(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 October 2013 (24.10.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/156408 A1

(51) International Patent Classification:
B01L 3/02 (2006.01)

(21) International Application Number:
PCT/EP2013/057711

(22) International Filing Date:
12 April 2013 (12.04.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/625,999 18 April 2012 (18.04.2012) US

(71) Applicant: **SIAS AG** [CH/CH]; Etzelstrasse 30, CH-8634 Hombrechtikon (CH).

(72) Inventor: **FINK, Pius**; Holgassstrasse 47, CH-8634 Hombrechtikon (CH).

(74) Agent: **TROESCH SCHEIDEGGER WERNER AG**; Jacques Troesch, Schwäntenmos 14, CH-8126 Zumikon (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: PIPETTING ARRANGEMENT AND METHOD OF CONTROLLING PIPETTING

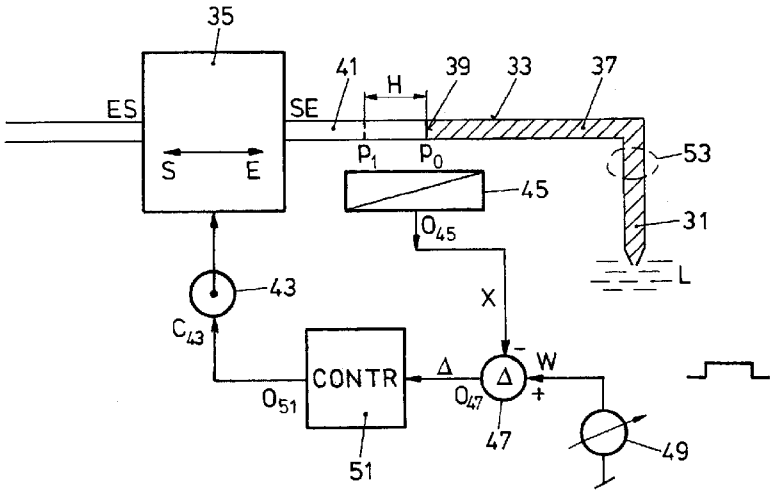

FIG.3

(57) Abstract: The stroke of a liquid column (37) within a flow connection line (33) interconnecting a pump (35) and a pipette (31) is monitored by a sensor arrangement (45) and is negative feedback controlled on a settleable, desired value (W) by acting upon the operation of the pump (35) as an adjusting member within the negative feedback loop.

WO 2013/156408 A1

PIPETTING ARRANGEMENT AND METHOD OF CONTROLLING PIPETTING

The present invention generically relates to the field of accurately preparing and handling very small doses of liquids, down to e.g. several hundreds nano-liters. Such liquid handling techniques are especially used in context with medical, chemical or biochemical analyses, e.g. in pharmaceutical, medical or food industry laboratories.

Thereby, as probes e.g. to be analyzed, small samples of liquids of accurately known volumes and often at a high repetition rate, e.g. in context with blood analyses of large populations, are handled.

Figure 1 shows schematically and simplifies a known pipetting arrangement which operates according to known methods of controlling. Via a flow connection line 3 as of a pipe, a pipette 1 is connected to a suction/ejection port SE of a bi-directionally actuatable pressure source, i.e. a pump 5. An ejection / suctioning port ES thereof is connected (not shown in figure 1) customarily to a liquid reservoir. The pump 5, e.g. a piston pump, a flexible-hose pump or a gear pump, and further a part of connection line 3 and of a downstream flow connection line 3' from the ejection / suctioning port ES to and including the addressed liquid reservoir are customarily filled with a liquid medium, whereas the remaining part of connection

line 3 up to the pipette 1 may be filled with at least one different medium which may be liquid or gaseous.

As schematically shown in figure 1, the pump 5 is activated in S-pumping direction to suction a dose of liquid L into pipette 1. The addressed dose is conveyed or, more generically, handled during a handling time and is then ejected at least to a predetermined part from the pipette 1 by activating pump 5 in ejecting direction E so as to eject the or a dose e.g. into a reception recipient for further treatment as for analysis. Pump 5 is controlled for most accurately performing the suction movement in S direction and the ejection movement in ejecting direction E.

This is e.g. performed as schematically shown in figure 2. Pump 5, as shown by example as a rotary gear pump 5_G, is driven by a rotary drive 7. E.g. by an angle encoder as a position detector 9, the prevailing angular position of gear pump 5_G is monitored. The output signal of detector 9 is led to a difference forming unit 11. There a difference signal Δ is formed from the signal dependent on actual angular position X and from a desired angular position signal W, which is preset at a presetting unit 13. At the output of difference forming unit 11, the difference signal Δ accords with the difference of the momentarily prevailing angular position of pump 5_G and the preset or desired value W, preset at unit 13. This difference signal Δ as a control deviation signal is fed via a controller unit 15 to a control input C_7 of the rotary drive 7. Thus, there is established by a negative feedback control loop a highly

accurate control of movement and position of the pump 5_G in suctioning S and in ejecting E directions. Clearly such control and especially negative feedback control of the movement of the gear pump 5_G, may also be established for any kind of be-directionally acting pump 5 as more generically shown in figure 1.

By such control of the position or movement of pump 5 the volume of liquid suctioned into the pipette 1 and of liquid ejected from pipette 1 may customarily not be controlled accurately enough. Therefore and as schematically shown in figure 1, there is provided customarily upstream the pipette 1 a valve arrangement 17 which is controlled by a control unit 18 in open or close state to most accurately interrupt the suctioning effect of pump 5 as well as the ejection effect of the pump when the desired dose is suctioned into or ejected from pipette 1.

It is an object of the present invention to improve prior art methods of controlling pipetting and, respectively, of methods of producing a dose of liquid and of pipetting arrangements.

This is achieved by a method according to the present invention of controlling pipetting, in which a pump is operationally connected to a pipette by a flow connection line. At least a part of the flow connection line to the pipette is filled with a liquid medium column. A volume of a liquid is suctioned into the pipette, a volume of liquid is ejected from the pipette. Both these actions of

suctioning and of ejecting do include moving the column of the liquid medium by the pump. The method comprises further the step of monitoring at least one of in or along the flow connection a stroke of the column and controlling the pump in dependency of the result of such monitoring.

We thereby understand under the term "stroke of the column" an amount of displacement of the column of liquid medium within the flow connection line between the pipette and the pump.

We further understand under a "column of a liquid medium" an amount of at least one liquid medium continuously filling a part of the flow connection line. If a cushion or bulb of gaseous medium is present within such column it has only neglectable effect upon overall incompressibility of the column.

Thus, under the most generic aspect of the present invention a stroke of a column of liquid medium in the flow connection line is monitored, whereby such column may be preceded towards the pump by one or more than one columns of a gaseous medium or may be succeeded towards the mouth of the pipette by one or more than one columns of gaseous medium.

If the addressed liquid column, the stroke of which being monitored, is preceded in direction towards the pump by at least one column or cushion of a gaseous medium this will affect the transmission characteristics of the operation of

the pump upon the movement of the addressed liquid column within the connection line. This due to the fact that such column of gaseous medium spring-like interacts between the pump and the addressed column of liquid medium due to compressibility of the gaseous medium.

Therefore and to establish a rigid movement transmission between operation of the pump and the addressed column of liquid medium, the stroke of which being monitored, in one variant of the method according to the invention, which may be combined with any variant succeedingly addressed, if not in contradiction, the liquid column the stroke of which being monitored is established up to the pump and the liquid medium of this column further fills the pump. There is thereby established a rigid movement transmission of the operation of the pump upon the movement of the addressed liquid medium column due to incompressibility of liquid media.

Further, if the addressed liquid column the stroke of which being monitored is succeeded towards the pipette by at least one column or cushion of a gaseous medium, this may affect the accuracy with which the stroke as monitored of the liquid medium column is decisive for a volume of a liquid suctioned into the pipette or of the volume of a liquid ejected from the pipette. This again due to compressibility of gaseous medium.

Thus and as a further variant of the method according to the present invention, which may be combined with any variant already addressed and with any variant to be succeedingly addressed, if not in contradiction, the column

of liquid medium the stroke of which being monitored has an end face which is directly exposed either to the mouth of the pipette or to an end phase of a liquid suctioned into the pipette and directed towards the pump.

Thereby, at most one single column or cushion of gaseous medium affects the addressed accuracy by which the stroke which is monitored determines the volume of liquid suctioned into or ejected from the pipette.

Further departing from the fact that the extent of such column or cushion of gaseous medium interposed between the end face of the liquid medium column the stroke of which being monitored and the mouth of the pipette or the end face of a liquid suctioned into the pipette may affect the accuracy with which the stroke as monitored is decisive for the volume of liquid suctioned into the pipette or ejected from the pipette, in a further variant of the method according to the invention, the extent of such column of gaseous medium is minimized.

Taking into account that the addressed column of liquid medium the stroke of which being monitored needs not necessarily be formed by one single liquid medium, but may be formed by two or more liquid media, it is often possible to establish the extent of such liquid column practically up to the mouth of the pipette, thereby taking care of providing a liquid medium directly exposed to the mouth of the pipette which is compatible with the liquid to be suctioned into the pipette and ejected from the pipette.

If interposing a gaseous medium between the column and the mouth of the pipette the extent thereof is minimized just

to ensure material isolation from the liquid of the column of the liquid structure into the pipette.

Practically every be-directionally acting pump as e.g. and especially a gear pump has e.g. unequal pumping effects in one direction and in the other direction. Such different pumping effects may additionally vary over time due to aging, temperature of the liquid medium filling the pump and its viscosity etc. so that the pumping effect of the pump in both directions is a source of error. This source becomes mute if, according to the present invention, it is the stroke of the addressed column which is monitored instead of monitoring position or movement of the pump.

In one variant of the method according to the present invention, which may be combined with any of the already addressed or subsequently addressed variants, if not in contradiction, monitoring of the stroke of the liquid medium column comprises monitoring the stroke of an interface surface between different media in or at the column the stroke of which being monitored.

Thereby, such interface may be an interface between two different liquid media, both forming the column of liquid medium the stroke of which being monitored or may be a front or end face of the addressed column exposed to a gaseous medium.

In one further variant of the method according to the present invention which may be combined with any already

addressed or subsequently addressed variants, if not in contradiction, a desired value of a stroke for the liquid medium column is preset. A difference signal dependent from such preset desired value and from a signal dependent from monitoring of the prevailing stroke is formed. The stroke of the liquid medium column is negative feedback controlled whereby the difference signal is exploited as a control deviation and the pump is exploited as an adjusting member in that the control derivation signal is operationally connected to a control input for the pump. Thereby, there is established the addressed stroke as monitored to become equal to the desired stroke with an accuracy which accords with the controlling effect of the negative feedback controlling.

Please note that we understand under the difference of two signals A and B the expression (A-B).

Thereby, it is perfectly known to the artisan skilled in negative feedback control art that by accordingly shaping e.g. the frequency course of the open loop amplification of the negative feedback control, very high accuracy may be achieved with respect to the monitored entity becoming equal to the desired entity e.g. by tailoring the addressed frequency characteristic of the open loop with proportional/integral behaviour thereby maintaining stability of the closed negative feedback control loop.

In a further variant of the method according to the invention, which may be combined with any pre-addressed or

succeedingly addressed variants, unless in contradiction, at least two desired values of a stroke for the liquid medium column are preset. Difference signals from signals dependent on the preset desired values and a signal dependent from the monitoring of the stroke are formed. Negative feedback controlling the stroke of the column is performed thereby exploiting first a first difference signal dependent from the first of the desired values and then exploiting a second difference signal dependent from the second of the desired values as control deviation and, in both cases, the pump as an adjusting member. Thereby, there is established the stroke as monitored to become first equal to the first desired value then equal to the second desired value with an accuracy according to the controlling effect of negative feedback controlling.

Thereby, the first desired value may be the desired stroke value for suctioning of a liquid into the pipette and the second desired value of the stroke may accord with the stroke of the column for ejecting the liquid from the pipette. Clearly in such case the two desired values are established with inverse signums as the desired stroke for suctioning the liquid is directed towards the pump and the stroke for ejecting the liquid is directed from the pump. The extents of these strokes may be unequal or equal.

In a further variant of the method according to the present invention, which may be combined with any of the previously and suceedingly addressed variants, unless in

contradiction, monitoring the stroke comprises monitoring relative position of the column in the flow connection over time.

By monitoring the relative position of the column in the flow connection over time in fact the movement of such column is monitored. Presetting the desired value comprises presetting a desired course of relative positions over time of the column, i.e. a desired movement of the column over time. The negative feedback controlling thus comprises negative feedback controlling the movement of the column by exploiting a difference result of the signal which represents the desired course of positions with a signal which represents the monitored and thus actual position as a control deviation. By such negative feedback control, the suctioning stroke as well as the ejecting stroke may be accurately negative feedback controlled by presetting the respective forward and backward movements of the liquid medium column and additionally the desired stroke may be realised with a desired movement characteristic e.g. with slow or more rapid approach towards the desired stroke value.

We speak of a "relative" position of the column in the flow connection line, because it is only important what position the column assumes with respect to a freely selectable reference position along the flow connection line. The absolute position of the column along the flow connection line is of no relevancy.

In a further variant of the method according to the invention which may be combined with any of the previously

addressed or subsequently addressed variants, unless in contradiction, the volume suctioned into the pipette and/or ejected from the pipette is controlled without operating an opening/closing valve arrangement in the flow connection line between the pipette and the pump.

In a further variant of the method according to the invention, which may be combined with any of the previously addressed variants, unless in contradiction, the pump is a rotary gear pump.

The present invention is further directed on a method of producing a dose of a liquid by pipetting in which method a pump is operationally connected to a pipette by a flow connection line, at least a part of the flow connection line is filled with a liquid medium column. Liquid is suctioned into the pipette and liquid is ejected from the pipette, both including moving the column by the pump. The method further comprises the step of monitoring, in or adjacent the flow connection line, a stroke of the addressed column in the flow connection line and controlling the pump in dependency of the result of the addressed monitoring.

As for the controlling method addressed above, monitoring the stroke is established by sensing a geometric entity which finally defines for a difference of positions of the column of liquid medium in the flow connection line, be it

e.g. sensing directly the relative position of the addressed column or propagation speed over time etc.

In one variant of the method of producing a dose according to the present invention, which variant may be combined with any of the succeedingly addressed variants, unless in contradiction, and as was already addressed in context with the method of controlling, the liquid column is established up to the pump and the liquid medium of the column fills the pump.

In a further variant of the addressed method of producing a dose, which may be combined with any of the precedingly addressed and succeedingly addressed variants of such method, unless in contradiction, the liquid medium column has an end face directly exposed to the mouth of the pipette or to an end face of a liquid volume suctioned into the pipette.

In a variant of the just addressed variant of the method of producing a dose the extent of a column of gaseous medium between the end face of the liquid medium column and the mouth of the pipette is minimized e.g. to an extent for ensuring material isolation from the column of liquid medium or the liquid to be suctioned into the pipette.

In a further variant of the method of producing a dose which may be combined with any of the preaddressed and of the succeedingly addressed variants, unless in contradiction, monitoring the stroke of the column comprises monitoring the stroke of an interface between different media in or of the addressed column.

In one variant of the method of producing, which may be combined with any preaddressed and succeedingly addressed variants of such producing method, if not in contradiction, a desired value of a stroke for the liquid medium column is preset. There is formed a difference signal, which depends from the preset desired value and from a signal, which is dependent from monitoring the prevailing stroke.

The stroke of the column within the flow connection line is negative feedback controlled thereby exploiting a signal which is dependent from the addressed difference signal as a control deviation signal and the addressed pump as an adjusting member. Thus, a signal dependent on the addressed difference signal is operationally connected to a control input for controlling operation of the pump. There is established the stroke as monitored and thus the prevailing stroke in the flow connection line to become equal to the desired stroke with an accuracy which accords to the controlling effect of the negative feedback control loop.

In a further variant of the method of producing, which may be combined with any previously addressed variant of that method and with any subsequently addressed variant of that method, unless in contradiction, at least two desired values of a stroke for the liquid medium column are preset.

Two difference signals are formed respectively dependent from one of the two desired values and from the signal dependent from monitoring the stroke.

Consecutively, the stroke of the column in the flow connection line is negative feedback controlled, thereby exploiting first a signal dependent from a first of the two difference signals, and then exploiting a second signal dependent from the second of the difference signals as respective control deviation signals and, in both cases, the pump as an adjusting member. Thereby, there is established the stroke as monitored, i.e. the momentarily prevailing stroke, to be or to become first equal to the first desired value then equal to the second desired value with an accuracy which accords to the controlling effect of the negative feedback control loop.

In a further variant of the producing method, which may be combined with any of the pre-addressed or to be addressed variants of such producing method, unless in contradiction, monitoring the stroke of the liquid medium column in the flow connection line comprises monitoring a position of the column in the flow connection line over time. Presetting the desired value thereby comprises presetting a desired course of relative positions over time of the column and thus, in fact, presetting a desired movement of the addressed column over time. Negative feedback controlling comprises negative feedback controlling a movement of the column by exploiting a difference result of a signal

representing the desired course of positions and of a signal representing the monitored instantaneously prevailing position as a control deviation signal.

The addressed position may be said "relative" position in the flow connection line, as defined with respect to an arbitrarily selected fixed position along the flow connection line. Because according to the generic approach of the present invention it is the stroke of the liquid medium column in the flow connection line which is monitored, it is of no importance at which absolute positioning of the column along the flow connection line such stroke is established and monitored. Therefore, and if the stroke is monitored via subsequent monitoring of the position of the liquid medium column, such positions may be said "relative" to an arbitrarily selected fixed position along the addressed flow connection line.

Thus, the instantaneously prevailing position of the column as monitored is negative feedback controlled to follow, over time, a desired sequence of desired positions and thus to follow a desired movement.

On one hand, one or more than one stroke forwards and/or backwards are negative feedback controlled and additionally the time course of movement of the liquid medium column to achieve the desired stroke value is controlled. If, e.g., there is provided between the liquid medium column and the pipette mouth a relevant column or cushion of a gaseous medium, it may be advisable, to negative feedback the movement of the addressed liquid medium column so slowly

that the gaseous medium column does not act as an oscillating spring member.

In a further variant of the method of producing which may be combined with any of the preaddressed variants and with any of the succeedingly addressed variants of such producing method, if not in contradiction, the volume as suctioned into the pipette and/or as ejected from the pipette is controlled without operating an opening/closing valve arrangement in the flow connection line.

In a further variant of the method of producing, which may be combined with any of the preaddressed variants of such producing method, if not in contradiction, the pump is selected to be a rotary gear pump.

The invention is further directed on a pipetting apparatus, which comprises a bi-directionally operable pump. A flow connectional line is provided from the pump to a pipette mouth and a continuous liquid medium column fills at least a part of the addressed flow connection line. A controlling unit is provided for the operation of the pump which unit comprises a control input for a signal to control the addressed operation. There is further provided a sensing arrangement, at least one of in and of along the flow connection line, which arrangement generates at an output an output signal indicative for a stroke of said column in the flow connection line. The addressed output of the sensing arrangement is operationally connected to the

control input of the controlling unit for the operation of the pump.

In one embodiment of the apparatus according to the present invention, which may be combined with any of the subsequently addressed embodiments, unless in contradiction, the liquid column is established up to the pump and a liquid of the addressed column fills also the pump.

In a further embodiment of the apparatus, which may be combined with any of the precedingly and of the succeedingly addressed embodiments, unless in contradiction, the column has an end face directly exposed to the mouth of the pipette.

This means that between the addressed end face of the column of liquid medium and the mouth of the pipette there is at the most a column of a gaseous medium.

In a further embodiment of the just addressed embodiment, the extent of a column of a gaseous medium between the end face of the addressed column of liquid medium and the mouth of the pipette is minimal as just to ensure material isolation of the column from a liquid suctioned into the pipette or there is no such column of gaseous medium provided at all.

In a further embodiment of the apparatus, which may be combined with any precedingly and succeedingly addressed embodiments, unless in contradiction, the sensing arrangement senses a position of an interface in or of said column of liquid medium, which interface is established between different media. Thus, either such interface is

formed by different liquid media forming together the addressed column or the addressed end face is established by an end face of the column towards a gaseous medium.

It might even be possible to provide within the column just for sensing purposes a minimum volume gaseous bubble or cushion and sensing position of such cushion or bubble of gaseous medium within the addressed column and along the connection line.

In one embodiment of the apparatus according to the invention, which may be combined with any precedingly and subsequently addressed embodiments, unless in contradiction, such apparatus further comprises a presetting unit with an output. Further, the apparatus comprises a difference forming unit with a first and with a second input for signals the difference therefrom being formed by the difference forming unit and with an output for a result signal of the difference forming by the addressed unit. The output of the sensing arrangement and the output of the presetting unit are respectively operationally connected to the first and to the second input of the difference forming unit and the output of this unit is operationally connected to the control input of the controlling unit for the operation of the pump.

In a further embodiment of the pipetting apparatus according to the invention, which may be combined with any embodiment already addressed and with any embodiment as

will be addressed, unless in contradiction, the sensing arrangement generates an output signal which represents a prevailing relative position of the column in the flow connection line. The presetting unit generates an output signal which represents a desired time course of positions of the column in the flow connection line. Thus and by the pre-addressed negative feedback control, the prevailing position of the column in the flow connection line is negative feedback controlled to follow the course of positions and thus the movement as desired and as preset by the presetting unit.

In a further embodiment of the apparatus according to the invention, which may be combined with any precedingly and succeedingly addressed embodiments, unless in contradiction, the sensing arrangement senses a prevailing position of the column along the flow connection line.

In a further embodiment of the apparatus according to the invention, which may be combined with each embodiment as was already addressed, the pump is a rotary gear pump.

The present invention shall now be further exemplified with the help of figures. The figures show:

Figure 1: A schematical representation of a prior art embodiment for controlling pipetting.

Figure 2: Still schematically a prior art embodiment for pipetting control in which the movement of a pipetting pump is negative feedback controlled.

Figure 3: In a schematical representation a pipetting arrangement according to the present invention and

operating a method of controlling pipetting as well as a method of producing a dose of a liquid according to the present invention.

Figure 4: A part of a pipetting arrangement according to the present invention, still schematically, wherein the interface between two media in a flow connection line between a pump and the nozzle of the pipette is position-monitored.

Figure 5: A part of an arrangement according to the present invention, wherein a volume of gaseous medium is minimized just to establish material isolation between a liquid medium within the arrangement from a medium to be suctioned into and ejected from a pipette.

Figure 6: Still schematically a part of an embodiment according to the present invention, wherein a bubble of gaseous medium is applied within a liquid medium in a flow communication line between a pump and a pipette so as to monitor position and/or movement of the liquid medium column.

Figure 7: A further embodiment of the present invention, still schematically, which operates the methods according to the present invention.

Fig. 3 shows simplified and schematically a signal flow/functional block diagram of a pipetting arrangement according to the present invention operating a method of controlling pipetting and of producing a dose of liquid according to the present invention. A bi-directionally operable pump 35 is linked by a flow connection line 33 as of a tube to a pipette 31. The pump 35 has a

suctioning/ejection port SE and an ejection/suctioning port ES. Whereas port SE is connected to the flow connection line 33, port ES may be, in the embodiment of fig. 3, open to ambient.

A column of liquid medium 37 fills the pipette 31 as well as a part of the flow connection line 33. The position of the column of liquid medium within pipette 31 and flow connection line 33 may be defined by the end face 39 of the liquid medium column pointing towards the pump. In this embodiment there succeeds in direction towards the pump 35 adjacent to end face 39 a column of gaseous medium 41. Thus, end face 39 is a liquid/gas interface. The bi-directionally operable pump 35 is operated forwards and backwards according to the double-arrow S-E by a drive 43 which has a control input C_{43} for control signals controlling, via drive 43, the operation of pump 35.

If the pump 35 is operated in direction S by drive 43 the liquid medium column 37 is suctioned towards pump 35. If pump 35 is operated by drive 43 in inverse direction E, the column of liquid medium 33 is moved in direction towards pipette 31. For taking up a dose of a liquid L the pump is operated in S direction, generating a stroke H of the liquid medium column 37 towards pump 35. Thereby, a liquid L is suctioned into pipette 31 with a volume which accords with the volume of liquid medium displacement in the flow connection line 33 according to stroke H. Once the dose of liquid L is taken up into pipette 31 and as customarily known from the pipetting art, the pump 35 is disabled or

stopped and the dose of liquid L within pipette 31 is handled according to the respective application and needs.

Then the pump 35 is restarted operating in direction E, thereby propelling the liquid medium column 37 towards the pipette 31 to eject a dose of liquid L' into a reception recipient (not shown in fig. 3).

If a dose to be ejected has a same volume as the volume of liquid which was previously suctioned into pipette 31, then the ejection stroke of liquid column 37 will be equal to the stroke for suctioning, but clearly in inverse direction, i.e. towards pipette 31.

As shown in fig. 3 the stroke of the liquid medium column 37 is clearly identified by the stroke of end face 39.

There is provided a sensor arrangement 45. For simplicity reasons it is assumed that the flow connection line 33 is transparent. Thus, the sensor arrangement 45 may be e.g. an optical/electrical converter, e.g. a digital picturing sensor with e.g. a CCD optical/electrical converter followed by a picture recognition unit to recognize the instantaneous location of face 39. With today's very high resolutions of optical/electrical pixel-based converters a very high accuracy of locating the interface 39 along the sensor arrangement 45 may be reached.

The sensor arrangement 45 generates at its output O_{45} an output signal X which is indicative of the instantaneous position of interface 39. This signal X or a signal dependent therefrom is fed to one input of a difference forming unit 47. To the second input of the difference forming unit 47 a signal W is applied which is dependent

from or which represents a desired position to which the end face 39 of liquid medium column 37 is to be brought. The desired position is selected at preselecting unit 49. The difference of the initial position of interface 39 p_o to the desired position p_1 is the stroke H which the interface 39 and therewith all the column of liquid medium 37 shall be moved.

At the output O_{47} the difference forming unit 47 generates a signal Δ which is representative of the difference of the preselected "desired" signal W and the signal representing the momentarily prevailing position of the interface 39, X. A controller unit 51 provides for a frequency dependent amplification of the signal Δ. The output of the controller unit 51, O_{51}, is operationally connected to the control input C_{43} of driver unit 43. Thus, there is established a negative feedback control loop with the pump 35 as an adjusting member so as to accurately drive the position of interface 39 to that position which is selected by unit 49 and thus to perform by the liquid medium column 39 the desired stroke H. The frequency behaviour of controller unit 51 as perfectly known to the skilled artisan in negative feedback control art is tailored to establish a high gain, thereby maintaining stability of the overall negative feedback loop so as to achieve that the interface 39 reaches the desired position p_1 with a desired accuracy.

Because the stroke H performed in direction towards the pump 35 is decisive for the respective stroke of the liquid medium column 39, it is also decisive for the volume of liquid L suctioned into pipette 31. Any leakage of the pump

35 or any other occurrence which influences the instantaneous position of interface 39 may be disregarded, due to the negative feedback loop. No valve arrangement is necessary to determine the exact volume of the dose of liquid L suctioned into the pipette and arranged e.g. between the pipette 31 and the pump 35 as shown in dashed line at 53.

In context with fig. 3 sensing of the momentarily prevailing stroke to be negative feedback controlled to accurately perform a desired stroke is realized by making use of digital picture evaluation techniques for the interface 39 of the liquid medium column. Nevertheless, it is evident that dependent on the optical and/or electrical characteristics of the wall of flow connection line 33, on optical and/or electrical characteristics of the liquid medium of column 37, etc. different sensing methods and sensing arrangements may be used to accurately trace the buildup of a desired stroke H.

Further and with an eye on fig. 3 in this embodiment the column of liquid medium 37 precedes a column of gaseous medium 41, pump 35 is possibly also operating in a gaseous medium. Generically an inclusion of a gaseous medium between the liquid medium column 37 and the pump 35 does not affect final reach of a desired stroke according to position p_1 of fig. 3, but does possibly affect the transmission of pump operation upon the liquid column 37 due to compressibility of gas.

Nevertheless, to establish a "quasi" rigid movement transmission from pump 35 upon the liquid medium column 37

in one embodiment according to fig. 4 the liquid column 37_A in the flow connection line 33 is established up to port SE_A of the pump 35_A and further fills the pump 35_A. According to fig. 4 and as an example a rotary gear pump 35A is applied as a bi-directionally operating pump 35 as of fig. 3. The column of liquid medium extends in analogy to the embodiment of fig. 3 from the mouth of the pipette 31, but now up to the port SE_A of rotary gear pump 35A and the liquid of the column 37_A fills the pump 35_A and at least a part of the downstream line 55. So as to establish a clearly position-detectable area along the column of liquid medium 37_A and as schematically shown in fig. 4 the liquid column 37_A is established by a first liquid medium 37_{A1}, which liquid medium also fills the pump 35A and by a second liquid medium 37_{A2}, which is different from the first addressed liquid medium 37_{A1} and extends to the mouth of pipette 31. Thereby, an interface surface 39_A is established between the respectively selected liquid media, in opposition to the interface surface 39 of fig. 3 which is formed between liquid and gaseous media.

The remaining members of the embodiment according to fig. 4 are equal to those explained in context with fig. 3 and are thus not explained again.

The embodiment of fig. 4 has for some applications the advantage that the liquid medium operated in the pump is selected different from the liquid medium down to the mouth of pipette 31 so that latter may be selected according to the liquid L to be handled to make sure that the addressed liquid L is not negatively influenced in an unacceptable

manner by the liquid medium of the liquid medium column 37_A.

In some applications it might be necessary to separate the liquid of the liquid medium column from the liquid L to be handled by a column or a cushion of gaseous medium. Whereas a column or cushion of gaseous medium upstream, i.e. from the liquid medium column towards the pump, does not harm accuracy with which a predetermined stroke is realized due to the negative feedback control, a gaseous medium column or cushion upstream, i.e. towards the pipette 31 of the liquid medium column, does in fact affect the accuracy with which a predetermined stroke of the liquid medium column is decisive for the volume of liquid L suctioned into the pipette or respectively is ejected from the pipette. This due to compressibility of such gas.

If the necessity arises to separate the liquid medium of the liquid medium column from a liquid as of L to be handled in the pipette by a gaseous medium, then the volume of such gaseous medium 57 as schematically shown in fig. 5 should be minimized just sufficient to establish material isolation from the liquid medium of column 37 from a liquid L to be suctioned into and ejected from the pipette.

With an eye on fig. 4 we have established two different liquid media forming the interface 39_A to be position-tracked by the sensor arrangement 45. In one further embodiment according to fig. 6 a good marking within the column of liquid medium the stroke of which being sensed may also be realized by a bubble or cushion 59 within the liquid medium forming the liquid medium column 37_B. Thus,

according to the embodiment of fig. 6 and having an eye on the embodiment of fig. 4 the two different liquid media 37_{A1} and 37_{A2} of the embodiment of fig. 4 may be replaced by one single liquid medium 37_B having a position marker as of an air bubble or air cushion 59 therein.

In the embodiment of fig. 3, which may be combined with all the embodiments as addressed in context with fig. 4 to 6 with respect to different tailoring of the liquid medium column, the stroke of which or the position of which being monitored, it is perfectly clear that once by applying e.g. a steplike positive signal W at the preselecting unit 49 and thereby suctioning a predetermined volume of liquid L into pipette 31, the equal volume will be ejected from the pipette 31 as W returns to the initial value established by the selection unit 49 as shown in fig. 3. Thus, in fact two different strokes are pre-established by unit 49 of equal extent, but with inverse signum.

Nevertheless, it is perfectly clear that two or more than two desired values for a stroke of the liquid medium column may be applied by the preselecting unit 49 consecutively in time so as to either consecutively suction equal or unequal volumes of liquid L into the pipette, e.g. of different liquids, and/or to eject from the pipette equal or unequal doses of liquid consecutively in time towards respective targets.

Whereas by applying as a signal representing a desired stroke a step-like signal as exemplified in context with fig. 3 the movement of the liquid medium column by the adjusting member, namely pump 35, results from the settings

and from the behaviour of the overall negative feedback control loop, possibly including a proportional integral controller unit 51 to optimize accuracy, it might be desired in some applications to also control the movement of the liquid medium column as approaching the desired stroke value. This is accomplished by the embodiment according to fig. 7 which resides on the explanations in context with fig. 3 and may be combined with all other embodiments described.

The embodiment of fig. 7 accords with that of fig. 3 and therefore the respective units and signals are addressed by the same reference signs.

According to the embodiment of fig. 7 the presetting unit generates an output signal which accords with the desired approach of interface 39 to a predetermined position p_1 or back to position p_o according to the respective forwards and backwards strokes of the liquid medium column 37. As exemplified in fig. 7 the predetermining unit 49a generates a predetermined time course of output signal U(t) e.g. according to a course asymptotically approaching slowly an end value. The negative feedback control loop which is tailored to accurately follow the signal U(t) as established by the preselecting unit 49a, controls pump 35 in such a manner that the end face 39 performs a movement according to U(t), thus propelling the liquid medium column with the preselected movement towards the desired end value of the stroke H_S or respectively H_E.

The skilled artisan recognizes that there are multiple possibilities also dependent on specific applications to

realize the present invention which in fact reside generically on the fact of negative feedback controlling the stroke of the liquid medium column in the flow connection line between a bi-directionally operable pump and a pipette so as to most accurately control the volume of a liquid or possibly even a powderous medium suctioned into the pipette and respectively ejected from the pipette.

Claims

1. A method of controlling pipetting in which a pump is operationally connected to a pipette by a flow connection line, at least a part of the flow connection line to the pipette is filled with a liquid medium column, and wherein a volume of liquid or powder is suctioned into the pipette or a volume of liquid is ejected from said pipette, which both include moving said column in said flow connection line by said pump, comprising the step of monitoring a stroke of said column and controlling said pump in dependency of the result of said monitoring.

2. The method of claim 1, wherein said liquid column is established up to the pump and a liquid medium of said column fills said pump.

3. The method of one of claims 1 or 2, wherein said liquid medium column has an end face directly exposed to the mouth of said pipette.

4. The method of claim 3, wherein an extent of a column of gaseous medium between said end face and the mouth of said pipette is minimized.

5. The method of one of claims 1 to 4, wherein monitoring said stroke comprises monitoring the stroke of an interface surface between different media in or of said column.

6. The method of one of claims 1 to 5, comprising

- presetting a desired value of a stroke for said liquid medium column;

- forming a difference signal dependent from said preset desired value and a signal dependent from said monitoring of said stroke;
- negative feedback controlling said stroke of said column exploiting a signal dependent on said difference signal as a control deviation and said pump as an adjusting member.

7. The method of one of claims 1 to 6, comprising

- presetting two desired values of a stroke for said liquid medium column;
- forming two difference signals from signals dependent from said preset desired values and a signal dependent from said monitoring of said stroke;
- negative feedback controlling consecutively said stroke of said column, thereby exploiting first a first difference signal dependent from a first of said two desired values and then exploiting a second difference signal dependent from the second of said desired values as control deviations and said pump as an adjusting member.

8. The method of one of claims 1 to 7, wherein monitoring said stroke comprises monitoring a position of said column in said flow connection line over time and presetting said desired value comprises presetting a desired course of positions over time of said column.

9. The method of one of claims 1 to 8, wherein said volume suctioned into the pipette and/or said volume

ejected from said pipette is controlled without operating an opening/closing valve arrangement in the flow connection line.

10. The method of one of claims 1 to 9, wherein said pump is a rotary gear pump.

11. A method of producing a dose of a liquid or powder by pipetting in which a pump is operationally connected to a pipette by a flow connection line, at least a part of the flow connection line is filled with a liquid medium column and wherein liquid is suctioned into the pipette and liquid is ejected from said pipette which both include moving said column by said pump comprising the step of monitoring a stroke of said column and controlling said pump in dependency of the result of said monitoring.

12. The method of claim 11, wherein said liquid column is established up to the pump and the liquid medium of said column fills said pump.

13. The method of one of claims 11 or 12, wherein said liquid medium column has an end face directly exposed to the mouth of said pipette or to an end face of a liquid volume suctioned into said pipette.

14. The method of claim 13, wherein an extent of a column of gaseous medium between said end face and the mouth of said pipette is minimized.

15. The method of one of claims 11 to 14, wherein monitoring said stroke comprises monitoring the stroke of an interface between different media in or of said column.

16. The method of one of claims 11 to 15, comprising

- presetting a desired value of a stroke for said liquid medium column;
- forming a difference signal dependent from said preset desired value and a signal dependent from said monitoring of said stroke;
- negative feedback controlling said stroke of said column, thereby exploiting a signal dependent from said difference signal as a control deviation and said pump as an adjusting member.

17. The method of one of claims 11 to 16, comprising

- presetting two desired values of a stroke for said liquid medium column;
- forming two difference signals dependent from said preset desired value and a signal dependent from said monitoring of said stroke;
- negative feedback controlling consecutively said stroke of said column, thereby exploiting first a signal dependent from a first of said difference signals and then exploiting a second signal dependent from the second difference signal as control deviation signals and said pump as an adjusting member.

18. The method of one of claims 11 to 17, wherein monitoring said stroke comprises monitoring a position of said column in said flow connection line over time and presetting said desired value comprises presetting a desired course of positions of said column.

19. The method of one of claims 11 to 18, said volume suctioned into said pipette and/or said volume ejected from said pipette is controlled without operating an opening/closing valve arrangement in said flow connection line.

20. The method of one of claims 11 to 19, wherein said pump is a rotary gear pump.

21. Pipetting apparatus comprising a bi-directionally operable pump, a flow connection line from the pump to a pipette mouth, a liquid medium column filling at least a part of said flow connection line, a controlling unit for the operation of said pump comprising a control input for a signal to control operation of said pump, a sensing arrangement at least one of in and of along said flow connection line generating at an output an output signal dependent on a stroke of said column in said flow connection line, said output being operationally connected to said control input.

22. The apparatus of claim 21, wherein said liquid column is established up to said pump and a liquid of said column fills said pump.

23. The apparatus of one of claims 21 or 22, wherein said column has an end face directly exposed to the mouth of said pipette.

24. The apparatus of claim 23, wherein an extent of a column of a gaseous medium between said end face and said mouth is minimal just to ensure material isolation of said column from a liquid suctioned into said pipette or there is no such column of gaseous medium provided.

25. The apparatus of one of claims 21 to 24, wherein said sensing arrangement senses position of an interface between different media in or of said column of liquid medium.

26. Pipetting apparatus according to one of claims 21 to 25, further comprising a presetting unit with an output, a difference forming unit with a first and with a second input, a difference of signals applied thereto being formed by said difference forming unit and with an output for a result signal of said difference forming, the output of said sensing arrangement and the output of said presetting unit being respectively operationally connected to said first and second inputs, the output of said difference forming unit being operationally connected to said control input.

27. The pipetting apparatus of one of claims 21 to 26, wherein said sensing arrangement generates an output signal representing prevailing position of said column in said flow connection line, said presetting unit generating an output signal representing a desired time course of positions of said column in said flow connection line.

28. The pipetting apparatus of one of claims 21 to 27, wherein said sensing arrangement senses a prevailing position of said column along said flow connection line.

29. The pipetting apparatus of one of claims 21 to 28, wherein said pump is a rotary gear pump.

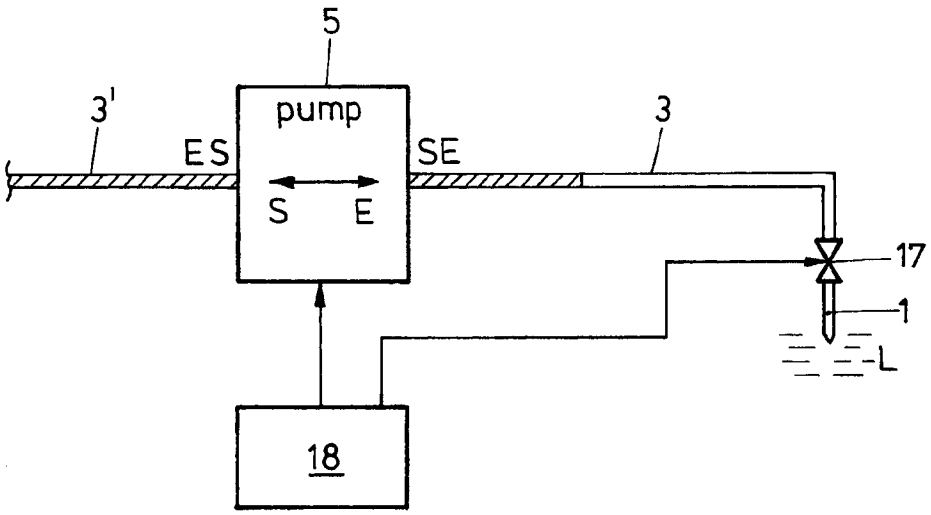

FIG.1

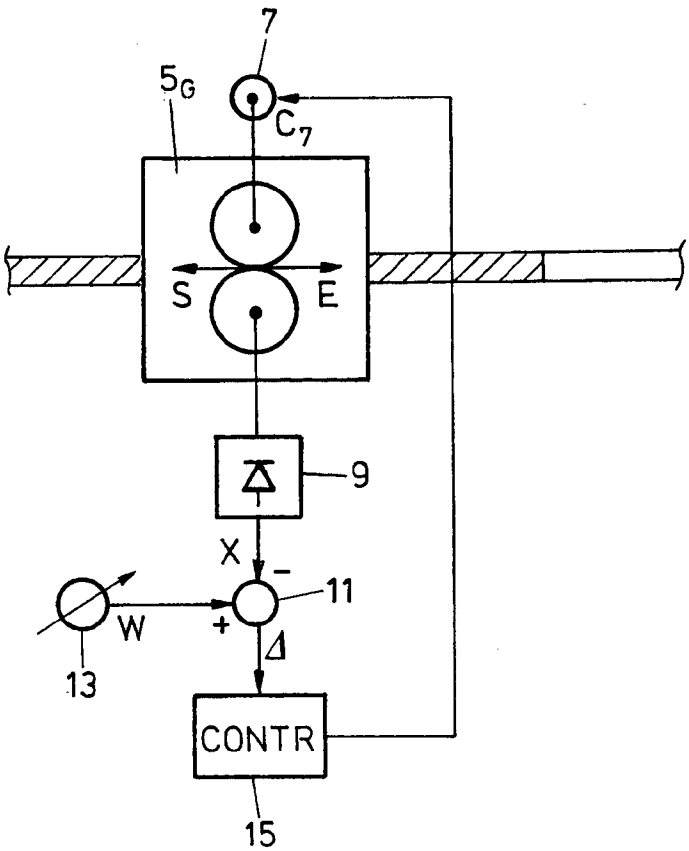

FIG. 2

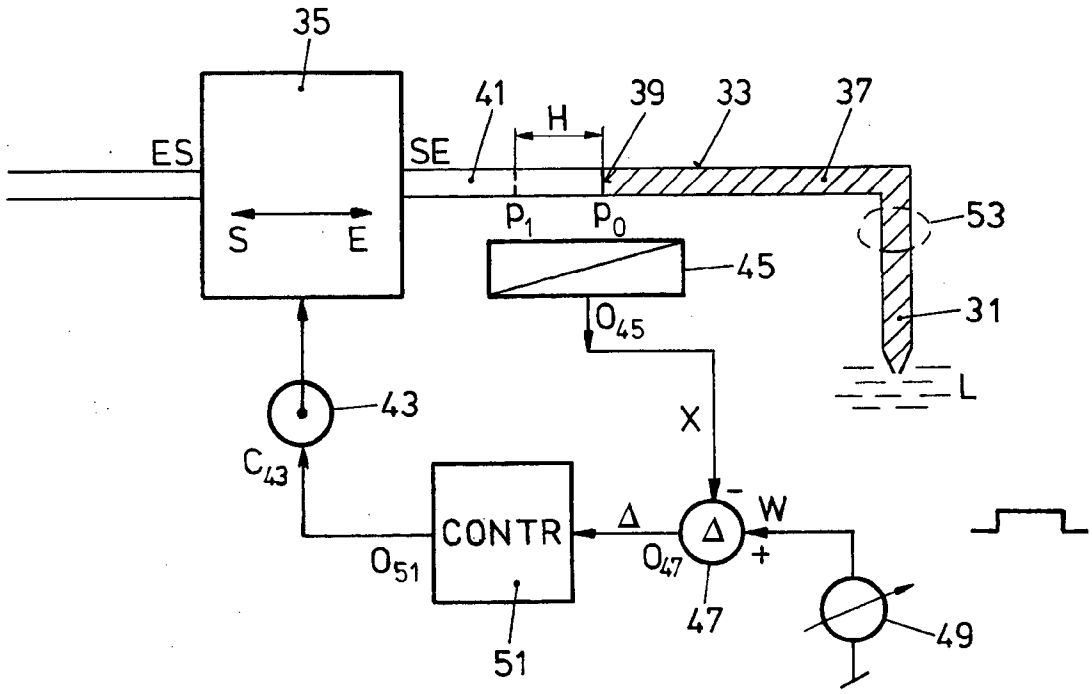
35
41
39
33
37
H
ES
SE
S
E
P_1
P_0
53
45
O_{45}
31
L
43
X
C_{43}
CONTR
Δ
W
O_{51}
O_{47}
47
49
51

FIG.3

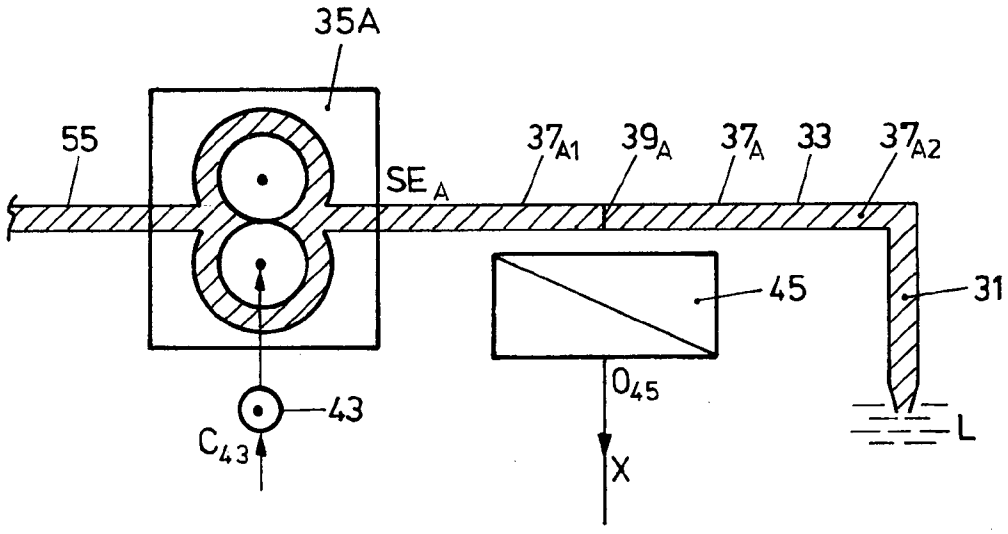
35A
55
37_{A1}
39_A
37_A
33
37_{A2}
SE_A
45
31
O_{45}
43
C_{43}
X
L

FIG.4

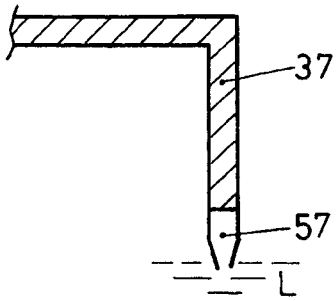

FIG.5

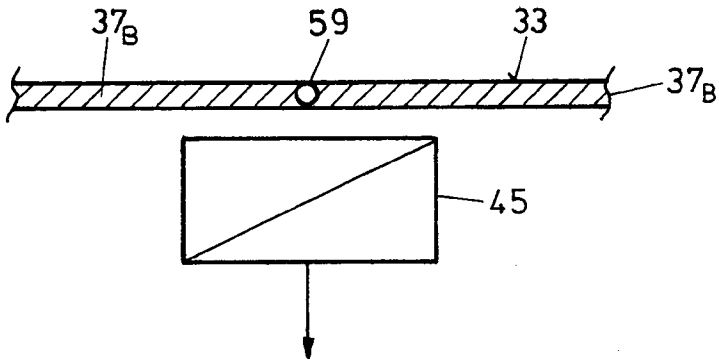

FIG.6

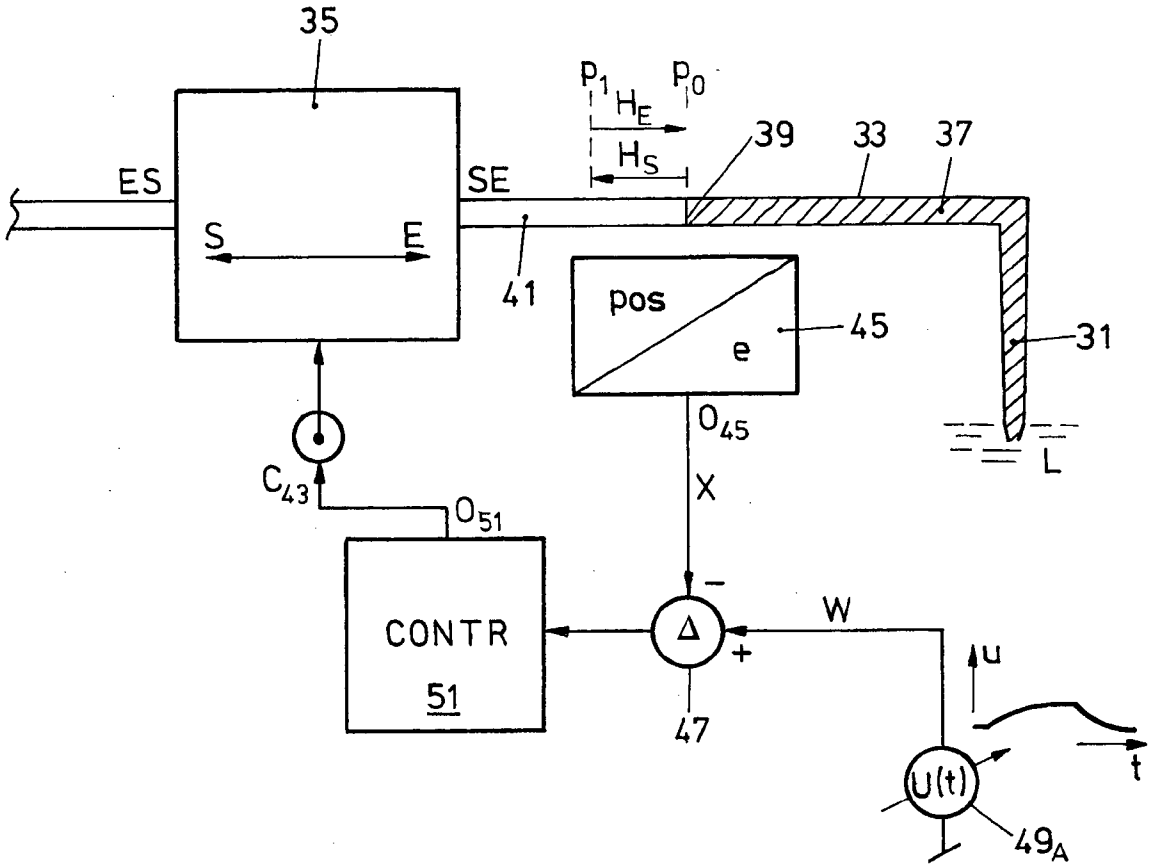
35
ES
S
E
SE
P_1
H_E
P_0
H_S
39
33
37
41
pos
e
45
31
L
O_{45}
X
C_{43}
O_{51}
CONTR
51
Δ
−
+
W
47
u
U(t)
t
49_A

FIG.7

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/057711

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01L3/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 246 704 A1 (HOFFMANN LA ROCHE [CH]; ROCHE DIAGNOSTICS GMBH [DE]) 3 November 2010 (2010-11-03) claim 15; figure 1	1-29
A	EP 2 193 848 A1 (HOFFMANN LA ROCHE [CH]; ROCHE DIAGNOSTICS GMBH [DE]) 9 June 2010 (2010-06-09) the whole document	1-29
A	WO 03/065049 A2 (INNOVADYNE TECHNOLOGIES INC [US]) 7 August 2003 (2003-08-07) the whole document	1-29
A	US 6 203 759 B1 (PELC RICHARD E [US] ET AL) 20 March 2001 (2001-03-20) the whole document	1-29

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2013	14/08/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Skowronski, Maik

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/057711

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/35761 A1 (ABB FLEXIBLE AUTOMATION AS [NO]; ANFINDSEN OLE ARNT [NO]) 20 August 1998 (1998-08-20) the whole document	1-29
A	US 2007/241130 A1 (CURTIS RICHARD H [US] ET AL) 18 October 2007 (2007-10-18) the whole document	1-29
A	EP 0 682 258 A1 (CIBA CORNING DIAGNOSTICS CORP [US] BAYER AG [US]) 15 November 1995 (1995-11-15) the whole document	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/057711

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2246704 A1	03-11-2010	AT 552507 T	15-04-2012
		EP 2246704 A1	03-11-2010
		US 2011111506 A1	12-05-2011
EP 2193848 A1	09-06-2010	EP 2193848 A1	09-06-2010
		US 2010132487 A1	03-06-2010
WO 03065049 A2	07-08-2003	AT 377763 T	15-11-2007
		CA 2473860 A1	07-08-2003
		DE 60317305 T2	28-08-2008
		EP 1470427 A2	27-10-2004
		JP 4621777 B2	26-01-2011
		JP 2005516220 A	02-06-2005
		JP 2009162761 A	23-07-2009
		JP 2009168816 A	30-07-2009
		US 2003167822 A1	11-09-2003
		US 2003170903 A1	11-09-2003
		US 2007155019 A1	05-07-2007
		WO 03065049 A2	07-08-2003
US 6203759 B1	20-03-2001	US 6203759 B1	20-03-2001
		US 2001014477 A1	16-08-2001
		US 2001016177 A1	23-08-2001
WO 9835761 A1	20-08-1998	AU 4881597 A	08-09-1998
		CA 2280112 A1	20-08-1998
		DE 69726185 D1	18-12-2003
		DE 69726185 T2	02-09-2004
		EP 0958064 A1	24-11-1999
		JP 2001512363 A	21-08-2001
		SE 508511 C2	12-10-1998
		SE 9700543 A	18-08-1998
		US 6161772 A	19-12-2000
		WO 9835761 A1	20-08-1998
US 2007241130 A1	18-10-2007	US 2007241130 A1	18-10-2007
		US 2012104040 A1	03-05-2012
		WO 2007126908 A2	08-11-2007
EP 0682258 A1	15-11-1995	AT 200581 T	15-04-2001
		AU 676414 B2	06-03-1997
		AU 1147195 A	16-11-1995
		CA 2138857 A1	10-11-1995
		DE 69520614 D1	17-05-2001
		DE 69520614 T2	15-11-2001
		EP 0682258 A1	15-11-1995
		JP 3726919 B2	14-12-2005
		JP H08170963 A	02-07-1996
		PL 306731 A1	13-11-1995
		US 5503036 A	02-04-1996