling system, a pipettor, an automatic pipetting device 17 or the like.

25

The measuring arrangement 1 and/or the pumping device 16 can comprise and/or be connected to a computer or a control unit 16A which is configured to control the pumping device 16 in such a way that the fluidic sample 2 is pumped forwards and backwards through the flow cell 3 during the measurement of the fluidic sample 2.

30

The control unit 16A can be an integral component of the pumping device 16. It is also possible that the control unit 16A comprises a computer or is part of a computer.

35

The control unit 16A can be data connected to the analysis unit 14 and/or the regulation and control unit 29. The connection can be wired, in particular via a cable.

Alternatively, the connection can be wireless, for example configured as a Bluetooth or WIFI connection.

5 Additionally or alternatively, the regulation and control unit 29 might be configured to control and/or regulate the pumping device 16, but using commercial available systems might be more cost efficient to have at least an independent regulation and/or control unit for the pumping device 16.

10 Preferably the pumping device 16 shown in Fig. 1 can be fluidically connected to the flow cell 3 and detached from the flow cell 3 as described in the following. Fig 1 shows a state in which the pumping device 16 is connected to the flow cell 3.

15 The flow cell 3 is preferably fluidly connected to an adapter 18. The adapter 18 is preferably designed for receiving the fluidic sample 2. The flow cell 3, in particular the input 6, can directly be connected to the adapter 18 or can be connected to the adapter 18 via a tube T or the like. As shown in Fig. 1, the flow cell 3, in particular the outlet 7, can be connected to a waste outlet O via a second tube T1.

20 The adapter 18 preferably comprises a receiving opening 19 for receiving the fluidic sample 2 as shown in Fig. 1.

25 Preferably, the automatic pipetting device 17 and/or the pumping device 16 comprises an injection needle 20 for dispensing the fluidic sample 2. The pumping device 16, the automatic pipetting device 17 and/or the injection needle 20 is/are designed to fluidly connect the injection needle 20 to the adapter 18 and/or to disconnect a fluid connection between the injection needle 20 and the adapter 18.

30 FIG. 3 shows a cross-section of the adapter 18. The receiving opening 19 is preferably formed by an at least essentially funnel-shaped receiving section.

Preferably, at least a section of the injection needle 20 can enter the adapter 18 in order to inject the fluidic sample 2 into the adapter 18.

35 The injection needle 20 and/or the adapter 18 can comprise a seal 21, in particular a plastic seal, to ensure a fluid-tight connection between the injection needle 20 and the adapter 18.

The seal 21 can be an O-ring as shown in Fig. 1 and Fig. 3. Another design of the seal 21 is also possible. For example, the seal 21 may be a membrane.

5 In the preferred embodiment shown in Fig. 1 and Fig. 3, the adapter 18 comprises the seal 21. The seal 21 is preferably arranged at least essentially immediately adjacent to the receiving section and/or the receiving opening 19.

10 The seal 21 is preferably arranged in such a way that the connection between the injection needle 20 and the adapter 18 is fluid-tight when at least a part/section of the injection needle 20 is arranged within the adapter 18. In particular, the seal 21 can be connected to the adapter 18.

15 The seal 21 is preferably configured to ensure a fluid-tight connection between the adapter 18 and the needle 20 when the needle 20 is at least partly inserted into the receiving opening 19 of the adapter 18.

20 The seal 21 is preferably further configured to seal the adapter 18 from the environment when the needle 20 is separated from the adapter 18. The entry of air into the adapter 18 can thus be prevented in a particularly reliable manner in both cases.

25 The measuring arrangement 1 preferably comprises a detection device 22. The detection device 22 is designed in particular to detect whether the injection needle 20 is fluidly connected to the adapter 18 and/or when the injection needle 20 is not connected to the adapter 18 or is disconnected from the adapter 18.

The detection device 22 can be arranged in the area of the receiving opening 19. It is possible that the detection device 22 is mechanically coupled to the adapter 18, as shown in Fig. 1.

30 In particular, the detection device 22 can be designed as a light barrier 23 or can comprise a light barrier 23. Preferably, the light barrier 23 is interrupted when the needle 20 is connected to the adapter 18 in a fluid-tight manner. However, it is also possible for the light barrier 23 to be interrupted when the needle 20 is separated from the adapter 18.

35

Alternatively or additionally, it is also possible that the detection device 22 comprises a pressure sensor and/or pushbutton or the like, or that the detection device 22 is designed as a pressure sensor or pushbutton or the like.

5 The measuring arrangement 1 might comprise a detection unit 22A which is data connected to the detection device 22 for transmitting and/or receiving signals. The connection between the detection device 22 and the detection unit 22A can be wired, in particular realized by means of a cable. Alternatively, it is also possible for the connection between the detection device 22 and the detection unit 22A to be wire-
10 less, for example as a Bluetooth or WIFI.

The detection unit 22A can be data connected to the analysis unit 14 and/or the regulation and control unit 29. The connection can be wireless. Alternatively, it is also possible for the connection between the detection device 22 and the analysis unit 14
15 and/or regulation and control unit 29 to be wireless, for example as a Bluetooth or WIFI connection.

In particular, the detection unit 22A can be a part of the same computer as the analysis unit 14 and/or regulation and control unit 29.
20

In particular, the detection device 22 generates a signal when the needle 20 is connected to the adapter 18, in particular when a, in particular new, sample 2 is being filled into the adapter 18 and thus a new sample 2 is fed into the flow cell 3.

25 The detection device 22 preferably sends the signal to the detection unit 22A that the needle 20 is connected to the adapter 18. Preferably, a date-time associated to the moment when the fluidic sample 2 is injected into the flow cell 3 is then recorded in particular by the detection unit 22A.

30 In particular, the recorded date-time information provided by the detection device 22 and/or detection unit 22A is used to link individual data sets or spectra provided by the analysis unit 14 to individual samples, in particular for associating data sets or spectra to the respective samples, in particular by using data processing and/or code programs. In particular the date time will be recorded for parsing the spectra after all
35 measurements, in particular after completing a measurement run for multiple samples the acquired spectral data will be divided into data sets associated to the individually recorded date times. It is then possible, even for continuous measurements,

to automatically differentiate between data associated to different successive fluidic samples 2. By this a serial measurement of multiple samples 2 can be conducted in an efficient manner.

5 In Fig. 6 to Fig. 8 the flow cell 3 is shown during a measurement. Fig. 6 shows a flow cell 3 prefilled with liquid to keep the flow cell 3 free of air bubbles. Fig. 7 shows the flow cell 3 filled with the fluidic sample 2 and Fig. 8 shows the flow cell 3 filled with the fluidic sample 2, wherein a part of the fluidic sample 2 is pumped backwards.

10 As shown in Fig. 6, the flow cell 3 comprises an input section 6A and an output section 7A. The input section 6A extends preferably along the input axis A. The output section 7A preferably extends along the output axis B.

The input section 6A and the output section 7A are preferably arranged on a radial
15 outer side of the measuring section 8. In this case, the term "radial" refers to the measuring axis C.

The input section 6A preferably comprises an input diameter 6D and the output
20 section 7A an output diameter 7D.

In the context of the present invention, the term "diameter" is to be understood as the maximum extension of the input section 6A and/or the output section 7A perpendicular to the input axis A and/or output axis B.

25 The measuring section 8 preferably comprises a measuring section diameter 8D and a measuring section height 8H.

In the context of the invention, the term "diameter" regarding the measuring section 8 is to be understood as the maximum extension of the measuring section 8
30 perpendicular to the measuring axis C.

In the context of the invention, the term "height" regarding the measuring section 8 is to be understood as the maximum extension of the measuring section 8 along the measuring axis C.

35 The input diameter 6D and/or the output diameter 7D is preferably smaller than the measuring section height 8H.

In particular, the input diameter 6D and the output diameter 7D are at least essentially identical.

5 Further, the input diameter 6D and/or the output diameter 7D is preferably smaller than the measuring section diameter 8D.

10 Preferably the measuring section height 8H corresponds to at least 1,1 times, preferably at least 1,2 times, and/or less than 1,5 times, preferably less than 1,4 times the input diameter 6D and/or the output diameter 7D.

15 The measuring section diameter 8D preferably corresponds to at least 4 times, preferably at least 4,6 times, more preferably at least 5,2 times, and/or less than 6,6 times, preferably less than 6 times, more preferably less than 5,4 times, the measuring section height 8H.

20 In particular, the measuring section diameter 8D corresponds to at least 2 times, preferably at least 2,4 times, more preferably at least 2,8 times, and/or less than 4 times, preferably less than 3,5 times, more preferably less than 3,1 times, the input diameter 6D and/or the output diameter 7D.

25 The input section 6A and/or the output section 7A in particular comprise/s a length of approx. 14,35 mm. The input diameter 6D and/or the output diameter 7D can be approx. 0,79 mm. The measuring section diameter 8D is approx. 5,3 mm. The measuring section height 8H can be approx. 1 mm.

30 Before a sample 2 is measured and/or analyzed, the flow cell 3 and the adapter 18 as well as the connection, in particular the tube T, between the flow cell 3 and the adapter 18 can be prefilled with purified water 24. Preferably, there are no gas bubbles in the flow cell 3. In particular, the purified water 24 does not contain gas bubbles.

35 It is also possible that the flow cell 3, the adapter 18 as well as the connection, in particular the tube T, between the flow cell 3 and the adapter 18 are filled with air or another gas.

The measurement and/or analysis can be started by a user input. To do this, the regulation and control unit 29, the detection unit 22A, the control unit 16A of the pumping device 16 and the analysis unit 14 can be started, in particular, together through a user input and/or command.

5

The needle 20 or at least a part of the needle 20 can enter into the adapter 18 or can be connected to the adapter 18, creating a fluid-tight connection between the needle 20 and the adapter 18. The light barrier 23 is preferably broken by the needle 20 whereby the detection device 22 recognizes that the needle 20 is connected to the adapter 18 in a fluid-tight manner. In particular, the detection device 22 sends a corresponding signal to the detection unit which can automatically record the exact date time when the light barrier 23 is broken by the needle 20. As can be seen in the schematical measurement arrangement as shown in Fig. 1, the light barrier can be arranged in such a way that the needle 20, in particular on its way downwards for entering the adapter 18, passes the light barrier 23 before the tip of the needle 20 enters the adapter 18 and/or before the needle 20 is connected to the adapter. Although such an arrangement of the light barrier 23 at a set distance to the receiving opening 19 of the adapter 18. results in recording a date time slightly earlier than the (full) insertion of the needle 20 in the adapter 18, the recorded date time forms an individual time stamp associated with the connection of the needle 20 to the adapter 18 and thus with the measurement of the fluidic sample 2 the needle 20 dispenses into the adapter 18.

25

If the pumping device 16 is connected to the flow cell 3, for example via the injection needle 20 and the adapter 18 as shown in Fig. 1, the fluidic sample 2 can be passed through the flow cell 3.

30

The pumping device 16 can fill the fluidic sample 2 or a defined volume of the fluidic sample 2 into the adapter 18, whereby the fluid sample 2 is preferably conveyed/fed into the flow cell 3. At least a part of the sample 2 is preferably conveyed through the measuring cell 3. The sample 2 can enter the measuring section 8 via the input 6 and be discharged from the measuring section 8 via the output 7.

35

Preferably, the defined volume of the fluidic sample is in the range of 40 μ L to 2mL, in particular in the range of 300 μ L and 1000 μ L.

First, the pumping device 16 can inject the entire volume of the fluidic sample 2 into the adapter 18. As a result, the fluidic sample 2 is pumped/moved forwards - in particular from bottom to top – in the main flow direction MF through the flow cell 3 as indicated by arrow X in Fig. 7. While the fluidic sample 2 is being conveyed and/or
5 fed through the flow cell 3, the fluidic sample 2 can be measured and/or analyzed by interaction with the electromagnetic radiation.

The fluidic sample 2 can flow through the flow cell 3 from bottom to top, as described above. In particular, the sample 2 is fed through the flow cell 3 by means of the
10 pumping device 16.

The sample 2 can form an at least essentially laminar flow within the flow cell 3, the tube T and/or the Adapter 18, the input 6, the measuring section 8 and/or the output 7. It is also possible that the sample 2 forms a turbulent flow at least within a section
15 of the flow cell 3.

As Fig. 1 shows, the pumping device 16 can have a reciprocating piston system 30 for pumping the sample 2. The piston can be moved at a constant or variable velocity and/or a constant or variable acceleration in order to pump the sample 2 through the
20 flow cell 3.

The volume of the fluidic sample 2 should be larger than the dead volume of the measuring arrangement 1.

25 The term “dead volume” is preferably to be understood as the, preferably internal, volume of the flow cell 3, the adapter 18 and the tube T.

Preferably, the volume of the fluidic sample 2 corresponds to at least 1,5 times, preferably at least 2 times, more preferably at least 3 times, the dead volume. In particular preferable, the volume of the fluidic sample 2 corresponds to less than 10 times
30 or at most 10 times the dead volume.

Alternatively or additionally, the volume of the fluidic sample 2 corresponds to at least 3 times, preferably at least 4 times, more preferably at least 6 times, the volume of
35 the flow cell 3. In particular preferable, the volume of the flow cell 3 is about half the volume of the dead volume.

In particular, the pumping device 16 is configured to pump the fluidic sample 2 forwards through the flow cell 3 during the measurement and/or analysis of the fluidic sample 2.

5 The sample 2 is preferably pumped through the flow cell 3 at a constant velocity/speed.

10 In particular, turbulences associated with flow acceleration and/or velocity changes should be avoided or minimized. When an overall constant flow through the flow cell 3 in the overall run time of the experiment is not possible – in particular in view of the predefined number of forward and back pumping steps handled by the automatic pipetting device and/or the pumping device 16 – the flow's velocity profile for each individual fluidic sample 2 should preferably comprise a time interval wherein the flow through the flow cell 3 has a constant velocity.

15 A particularly uniform flow behavior of the liquid sample 2 in the flow cell 3 can be achieved when the residence time is greater than one second.

20 The term "residence time" according to the invention is preferably to be understood as the time required to convey and/or pump the volume of a single fluidic sample 2 which is pumped, in particular unidirectionally and/or in one direction, and/or introduced into the adapter 18. In particular, the residence time corresponds to the time during which there is any unidirectional flow of fluidic sample 2 between the needle 20 and the flow cell 3 or vice versa, preferably to the time span within which the
25 needle 20 (eventually) dispenses fluidic sample 2 into the adapter 18 and/or aspirates fluidic sample 2 from the adapter 18. Without any backwards pumping, the residence time would correspond to the time the fluidic sample 2 is pumped unidirectionally into the adapter 18.

30 With forwards and backwards pumping, the residence time is to be understood as the time required to pump the fluidic sample 2 unidirectionally backwards or forwards. The term "unidirectionally and/or in one direction" is preferably to be understood as meaning that the fluidic sample 2 is pumped from the adapter 18 towards the flow cell 3 or from the flow cell 3 towards the adapter 18.

35 To determine a residence time for unidirectional pumping, the volume of the fluidic sample 2 to be pumped in one direction is divided by the volumetric pumping speed

at which the fluidic sample 2 is pumped by the pumping device 16 in that particular direction.

5 In the context of the invention, the term "volume of the fluidic sample" preferably refers to the volume of a single fluidic sample 2 that is to be pumped in one direction, in particular the volume of the sample 2 which is aspirated and/or dispensed by the needle 20 and/or pumped by the pumping device 16.

10 In particular, when a single fluidic sample 2 is (eventually completely) dispensed into the adapter 18, the residence time is the time required to dispense the whole fluidic sample 2 into the adapter 18.

15 When the fluidic sample 2 is pumped backwards, the residence time is the time required to pump the amount of the fluidic sample 2 to be pumped backwards, in particular in the direction from the flow cell 3 to the adapter 18.

20 When the fluidic sample 2 is pumped forwards after a backwards pumping step/process, the residence time is the time required to pump the amount of the fluidic sample 2 to be pumped forwards, in particular in the direction from the adapter 18 to the flow cell 3.

25 In particular, the residence time is greater than 1 second, preferably greater than 1,5 seconds, more preferably greater than 2 seconds, and/or less than 6 seconds, preferably less than 5 seconds, more preferably less than 4 seconds. The residence time is preferably at least essentially 3 seconds.

30 With appropriate residence times, the introducing and/or mixing of gas bubbles in the flow cell 3 and/or the fluidic sample 2 can be avoided. In this way, the susceptibility to errors in the measurement can be further reduced. In particular, "clean" and/or correct spectra and/or Raman scattering intensities can be determined in this way.

35 If the residence times are too low, there is a risk of air entering and/or mixing in the flow cell 3 and/or the fluidic sample 2, which can cause the measurement to fail. On the other hand, the residence time effects the process and/or measurement time, in particular a high residence time would result in comparatively long process and/or measurement time. Furthermore, if the residence times are too high, the flow of the fluid sample might falter, in particular there might be a risk of standstill in the

measurement arrangement, resulting not only in an inefficient measurement but also in difficulties regarding the non-readiness of the system for consecutive measurements and for the maintenance of the measurement arrangement

5 The average flow velocity of the sample 2 in regard to the smallest cross-section of the flow cell 3 can be less than 700 mm/s, preferably less than 650 mm/s, more preferably less than 620 mm/s, and/or in particular at least essentially 612 mm/s, in relation to the smallest cross-section of the inlet 6 and/or outlet 7 of the flow cell 3. The flow velocity of the sample 2 can be more than 200 mm/s, preferably more than
10 300 mm/s, more preferably more than 400 mm/s in relation to the smallest cross section of the inlet 6 and/or the outlet 7.

If the sample 2 has been completely injected into the adapter 18, the area or section of the sample 2 furthest downstream in the flow direction, as shown by arrow X, is
15 behind the measuring section 8, in particular in the following tube T1. The sample 2 preferably extends over the, in particular entire, flow cell 3 and/or a buffer section 25, which adjoins the measuring section 8 and/or the output section 7A, as shown in Fig. 7.

20 The flow cell 3 is then preferably filled with the sample 2. The buffer section 25 adjoining the flow cell 3, in particular the output section 7A, is also filled with the fluidic sample 2.

In particular, the pumping device 16 is configured to pump the fluidic sample 2 forwards and backwards through the flow cell 3 during the measurement and/or analysis
25 of the fluidic sample 2.

A part of the fluidic sample 2 can be returned from the flow cell 3 by the pumping device 16. In particular, the pumping device 16 with the needle 20 is configured to
30 aspirate and to dispense fluidic samples 2. The aspiration function of the pumping device 16 is preferably used for sucking part of the formerly dispensed fluidic sample 2 back into the needle 20. For the return of part of the already dispensed fluid, for example, an underpressure is generated and/or the piston of the reciprocating piston system 30 is retracted within the pumping device 16. The fluidic sample 2 is then
35 conveyed and/or pumped backwards – in particular from top to bottom - opposite to the main flow direction MF through the flow cell 3 as indicated by arrow Y in Fig. 8.

While the fluidic sample 2 is being conveyed and/or fed backwards through the flow cell 3, the fluidic sample 2 can (also) be measured and/or analyzed.

5 In the context of the invention, the time span during which the fluidic sample 2 is pumped backwards is the residence time. For the determination of the residence time associated with the backwards pumping, the volume of the part of the fluidic sample 2 that is pumped backwards, in particular the volume of the part of the fluidic sample 2 which is aspirated by the needle 20 and/or pumped by the pumping device 16, is divided by the volumetric pumping speed at which the fluidic sample 2 is
10 pumped by the pumping device 16 and/or aspirated by the needle 20.

Preferably, the backwards pumping of the fluidic sample 2 follows immediately after the forwards pumping of the sample 2. In particular, there is no pause between the forwards and backwards pumping and vice versa. In this way, the time during which
15 the sample 2 flows laminarly and/or uniformly through the flow cell 3 can be maximized.

Fig. 8 shows the flow cell 3 with returned sample 2 after moving a part of the sample 2 backwards through the flow cell 3. The sample 2 preferably extends over the, in particular entire, flow cell 3 and/or a second buffer section 26 that adjoins at least the measuring section 8 and/or the output section 7A, as shown in Fig. 8. The second buffer section 26 is shorter than the buffer section 25 in main flow direction MF as shown in Fig. 7.

25 The flow cell 3 is then preferably filled with the sample 2. The second buffer section 26 adjoining the flow cell 3, in particular the output section 7A, is also filled with the fluidic sample 2.

30 Preferably less than 80%, more preferably less than 70%, in particular at least essentially 50%, of the volume of the sample 2 is pumped or conveyed backwards through the flow cell 3.

The retracted/reconveyed part of the fluidic sample 2 can then be conveyed/pumped forwards through the flow cell 3 again. The backward and subsequent forward movement of the part of the fluidic sample 2 can be repeated as often as required to
35 achieve a measurement or analysis with a high or sufficient quality.

To determine (again) the residence time when in the context of the invention the fluidic sample 2 is pumped forwards after a backwards pumping step and/or process, the volume of the fluidic sample 2 that is pumped forwards, in particular the volume which is dispensed by the needle 20 and/or the pumping device 16, is divided by the volumetric pumping speed at which the fluidic sample 2 is pumped by the pumping device 16 and/or dispensed by the needle 20.

Preferably, the volume of the fluidic sample 2 that is pumped forward first is greater than the volumes of fluidic sample 2 that are respectively pumped in the following backwards or forwards pumping/movements.

Optionally, the residence time of a new fluidic sample 2 that is first introduced into the adapter 18, in particular the time span associated to the first forward flow, can be equivalent to the residence time of a subsequent back-pumping of the part of the fluidic sample 2. Preferably, the residence time associated with each successive backwards and forwards pumping of a part of the fluidic sample 2 (after the first part of the fluidic sample 2 has been dispensed by the needle 20) are of the same or similar duration.

Preferably, the residence time of a new fluidic sample 2 that is first introduced into the adapter 18, in particular the time span associated to the first forward flow, is the same as the residence time of a subsequent back-pumping or of a subsequent forward-pumping of the part of the fluidic sample 2.

Preferably, the relation between the adapter 18 and the inlet 6 of the flow cell 3 remains unchanged during a measurement of a sample. The term "relation" in this case refers to the connection between the adapter 18 and the inlet 6 of the flow cell 3, in particular to the fact that the internal volume between the adapter 18 and the inlet 6 of the flow cell 3, in particular the internal volume of the adapter 18 and the tube T, is constant and/or remains unchanged.

Preferably, the pumping flowrate for the following backwards or forwards pumping/movement has a magnitude of the first forward flowrate, in particular of the flowrate with which a new fluidic sample 2 is first introduced into the adapter 18, multiplied by the proportion of the volume of the fluidic sample 2 which is pumped forwards or backwards. When 50% of the initial volume of the fluidic sample is pumped backwards, the pumping flowrate of the backwards movement preferably

corresponds to 50 % of the flowrate of the new fluidic sample 2 which was first introduced into the adapter 18.

5 Preferably, the residence time of a new fluidic sample 2 that is first introduced into the adapter 18 is at least essentially equal to the residence time of a subsequent backwards pumping/movement of the part of the fluidic sample 2 and also at least essentially equal to the residence time of a subsequent forwards pumping/movement of the part of the fluidic sample 2.

10 The fluidic sample 2 or a part of the fluidic sample 2 can be pumped forwards and backwards more than 10 times, preferably more than 20 times, more preferably than 30 times. Additionally or alternatively, the fluidic sample 2 or the part of the sample 2 can be pumped forwards and backwards less than 200 times, preferably less than 150 times, more preferably less than 110 times. It is also possible that the fluidic
15 sample 2 or a part of the fluidic sample 2 is pumped forwards and backwards between 40 times and 100 times.

The fluidic sample 2 does not have to be fed continuously in one direction, in particular the forward direction, through the flow cell 3. The sample 2 can be moved forwards and backwards through the flow cell 3 and thus, a small sample volume can be measured with a longer measurement duration without exposing sensitive molecules, in particular protein molecules, of the fluidic too long to the electromagnetic radiation 4, in particular thus a "burning" of the protein samples can be avoided. Otherwise, if the molecules/proteins were exposed to the electromagnetic radiation 4 too
20 long, the fluidic sample 2 or biological molecules/proteins could be damaged by the energy or heat introduced by the electromagnetic radiation 4. Furthermore, by thus lengthening the possible measurement time for a fluidic sample 2 by moving the sample 2 forwards and backwards through the flow cell 3, the required amount of the sample 2 can be reduced, in particular without a loss of quality for the measurement
25 data. It is possible in this way to reduce the amount of sample 2 required, which can save costs.

The (overall) amount of fluidic sample 2 required for analysis can be reduced by moving the sample 2 forwards and backwards. By pumping forwards and backwards,
30 part of the fluidic sample 2 is continuously pumped through the flow cell 3 and measured and/or analyzed. Compared to a measurement in which the fluidic sample 2 is continuously pumped forwards at the same volumetric dispensing speed, a

significantly smaller sample quantity is therefore required. Forward and backward pumping can therefore lead to cost savings, especially with cost-intensive samples. There is also no need to store and/or provide large quantities of fluidic samples 2. The analysis can therefore be carried out in a particularly simple and cost-effective manner.

The measurement and/or analysis can also be conducted while the fluidic sample 2 is being pumped forwards and backwards. By means of the measurement and/or analysis, it can be recognized whether there are sufficiently few gas bubbles in the measuring section 8 to be able to carry out a sufficiently correct measurement and/or analysis.

In addition, gas bubbles contained in the flow cell 3 can be easily and efficiently removed from the measuring section 8 by directing the flow of the fluidic sample 2 through the flow cell 3 from bottom to top, in particular contrary to the force of gravity. If there are gas bubbles in the sample 2 and/or the measuring section 8, these can negatively influence the analysis of the sample 2. The gas bubbles can accumulate in the area of the output 7, as described above. The gas bubbles can be guided out of the measuring section 8 via the output 7. In this way, gas bubbles can be discharged from the measuring section 8 until there are sufficiently few gas bubbles in the measuring section 8 to be able to carry out a correct analysis and/or measurement of the sample 2.

By pumping the fluidic sample 2 forwards and backwards, the retention time of the fluidic sample 2 in the measuring flow cell 3, in particular in the measuring section 8, can be prolonged as described above.

In the production of pharmaceuticals, especially in purification and/or downstream processes, moving proteins, molecules and/or fluids can be passed through filters at predetermined flow rates. By pumping backwards and forwards, the inline measurement can be carried out in the flow cell 3 under a flow condition comparable to the flow condition in the purification and/or downstream process. In this way, the results determined using the measuring arrangement 1 can be transferred to purification and/or downstream processes. In this way, the measurement data obtained with the measuring arrangement 1 with flow cell 3 are better comparable with the purification and downstream processes. At the same time, the measurement data can be particularly reproducible.

The directional change between a forward and backward flow of the fluidic sample 2 is preferably conducted quickly. Preferably, a forward movement of the fluidic sample 2 immediately follows a backward movement and vice versa. In this way, the time of constant flow within the flow cell 3 can be maximized.

The method for measuring/analyzing the sample 2 is described below in detail with reference to the first embodiment, Fig. 1, Fig. 6 and Fig. 8.

As mentioned above, the measuring arrangement 1 can comprise a pumping device 16, in particular a fluent liquid handling system, preferably an automatic pipetting device 17.

The pumping device 16, in particular the fluent liquid handling system or automatic pipetting device 17, preferably comprises at least one reservoir 27, preferably for providing a systemic liquid, in particular water, preferably purified water 24, in particular for backing up the pressures and/or volumetric dispensing speeds generated by the pumping device 16, thus enabling a good reproducibility for aspirating, dispensing and/or pumping small volumes.

The measuring arrangement 1, preferably comprises at least one sample reservoir or sample well, in particular multiple reservoirs 31. The sample reservoirs 31 are accessible by the needle 20, in particular sample fluid can be withdrawn from the sample reservoirs 31 by the needle 20. In particular, the same needle 20 can fluidically connect to each sample reservoir 31.

In particular, the needle 20 can be moved into a sample reservoir 31 for receiving a fluidic sample 2.

Each sample reservoir 31 can be filled/prefilled with a sample 2. It is possible that the measurements/analyses of the different samples 2 are carried out automatically using the measuring arrangement 1, in particular the fluent liquid handling system or automatic pipetting device 17.

Preferably, the needle 20 can be moved, preferably automatically, from a sampling position to the adapter 18. In particular, the needle 20 receives a fluidic sample 2 by pipetting/drawing in fluid from a sample reservoir 31 in form of a sample well.

Preferably, different fluidic samples 2 to be analyzed are placed in a well plate 32, in particular a 96-well plate 32, wherein different wells, in particular cavities or sample reservoirs 31 can contain the different samples 2. Preferably, the (in particular commercial) liquid handling system, in particular the automatic pipetting device 17 can automatically be positioned for needle sampling at a respective sample well, sample the liquid from the respective sample reservoir 31 and inject the fluidic sample 2 into the adapter 18, one by one. In particular, each sampling can be followed by a through-flow of purified water 24 according to the preferred cleaning/purging method, which is described in the following in detail.

Preferably, and in particular regarding the sampling, it is not necessary to carry out manual operations after entering a start command, in particular via the control unit 16A of the pumping device 16 and/or the regulation and control unit 29 and/or the measuring device 9 and/or the detection unit 22A. All explanations of the method also refer to a method that is at least partially carried out manually.

In particular a start command can be entered in a computer, which is preferably data connected to the pumping device 16 and/or the control unit 16A and/or the regulation and control unit 29 and/or the spectrometer 15 and/or the receiver unit 13 and/or the detection unit 22A and/or the detection device 22 and/or the measuring device 9.

The measurement and/or analysis is/are preferably carried out automatically. The samples 2 can be measured and analyzed one after the other. In particular, the measurement arrangement 1 is configured to yield spectroscopic data/spectra of the flow cell 3 continuously. Preferably, when different fluidic samples 2 are successively injected into the flow cell 3, the moment in time a spectroscopic signal/spectrum is generated is matched to the sample present in the flow cell 3 at that respective moment in time. Alternatively, in particular for a measuring arrangement with a preferably continuous sampling, for instance of liquid derived from a site of a biological, physical and/or chemical reaction, in particular a bioreactor, it is also possible to perform a continuous measurement in which, for example, a reaction is monitored by a continuous measurement.

Preferably a laser is used as the light source 10S and/or emitter 10E. The laser power can be more than 250 mW, preferably more than 300 mW, more preferably more

than 400 mW, and/or less than 1 W, in particular at least essentially 350 mW or 495 mW.

5 The exposure time of the fluidic sample 2 can be more than 200 ms, preferably more than 300 ms, more preferably more than 400 ms, and/or less than 1000 ms, preferably less than 800 ms, in particular at least essentially 500 ms.

10 The fluidic sample 2 can be exposed with at least 5, preferably at least 10, more preferably at least 15, and/or less than 50, preferably less than 40, more preferably less than 30, exposures per scan by the light source 10S, emitter 10E and/or laser. The recorded spectra can then be averaged over the number of exposures.

15 The analysis unit 14 can be used to identify signals associated with particular molecules 11 to be monitored in the sample 2. For example, the frequency shift of a Raman band associated with a known molecule 11 can be compared with the frequency shift of a signal peak detected in the measurement.

20 Optionally, the measurement/analysis can be used to detect whether gas bubbles are contained in the measuring section 8, in particular to check whether the gas bubbles have been removed from the flow cell 3 and/or the measuring section 8. A reliable measurement and/or analysis can then be ensured.

25 For example, it is possible to recognize whether gas bubbles are present in the measuring section 8 of the flow cell 3, in particular based on the measured Raman spectrum or the intensity at a specific frequency shift.

30 In particular, by detecting the presence of air bubbles in the flow cell 3 between successively injected individual fluidic samples 2 consecutive spectral data can be associated more distinctly to the respective fluidic samples 2. It is also possible to determine the flow rate and/or velocity of the sample 2 in the flow cell 3, in particular in the measuring section 8, for carrying out the measurement.

35 After every injection of fluidic sample 2 to be measured, the flow cell 3 can be cleaned/purged. Alternatively, cleaning and purging steps can be repeated or skipped depending on the use-case. The needle 20 can continuously inject fluidic solution, in particular sample 2 or purified water 24, into the adapter 18 for sample measurement or flow cell cleaning/flushing. When an injection of one solution is

ended, the needle 20 can be pulled out of the adapter 18 so that the injection procedure can be continuously repeated as experimental requirement.

A cleaning/purging method of the flow cell 3 is explained in detail below.

5

After a fluidic sample 2 has been measured and/or analyzed, a cleaning/purging method can be carried out.

10

In a first purge/cleaning step, a cleaning fluid, in particular purified water 24, can be passed through the flow cell 3. The purified water 24 is preferably passed/pumped through the flow cell 3 with a first flow rate. The purified water 24 can remove/expel gas bubbles from the flow cell 3, in particular the measuring section 8. The cleaning fluid is conveyed and/or pumped forwards, in particular in the main flow direction MF.

15

In the context of the present invention, the term "large gas bubbles" refers to gas bubbles with a diameter of more than the smallest diameter of the inlet 6 and/or outlet 7 and/or 0,79 mm.

20

In a subsequent, second purge/cleaning step, the cleaning fluid – the purified water 24 – can be passed/pumped through the flow cell 3 with a second flow rate. In this way, small gas bubbles can be expelled/removed from the flow cell 3, in particular from the measuring section 8.

25

In the context of the present invention, the term "small gas bubbles" refers to gas bubbles with a diameter with a diameter less than or equal to the diameter of the inlet 6 and/or outlet 7 and/or of 0,79 mm.

30

Preferably, the amount and/or volume of cleaning fluid used in the first and second step can be identical. It is also possible that the amount of cleaning fluid in the first and second step is different.

35

The volume of the purified water 24 used in the first and/or second step can each be at least 3 times, preferably at least 5 times, more preferably around 10 times of the dead volume of the measuring arrangement 1 and/or wherein the volume of the purified water 24 is less than 100 times, preferably less than 50 times, the dead volume of the measuring arrangement 1.

The volume of the purified water 24 used in the first and/or second step can each be at least 1,5 times, preferably at least 2 times, more preferably at least 3 times and/or wherein the volume of the purified water 24 is less than 100 times, preferably less than 50 times, the volume of the flow cell 3.

5

In particular, the second flow rate is greater than the first flow rate. In this way, it can be ensured that large and small gas bubbles are reliably removed from the flow cell 3.

10

Due to the lower flow rate in the first step, large gas bubbles are removed through the output 7 and effectively discharged from of the measuring section 8. Due to the high flow rate in the second step, small gas bubbles can be removed through the output 7 and effectively discharged from the measuring section 8.

15

In a subsequent, third purge/cleaning step, the cleaning fluid is preferably passed through the flow cell 3, in particular in the main flow direction MF, in order to keep the flow cell 3, in particular the measuring section 8, free of gas bubbles. The cleaning fluid, preferably the purified water 24, can be passed through the flow cell 3 with a third flow rate.

20

The first flow rate is preferably greater than the third flow rate. In particular, the second flow rate is greater than the third flow rate. Due to the lowest flow rate in the third step, the flow cell 3 can be filled with purified water 24, whereby the introduction of gas bubbles into the flow cell 3 can be reliably prevented.

25

The purified water 24 can be passed through the flow cell 3 with a medium flow rate in the first step, with a high flow rate in the second step and/or with a low flow rate in the third step.

30

In the context of the invention, the term "medium flow rate" can be understood as a flow rate which effects that the purified water 24 is present in the flow cell for at least 3 seconds and/or less than 5 seconds, in particular of at least essentially 4 seconds.

35

The flow velocity of the purified water 24 in the first step can be less than 600 mm/s and/or higher than 400 mm/s, in particular at least essentially 510 mm/s, regarding the smallest cross-section of the flow cell 3.

In the context of the invention, the term "high flow rate" can be understood as a flow rate which effects that the purified water 24 is present in the flow cell for at least 1,5 seconds and/or less than 2,5 seconds, in particular of at least essentially 2 seconds.

5 The flow velocity of the purified water 24 in the second step can be less than 1200 mm/s and/or higher than 800 mm/s, in particular at least essentially 1020 mm/s, regarding the smallest cross-section of the flow cell 3.

10 In the context of the invention, the term "slow flow rate" can be understood as a flow rate which effects that the purified water 24 is present in the flow cell for at least 9 seconds and/or less than 11 seconds, in particular of at least essentially 10 seconds.

The flow velocity of the purified water 24 in the first step can be less than 250 mm/s and/or higher than 150 mm/s, in particular at least essentially 204 mm/s, regarding
15 the smallest cross-section of the flow cell 3.

The volume of the purified water 24 used in the third step can be at least 2 times, preferably at least 4 times, the dead volume.

20 After cleaning, the flow cell 3 is preferably filled with purified water 24, which prevents air bubbles from entering the flow cell 3.

The needle 20 can also be cleaned every time a new solution is taken. In this way, the same needle 20 can be used for different samples 2 without contaminating the
25 samples 2.

After cleaning the flow cell 3, a new measurement can be carried out. The needle 20 can be removed from the adapter 18 so that another needle 20 can form a fluid-tight connection with the adapter 18. It is also possible to feed a new sample 2 into the
30 adapter 18 using the same needle 20.

Subsequently, in particular after cleaning the flow cell 3, the measuring arrangement 1 and/or the automatic pipetting device 17 can switch to an idle state.

35 Alternatively, another measurement of at least one sample 2 can be initiated.

After the cleaning/purging process, another fluidic sample 2 can be measured. The alternating measurement of a sample 2 and the cleaning/purging of the measuring arrangement 1 can be repeated several times, in particular more than 10 times, preferably more than 50 times, more preferably more than 100 times.

5

At least one of the method steps regarding the measurement and/or analysis and/or cleaning/purging described above can be carried out by means of a computer. In particular, the analysis unit 14, the control unit of the pumping device 16, the detection unit and/or the regulation and control unit 29 can comprise means for carrying out at least one method step, in particular at least one measuring step and/or analysis step.

10

The computer, the analysis unit 14, the control unit 16A of the pumping device 16, the detection unit 22A and/or the regulation and control unit 29 can comprise at least one data processing device 28 for this purpose. The data processing device 28 can in particular comprise a processor, a data storage medium, an internal and/or external database and/or a communication device for connection to the Internet and/or another computer.

15

Preferably, a computer program can be provided on the data storage medium that comprises instructions which, when the computer program is executed by a computer, cause the computer to execute the at least one method step.

20

In particular, a computer program is provided by which spectral data generated by the measurement are processed. Preferably, this data processing comprises a filtering and/or reduction of background and/or interference signals and/or other means of data preprocessing. The data processing preferably further comprises an enhancement and/or highlighting of spectral characteristics of interest. Particularly preferable, the data processing comprises the application of a frequency domain filter, in particular a Butterworth filter, in particular for noise reduction, and/or baseline removal algorithms, which can be in case of the processing of Raman spectral data, particularly useful for eliminating effects attributed to laser-induced fluorescence.

25

30

In particular, it is possible that the computer program has been designed using machine learning tools and/or comprises machine learning methods or an artificial neural network.

35

Preferable, the computer program or data processing routines are tailored to the recognition of spectral characteristics of a molecule 11 of interest. For this a series of benchmarking experiments with calibration samples containing this molecule of interest in known concentrations has preferably been used as an input for the machine learning and/or artificial neural network. Preferably, the machine learning comprises normalization strategies and/or correction algorithms and/or data driven modelling.

The artificial neural network can be trained with measurement data of calibration samples.

By application of various preprocessing methods, chemometric models and/or machine learning methods to the spectral data, the computer program can preferably identify a spectral characteristic of the molecule 11 of interest (for instance a protein) and quantify and/or give an estimate of the concentration of the protein in the measured sample based on the spectral data.

Fig. 4 shows another embodiment of the measuring arrangement 1. The difference to the embodiment shown in Fig. 1 is that in Fig. 4, a source of sample material, here depicted as a larger reservoir 27 is arranged in fluidic connection and upstream of the flow cell 3. Preferably, this source of sample material or reservoir 27 is configured as a chromatography line, for instance a cation exchange chromatography column or might even be a bioreactor. Thus, fluidic sample 2 can be measured inline in the flow cell 3.

Optionally, a second, in Fig. 4 smaller, reservoir is provided for purified water 24 for purging the flow cell 3 after individual sample measurements, for instance after fluid sample flow from a bioreactor. The reservoirs 24, 27 are preferably connected to the flow cell 3 via a valve V, enabling a selective and/or controlled fluid feed into the flow cell 3. However, in particular for an inline measurement of fluid from a chromatography line the flow cell 3 can also be connected directly to the output of the chromatography line. The embodiment shown in Fig. 4 preferably comprises no needle 20 or pipetting device.

As shown in Fig. 4, the two reservoirs can be connected to the tube T via the valve V. The pumping device 16 can be arranged between the valve V and the flow cell 3. In particular for inline measurements with a chromatography line, it is also possible

to convey the fluid to the flow cell 3 without using an associated pumping device 16, in particular only using the flow forces, like gravity, acting in the chromatography line.

5 During the reaction of the fluidic sample 2 in the bioreactor, a sample 2 can be guided and/or pumped from the, in Fig. 4 the lower, reservoir 27 and/or the bioreactor to be measured in the flow cell 3. After measurement, the flow cell 3 can be cleaned by a purging/cleaning method described above, using the purified water 24 in the second, in Fig. 4 the upper reservoir 27.

10 Fig. 5 shows another embodiment of the measuring arrangement 1. The difference to the embodiments shown in Fig. 1 and Fig. 4 is that only a part of the liquid sample 2 is passed through the flow cell 3. Thus, the measurement can be conducted inline in processes with larger volume flows and/or higher volume throughputs.

15 The flow cell 3 can be designed as a bypass to the conveying device 5 as shown in Fig. 5. The conveying device 5 can be a pipe P. Part of the fluid that flows through the conveying device 5 can be directed through the flow cell 3 as a bypass flow. The part of the fluid that flows through the flow cell 3 and/or the bypass flow can provide the fluidic sample 2.

20 The liquid sample 2 can be measured permanently. It is also possible to measure the liquid sample 2 at specific, predefined time intervals. For example, a measurement can be carried out for example every 7 seconds. In this way, a process can be monitored.

25 Preferably, in the embodiment shown in Fig. 5, the sample 2 is only conveyed and/or pumped forwards through the flow cell 3 along the main flow direction MF. However, it is also possible for the sample 2 to be pumped forwards and backwards through the flow cell 3 with a corresponding valve and/or pump arrangement.

30 Fig. 9 shows a Raman spectrum in form of a diagram in which the Raman counts are shown over the frequency shifts or Raman shifts.

35 The term "Raman counts" is preferably to be understood as the intensity of inelastically scattered light, in particular a number, correlated to detected inelastic scatterings I.

Thus, Fig. 9 shows the intensity of inelastically scattered light, in particular a number, correlated to detected inelastic scatterings I, over the frequency shifts or Raman shift.

5 The spectrum was generated for a test set-up in which the flow cell was filled with either water or air respectively. The intensity is shown on the y-axis, while the frequency shift on the x-axis. The dark black line D indicates the Raman spectrum for the flow cell filled with water. The light black line L indicates the Raman spectrum for the empty flow cell, in particular for the flow-cell filled with air. It can be seen how the spectral shifts which are characteristic for liquid water, notably the peak at 1645 cm⁻¹, in particular the Raman spectrum of water, is superimposed on a spectrum which is characteristic for the particular set-up used for this measurement.

Fig. 9 shows spectra measured for a flow cell 3 filled with water or air, wherein a measuring arrangement 1 with a probe 10 comprising a lens 10A2 made of sapphire was used. The thus obtained spectra for water and air both comprise a narrow peak at a frequency shift of approximately 418 cm⁻¹ which is identified a specific peak of sapphire. As the lens 10A2 of the Raman probe 10 is made of sapphire material, sapphire peaks can also be detected when the flow cell 3 is empty or full of air. However, when the flow cell 3 is filled with fluid, water in this case, the Raman signals corresponding to the fluid are superimposed on the peaks and/or signals corresponding to the measurement arrangement itself, in particular to the sapphire lens 10A2 in this case. According to such overlay effects, the intensity of the sapphire peak is higher for a water-filled flow cell 3 than for an empty flow cell 3. Accordingly, the intensity of the sapphire peak decreases when air enters the fluid filled flow cell 3. 20 When the Raman device is set at a standard parameter combination, where the laser power is set at 495 mW, exposure time at 500 ms, the number of Raman counts of air is only in the range of approx. 5800 at 418 cm⁻¹, while the spectrum obtained for water comprises a number of Raman counts of approx. 12700.

30 If a measurement is carried out, a count value of approx. 12700 at a frequency shift of 418 cm⁻¹ means that water, in particular water without gas bubbles, has been analyzed. If count values are clearly lower than 12700, a water-air mixture, in particular water with air bubbles, has been analyzed. If a count value of 5800 is measured, only air was analyzed.

35

Thus, the presence of specific system characteristic peaks can be used for an indicator of the presence of air, in particular in form of bubbles, in a set-up for testing aqueous liquids.

5 Fig. 10 shows a diagram of a continuous measurement of water with the same set-up, where only the frequency shift of 418 cm^{-1} is considered. The term "single Raman counts" on the y-axis marks that only the Raman counts for a single frequency have been evaluated.

10 At the beginning of the measurement, the intensity, in particular the number of Raman counts, is approx. 5800. In conjunction with Fig. 9, it can therefore be concluded that air bubbles are in the flow cell 3, in particular that the flow cell 3 only contained air. In particular, it can be seen that the measurement only detected air.

15 The cleaning/purging method described above is started at time t_1 . As Fig. 10 shows, the intensity during the measurement increases within a short time and reaches an intensity of approx. 12800 at time t_2 . Water is full of the flow cell 3 and measured and/or analyzed from time t_2 . As Fig. 10 shows, the air and/or air bubbles could thus be efficiently removed from the flow cell 3 in a particularly short time using the cleaning/purging method.
20

The time between t_1 and t_2 is in the present case preferably less than 2 minutes, further preferably less than 1,5 minutes, more preferably less than 1 minute, in particular at least essentially 40 seconds.

25 By means of a corresponding measurement, it is thus possible to check whether there is air in the flow cell 3 and/or whether a cleaning/purging cycle is necessary. In addition, it is also possible to check whether the cleaning/purging cycle has removed the air bubbles from the flow cell 3.

30 Fig. 11 shows the Raman response of a series of fluidic samples 2, in particular fractions and re-mixed fractions taken from a chromatography run of an overall sample containing proteins, wherein the detection of Raman scattered light was carried out with a measuring arrangement 1 according to the invention. The average Raman count or the intensity of Raman scattered light summed up for all frequency shifts is shown over a run time of the experiment.
35

For these measurements and/or for this experiment, an overall fluidic sample 2 containing proteins has been processed in a chromatography run and thereby divided into fractions corresponding to a successive chromatography steps. For this experiment as referred to here, the fractions taken from a chromatography run have been
5 used not only for individual fluidic samples 2, but also for the generation of other individual fluid samples 2 produced by re-mixing of fluids of two neighboring fractions according to different ratios.

The fluidic samples 2 to be analyzed have been placed in a 96-well plate 32 for
10 needle sampling. A commercial fluent liquid handling system, preferably a robotic workstation for liquid handling, in particular a pipettor and/or an automatic pipetting device 17, has been used for needle sampling and injecting the fluidic samples 2 into the flow cell 3, one by one.

Each sample measurement last for a certain pre-defined duration, followed by the
15 described cleaning/purging method with purified water 24. Accordingly, the run time of the experiment shown in Fig. 11 comprises for each individual sample, the time the robotic workstation requires for the handling of an individual sample, the measurement time and the time allowed for cleaning/purging after each measurement and
20 the overall run time of the experiment is limited by the number of individual samples to be tested.

As the curve in Fig. 11 shows, a large number of fluidic samples 2, in particular 183
25 samples, which have been measured with a Raman spectrometer over a run time of 14 hours in total. During this run time the automatic pipetting device 17 automatically injected the individual fluidic samples 2, in particular via adapter 18 and tubes T of the measuring arrangement 1, into the flow cell 3 with a cleaning/purging step following each injection and Raman spectra of the flow cell 3 were continuously recorded.

30 As these individual fluidic samples 2 contain different compositions, in particular different concentrations of a varying mixture, of proteins, the Raman response varies from each sample to another sample which is why different intensities of Raman scattered light are measured over time.

35 Fig. 12 shows the Raman response for a very similar experiment which was conducted using the previous prototype of the measurement arrangement. Herein the individual samples were taken from an identically conducted chromatography run

and were measured in the same order in a similar set-up. In the earlier prototype and/or method, the flow cell 3 was not arranged vertically but horizontally. In addition, the residence time was shorter and was essentially 2,5 seconds. Further, the earlier prototype and/or method did not comprise forwards and backwards pumping of the fluidic sample 2 during the measurement. Furthermore, in the earlier prototype and/or method, no three-stage cleaning/purging process was carried out. The flow cell was simply flushed and/or cleaned with purified water 24 in a single cleaning/flushing step.

10 The earlier method had a lower quality of individual Raman spectra and therefore led to a higher demand for data points, which in turn resulted in a longer runtime for the overall experiment, in particular 25 hours.

15 After approx. 9,5 h after the start of the measurement, there is a sudden increase in the average Raman intensity across all frequency shifts as shown in Fig. 12. As corresponding investigations have shown, this increase can be explained by the fact that a small piece of plastic from the prototype adapter has flowed and stuck in the flow cell 3. Even flushing with purified water 24 between the measurements, the stuck plastic could not be removed from the flow cell 3 without disassembling the flow cell.

20 The in-house made prototype takes a very long time to make and test before it could be applied for measurement but was not stable enough to be used for more than 80 measurements.

25 Repeating the measurement is time-consuming and cost-intensive, in particular waste of materials. For example, intensive processes have to be conducted to produce enough samples 2, wasting a lot of materials and gaining extra lab-work.

Fig. 11 shows a Raman detection of the same (reproduced) sample 2, which has been carried out with the proposed measuring arrangement 1. The proposed purging/cleaning method and the vertical arrangement of the flow cell 3 have been performed to avoid any kinds of air bubbles. Further the fluidic samples 2 were pumped forwards and backwards during the measurement. The proposed measuring arrangement 1 has been tested to be stable for more than 800 times measurements.

35 As shown in Fig. 11, all the measurements were carried out without any error. In particular, no air bubble and no plastics was found in the flow cell 3, whereby the measurement was not negatively influenced.

The comparison of the diagram shown in Fig. 11 and the diagram shown in Fig. 12 shows the improvements that are possible with the proposed measuring arrangement 1 and/or the proposed method.

5

The improvements can be achieved by the purging/cleaning method, the adapted residence time, the vertical arrangement of the flow cell 3 with the bottom-up-flow, the forwards and backwards pumping during the measurement and/or the adapted design of the adapter 18.

10

The vertical arrangement of the flow cell 3 with the bottom-up-flow can provide approx. 40 % of the overall improvement.

The purging/cleaning method can provide approx. 35 % of the overall improvements.

15

The adapted residence time can provide approx. 20 % of the overall improvements.

The adapted design of the adapter 18 can provide approx. 5 % of the overall improvements.

Reference Symbol List:

1	Measuring arrangement	20	Injection needle
2	Fluidic sample	21	Seal
3	Flow cell	22	Detection device
4	Electromagnetic radiation	22A	Detection unit
5	Conveying device	23	Light barrier
6	Input/inlet	24	Purified water
6A	Input Section	25	Buffer section
6D	Input diameter	26	Buffer section
7	Output/outlet	27	Reservoir (systemic liquid)
7A	Output section	28	Data processing device
7D	Output diameter	29	Regulation and control unit
8	Measuring section	30	Reciprocating piston system
8D	Measuring section diameter	31	Reservoir (sample)
8H	Measuring section height	32	Well plate
9	Measuring device		
10	Probe	A	Input axis
10A	Lens	B	Output axis
10A1	Lens	BS	Beam splitter
10A2	Lens	C	Measuring axis
10A3	Lens	D	Line
10A4	Lens	E	Elastic scattering
10A5	Lens	F	Filter
10B	light guide	I	Inelastic scattering
10E	emitter	L	Line
10S	light source	ME	Main emitting direction
11	Molecule	MF	Main flow direction
13	Receiver unit	MM	Main measuring direction
14	Analysis unit	O	Waste outlet
15	Spectrometer	P	Pipe
16	Pumping device	t1, t2	Time
16A	Control Unit	T, T1	Tube
17	Automatic pipetting device	V	Valve
18	Adapter	X	Arrow
19	Receiving opening	Y	Arrow

Claims:

1. Measuring arrangement for analyzing a fluidic sample (2) by means of electro-
magnetic radiation (4),
5 with a flow cell (3), and
a pumping device (16) for pumping the fluidic sample (2) through the flow cell (3)
10 **characterized in**
that the flow cell (3) comprises a measuring section (8), wherein the measuring section (8) is at least essentially disc-shaped or designed as a hollow cylinder, wherein the flow cell (3) is arranged such that the fluidic sample (2) flows through the flow cell
15 (3) from bottom to top to prevent or reduce gas bubbles in the flow cell (3), and/or
that the residence time in which the fluidic sample (2) is pumped is greater than 1 second, and/or
20 that the inlet of the flow cell (3) is fluidly connected to an adapter (18) for receiving the fluidic sample (2), wherein the pumping device (16) comprises an injection needle (20) for injecting the fluidic sample (2) into the adapter (18), and wherein the measuring arrangement (1) comprises a detection device (22) which is designed to detect when the injection needle (20) is fluidly coupled to the adapter (18) and when not.
25
2. Measuring arrangement according to claim 1, characterized in that the flow cell (3) is arranged in such a way that the fluidic sample (2) flows through the flow cell (3) at an angle to the vertical, the angle being less than or at least essentially equal to 33°, preferable less than 20°, more preferable less than 15°, in particular that the
30 flow cell (3) is arranged at least essentially vertically.
3. Measuring arrangement according to claim 1 or 2, characterized in that the measuring arrangement (1) is adapted to pump the fluidic sample (2) forwards and backwards through the flow cell (3) during the measurement of the fluidic sample (2),
35 and/or
that the measuring arrangement (1) comprises a computer which is configured to control the pumping device (16) in such a way that the fluidic sample (2) is pumped forwards and backwards through the flow cell (3) during the measurement of the
40 fluidic sample (2).

4. Measuring arrangement according to one of the proceeding claims, characterized in that the measuring arrangement (1) comprises an emitter (10E) for emitting electromagnetic radiation (4) and a receiver unit (13) for receiving and/or collecting electromagnetic radiation (4), wherein the emitter (10E) and/or the receiver unit (13) is arranged and/or designed in such a way that the electromagnetic radiation (4) emitted by the emitter (10E) and/or received and/or collected by the receiver unit (13) is aligned transversely, in particular perpendicularly, to the flow of the fluidic sample (2) through the flow cell (3).
5. Measuring arrangement according to one of the proceeding claims, characterized in that the measuring device (9) comprises a spectrometer (15), in particular a Raman spectrometer.
6. Measuring arrangement according to one of the proceeding claims, characterized in that the residence time in which the fluidic sample (2) is pumped is greater than 1,5 seconds, preferably greater than 2 seconds and/or less than 5 seconds, preferably less than 4 seconds, and/or preferably at least essentially 3 seconds.
7. Measuring arrangement according to one of the proceeding claims, characterized in that the volume of the fluidic sample (2) corresponds to at least 2 times, preferably at least 3 times, more preferably at least 5 times the dead volume of the measuring arrangement (1), and/or that the volume of the fluidic sample (2) corresponds to at least 2 times, preferably at least 3 times, more preferably at least 5 times the volume of the flow cell (3).
8. Measuring arrangement according to one of the proceeding claims, characterized in that the pumping device (16) is a pipettor or an automatic pipetting device (17).
9. Measuring arrangement according to one of the proceeding claims, characterized in that the pumping device (16) is designed to fluidly connect the injection needle (20) to the adapter (18) and/or to disconnect a fluidic connection between the injection needle (20) and the adapter (18).
10. Measuring arrangement according to one of the proceeding claims, characterized in that the detection device (22) comprises a light barrier (23).

11. Measuring arrangement according to one of the proceeding claims, characterized in that the measuring arrangement (1) is configured to clean and/or purge the flow cell (3) after the fluidic sample (2) has been analyzed and/or between two measurements, preferably wherein the cleaning and/or purging comprises three cleaning and/or purging steps.

12. Method for analyzing a fluidic sample (2) by means of a measuring arrangement (1), in particular according to one of the proceeding claims,
wherein the measuring arrangement (1) comprises a flow cell (3) and a pumping device (16) for pumping the fluidic sample (2) through the flow cell (3),

characterized in

that the flow cell (3) comprises a measuring section (8), wherein the measuring section (8) is at least essentially disc-shaped or designed as a hollow cylinder and wherein the fluidic sample (2) flows through the flow cell (3) bottom to top to prevent or reduce gas bubbles in the flow cell (3), and/or

that the residence time in which the fluidic sample (2) is pumped is greater than 1 second, and/or

that the measuring arrangement (1) injects the fluidic sample (2) via a needle (20) into an adapter (18) which is connected to the flow cell (3), wherein it is detected when the injection needle (20) is fluidly coupled to the adapter (18) and when not, and/or

that the flow cell (3) is purged and/or cleaned after the fluidic sample (2) has been analyzed, wherein the purging and/or cleaning of the flow cell (3) comprises at least the following steps,

wherein in a first step a cleaning fluid is passed through the flow cell (3) with a first flow rate to expel large gas bubbles from the flow cell (3),

wherein in a second step the cleaning fluid is passed through the flow cell (3) with a second flow rate to expel small gas bubbles from the flow cell (3),

wherein in a third step the cleaning fluid is passed through the flow cell (3) with a third flow rate to keep the flow cell (3) free of gas bubbles.

13. Method according to claim 12, characterized in that the fluidic sample (2) is pumped forwards and backwards through the flow cell (3) during the measurement.

14. Method according to claim 13, characterized in that the fluidic sample (2) or a part of the fluidic sample (2) is pumped forwards and backwards more than 10 times, preferably more than 20 times, preferably more than 30 times, and/or less than 200
5 times, preferably less than 150 times, preferably less than 100 times, and/or preferably between 40 and 100 times.

15. Method according to one of claims 12 to 14, characterized in that the fluidic sample (2) flows through the flow cell (3) at an angle to the vertical, the angle being
10 less than or at least essentially equal to 33° , preferably less than 20° , more preferably less than 15° , in particular that the fluidic sample (2) flows through the flow cell (3) at least essentially vertically.

16. Method according to one of claims 12 to 15, characterized in that the second
15 flow rate is greater than the first flow rate.

17. Method according to one of claims 12 to 16, characterized in that the first flow rate is greater than the third flow rate and/or wherein the second flow rate is greater than the third flow rate.

20 18. Method according to one of claims 12 to 17, characterized in that the volume of the cleaning fluid used in the first, second and/or third step corresponds to at least 2 times, preferably at least 3 times, more preferably at least 5 times the dead volume of the measuring arrangement (1), and/or

25 the volume of the cleaning fluid used in the first, second and/or third step corresponds to at least 2 times, preferably to at least 3 times, more preferably to at least 5 times, the volume of the flow cell (3).

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