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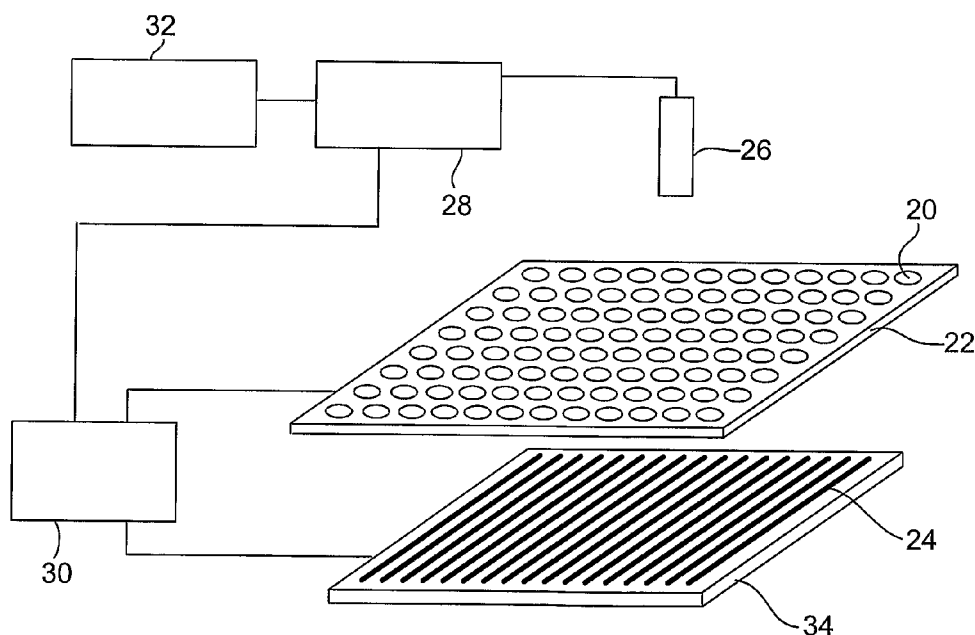
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(54) Title: METHOD AND APPARATUS FOR MEASURING SURFACE CONFIGURATION



(57) Abstract: An method and corresponding apparatus for measuring the configuration of a surface of a medium are disclosed. The apparatus comprises: a pattern; a detector arranged to sense the pattern via the surface of the medium and to produce an output signal; a driver arranged to move the medium and pattern relative to each other; and a processor arranged to measure the variation in the output signal of the detector while the medium and the pattern are in motion relative to each other to measure the distortion of the pattern when sensed via the surface of the medium.

WO 2007/039729 A1

METHOD AND APPARATUS FOR MEASURING SURFACE CONFIGURATION

The present invention relates to a method and apparatus for measuring the
5 configuration of a surface, in particular the surface of a liquid-liquid or liquid-gas
interface, but also other surfaces, such as membranes. In its application to measuring
liquid-liquid, liquid-gas interfaces it is useful in measuring various properties of
liquids, such as surface tension.

The configuration of the surface of a liquid contained, for instance, in a well
10 is dependent inter alia upon the surface tension of the liquid and the contact angle
between the liquid and the well.

Previously there has been disclosed in GB 2408572 a proposal for measuring
the surface configuration of a liquid medium by imaging a predefined pattern
through the medium and determining the distortion in the image. Although this
15 method works satisfactorily, it has a number of drawbacks. For example, it can
involve quite sophisticated image analysis to obtain information on the distortion of
the image. This can require complicated digital image processing hardware and
software which can be expensive to implement. Furthermore, there is a problem that
the distortion of the image, such as demagnification caused by variation in surface
20 tension, can have a very large dynamic range, so it can be difficult to provide a
pattern that can be imaged and identified in all circumstances. If the demagnification
is too small or the pattern is too coarse, then there are insufficient features visible to
enable accurate recognition and measurement of the image of the pattern.
Conversely, if the demagnification is too great and/or the pattern is too fine, then it
25 can be difficult to resolve the features in the image of the pattern, so again it is not
possible to accurately measure the distortion.

It is desirable to provide an improved method and apparatus for measuring
surface configuration.

30 According to one aspect of the present invention there is provided a method
of measuring the configuration of a surface of a medium comprising:

providing a pattern and a detector for sensing the pattern via the surface of the medium and producing an output signal;

moving the medium and pattern relative to each other; and

measuring the variation in the output signal of the detector while the medium
5 and the pattern are in motion relative to each other to measure the distortion of the pattern when sensed via the surface of the medium.

According to another aspect of the invention there is provided a method of measuring the configuration of a surface of a medium comprising:

generating a pattern and providing a detector for sensing the pattern via the
10 surface of the medium and producing an output signal; and

using the output signal of the detector to measure the distortion of the pattern when sensed via the surface of the medium,

wherein the pattern is generated using an addressable array of elements.

According to another aspect of the invention there is provided an apparatus
15 for measuring the configuration of a surface of a medium comprising:

a pattern;

a detector arranged to sense the pattern via the surface of the medium and to produce an output signal;

a driver arranged to move the medium and pattern relative to each other; and

20 a processor arranged to measure the variation in the output signal of the detector while the medium and the pattern are in motion relative to each other to measure the distortion of the pattern when sensed via the surface of the medium.

According to another aspect of the invention there is provided an apparatus for measuring the configuration of a surface of a medium comprising:

25 a display device for generating a pattern;

a detector arranged to sense the pattern via the surface of the medium and to produce an output signal; and

a processor arranged to use the output signal of the detector to measure the distortion of the pattern when sensed via the surface of the medium,

30 wherein the display device comprises an addressable array of elements for generating the pattern.

Embodiments of the invention will now be described, by way of non-limitative example, with reference to the accompanying drawings in which:-

Figure 1 is a diagram illustrating the principles of the invention;

Figure 2 illustrates the progressive distortion of an imaged pattern as surface
5 tension decreases;

Figure 3 is a schematic view of an embodiment of the invention; and

Figure 4 illustrates a detection principle according to a further embodiment of the invention.

10 The invention will be better understood by reference to Figures 1 and 2 which illustrate an example of an effect measured by the invention. Two liquid samples are shown contained in single wells about 100mm above a rectangular grid pattern. The well on the left contains a non-ionic detergent $C_{10}E_8$ (octaethylene glycol monodecyl ether) diluted in ultrapure water has a low surface tension (of about 35mN/m) and so
15 the meniscus of the liquid is highly curved as shown in the side view 10. The grid imaged through the liquid appears distorted, in this case highly de-magnified, as illustrated in the view from above 12. This contrasts with the liquid sample in the well on the left, shown in side view 14, which has a high surface tension (of about 72mN/m) and in which the meniscus is not very curved and the degree of de-
20 magnification of the grid pattern, visible in the view from above 16, is low.

Figure 2 illustrates the way the distortion, in this case de-magnification, changes progressively with changing surface tension. It illustrates the effect as the concentration of detergent $C_{10}E_8$ (as in the Figure 1 example) is changed from 0M to 0.01M, corresponding to a surface tension range of about 72mN/m to 30mN/m.

25 It is found that the surface de-magnification effect is visible to the human eye at surfactant concentrations of one micromolar, thus demonstrating the sensitivity of the technique. Thus the degree of distortion of the pre-determined pattern is a measure of the surface configuration of the sample, and in this case of the surface tension of the liquid.

30 Figure 3 illustrates schematically an arrangement in which liquid samples are contained in wells 20 of a microtitre plate 22. The method works with small quantities of liquid, as low as 100 microlitres or 50 microlitres, e.g. when the liquid

is in the wells of a 96 well assay plate. A predefined pattern, in this case a series of black and white stripes 24, is viewed by a detector 26 through the microtitre plate 22. The pattern 24 may be illuminated. Preferably the imaging is performed monochromatically to improve accuracy.

5 It will be appreciated that in practice the plate 22 can be a multi-well (e.g. 96 well) plate of the normal experimental type, on a commercially available support (not shown). This support may include temperature control for the plate. Other types of container can, of course, be used, such as vials, test tubes or specially-made sample containers, with consistent shape and optical properties. When viewing from above
10 or below, only the base of the container needs to be transmissive, as is the case with some commercially available microtitre plates.

The detector 26 can be embodied in a variety of different ways. For example it can comprise a light-sensitive element, such as a photodiode, photomultiplier tube or light-sensitive resistor. There can be one such light-sensitive element for each
15 well 20 in the plate 22, or there may be a single light-sensitive element with an array of optical fibres, with one fibre positioned above each well; a fast switcher selects the light from which fibre is received by the light-sensitive element. Alternatively, the detector 26 can be a high resolution digital camera, such as a CCD. It could be a line-scan CCD for imaging one row of wells 20 (in this embodiment the row of wells
20 would be parallel to the black and white stripes of the pattern 24), or could be a CCD for viewing the entire plate 22 in one go. The detector 26 can comprise a cylindrically corrected machine vision lens prior to the light-sensitive portion. The output signal of the detector 26 is fed to a processor 28.

The apparatus further comprises a driver 30 that causes the plate 22 and
25 pattern 24 to move relative to each other, by the driver causing one or other or both of the plate 22 and pattern 24 to move. In one example the detector 26 and the plate 22 are stationary and the pattern 24 is controlled by the driver 30 to move. In another example the detector 26 and the pattern 24 are stationary and the plate 22 is controlled by the driver 30 to move. In both cases, the direction of motion is in the
30 horizontal direction perpendicular to the length of the black and white stripes of the pattern 24. In either case, when viewing one of the wells 20 from above, a sequence of dark and light stripes passing beneath the well is observed, either because of the

motion of the pattern itself, or because of the motion of the plate and the fact that a demagnified pattern is observed. Thus the signal from the detector or portion of the detector 26 viewing a point through the well 20 undergoes oscillations as the light received from that point alternately becomes bright and dark due to the real or
5 perceived motion of the stripes of the pattern 24.

The frequency of oscillation of the signal for a particular well is indicative of the demagnification and thus of the surface configuration and surface tension of the transmissive medium in that well. The frequency will, of course, be proportional to the speed of the relative motion between the plate 22 and the pattern 24, however,
10 one or more calibration runs can be performed using wells containing samples of known reference properties to provide a relationship between the signal frequency and the particular property being measured, such as surface tension. The calibration results can be stored in a data store 32 associated with the processor 28 either in the form of a look-up table or as a formula embodying a mathematical relationship.

15 Thus for each well 20, a time-varying signal is obtained, and this temporal variation will have a particular frequency depending on the distortion of the pattern when seen through the medium in the well. In the case of, for example, a stationary plate 22 with one light-sensitive element of the detector 26 centred on each well, then the oscillating signal is directly obtained as the pattern 24 is moved beneath the plate
20 22. In the case of, for example the detector 26 comprising a CCD viewing the entire plate 22 or row of the plate 22 as the plate 22 is moved relative to a stationary pattern 24, then the signal from one pixel of the CCD can be analysed and a periodically varying portion of that signal identified as a particular well 20 passes underneath.

Qualitative screening of wells in which surface tension effects are significant
25 can easily be achieved with the above embodiments of the invention simply by comparing the frequency of the signal from the detector 26 for a particular well with a predetermined threshold frequency. This can give a simple pass/fail result which can be useful as a pre-screen for a high-throughput screening (HTS) of multi-well plates in which the surface tension variations risk causing false positives or false
30 negatives.

It should be noted that where there is a simple single detector per well, such as a photodiode or photo multiplier tube, the processor 28 can be implemented

entirely in analogue circuitry; the frequency of the detected signal is converted to a voltage level which is then compared with a threshold voltage by a comparator to provide a binary pass/fail result. Alternatively, the processor 28 can be implemented in digital electronics, either hard wired dedicated electronics, or as software running on a general purpose microprocessor, for example in a personal computer, and which would conveniently be the case when using a CCD as the detector.

The invention may also be embodied to provide quantitative results by using the processor 28 to compare the output signal with data or formulae stored in the data store 32 to produce an output indicative of a property to be measured, such as surface tension, analyte concentration or surface activity.

An alternative method of analysing the signal output by the detector 26 will now be described with reference to Figure 4 of the accompanying drawings. Figure 4 is a plot of the intensity or amplitude of the signal along the vertical axis against spatial position along the horizontal axis. Two light-sensitive elements of the detector 26 receive the light intensity at particular points indicated by the vertical arrows in Figure 4. The two light-sensitive elements could, for example, be separate photodiodes or could be separate pixels in a CCD. The two elements are separated by a known distance d in the direction of relative motion of the pattern 26 and/or wells 20, but the distance d is less than the width of a well, so that both elements receive light from the same well.

The signal from each element oscillates as the pattern 24 or well 20 move past the detector 26, and both receive the signal of the same fundamental frequency. However, because there is a spatial separation between the elements, there is a phase difference between the signals of the two elements. In the illustration of Figure 4, the phase difference is approximately one quarter of a cycle. The phase difference is inversely related to the spatial period of the pattern as observed through the medium in the well 20; a small phase difference indicates a long period, and a large phase difference indicates a smaller period. Thus by measuring the phase difference it is possible to quantify the distortion of the pattern, such as the demagnification, and thereby evaluate the property being measured, such as surface tension. The advantage of measuring the phase difference in this way is that it is independent of the speed of the relative motion of the plate 22 and pattern 24; therefore it does not

require precise control of the speed by the driver 30. In the previously-described arrangement, in which the frequency of the signal is obtained, if the speed of motion of the plate 22 or pattern 24 changes, then the signal frequency changes and previous calibrations will be invalid for the purposes of comparing the measured frequency
5 with previously obtained absolute threshold frequencies. With this embodiment, the phase-difference can be used in the analysis in exactly the same way as described above for frequency, for example by comparison with a threshold, or used in a formula, to obtain a required output result related to surface configuration.

The invention may be embodied in an automated apparatus which can rapidly
10 make measurements on many plates. It will be appreciated that an entire multi-well plate can be evaluated in one pass and so successive plates can be passed on a conveyor between the imaging device and a pattern, illuminated if necessary, beneath the conveyor. Thus thousands of surface tension measurements can be made without human intervention. The speed of the method makes it suitable for screening all
15 wells of an assay for unexpected surface active compounds during high-throughput screening (HTS) of large libraries of compounds in any photometric assay (during any photometry where there may be unexpected surface effects). In this example, in which a plate is carried on a conveyer, according to an embodiment of the present invention it is unnecessary even to pause the conveyer to make the measurements
20 because motion is an integral part of the measurement, so the measurement apparatus can conveniently be situated between other analysis stations of a larger apparatus, for performing surface configuration measurements while the plate is in transit. This is particularly convenient for the arrangement in which the pattern 24 and detector 26 are stationary.

25 According to an alternative embodiment, as previously explained, the pattern 24 may be in motion. One way to achieve this would be, for example, with a pattern formed on a belt that continuously rotates underneath the plate 22. However, another preferred embodiment is to generate a pattern using a device such as a display 34 having an addressable array of elements. The display 34 could be any suitable
30 display, such as a liquid crystal display (LCD), cathode ray tube (CRT), light emitting diode (LED) array, plasma screen, electromechanical display or e-paper. One specific example is an LCD for a laptop computer which already has appropriate

driving circuitry. The addressable array of elements comprises the pixels of the display. In other contexts, the addressable array of elements may also be referred to as a programmable element array or a spatial light modulator, and may be emissive, transmissive or reflective.

5 The driver 30 controls the display 34 to produce a desired pattern and also to scroll the pattern across the display at a desired rate in order to create the relative motion between the pattern 24 and the plate 22. Even though the display 34 itself is stationary the pattern can be caused to move.

 According to this embodiment, the spatial period of the pattern 24 can be
10 changed. In order to enable an accurate determination of the spatial period of the pattern when viewed through the medium in a well, or equivalently the temporal frequency or phase difference of the output signal of the detector, it is necessary to have at least a minimum number of cycles of the pattern per well, for example, preferably at least 10. A mode of operation of the apparatus is for the driver 30 to
15 initially generate a high spatial frequency pattern 24 which is viewed through the wells by the detector 26. If the spatial frequency of the pattern is too high, it will not be resolved by the light-sensitive elements of the detector 26 and so an oscillating signal is not obtained. The processor 28 feeds this information back to the driver 30 which then successively reduces the spatial frequency of the pattern 24 until a well
20 defined number of cycles per well is obtained to enable accurate measurement, again using feedback from the processor 28 to the driver 30. Consequently the apparatus can avoid the situation in the top left hand portion of Figure 2 in which there are hardly any cycles per well which would mean that an accurate quantitative analysis would not be possible.

25 In fact, the arrangement described above could also be used with an entirely stationary apparatus in which neither the pattern 24 nor the plate 22 is moving, but in which the resolution of the pattern is dynamically changed in order to optimise the measurement being performed.

 A further advantage of using a display 34, such as an LCD screen, is that the
30 colour of the pattern 24 can be changed, as necessary, depending for example on the colour and light absorption properties of the medium in the wells 20 such that good contrast can be obtained.

It will also be appreciated that in any of the above-described embodiments of the invention the assay plate 22 can be handled remotely using conventional equipment and the plates can be sealed before being passed to the apparatus for measurement. This means that it is possible to use the system to make measurements
5 on extremely toxic or infectious liquids. Further, measurements can be made in a non-air atmosphere (e.g. under argon to avoid oxidative damage); to measure in the presence of highly volatile compounds; or to measure at a pressure above or below atmospheric.

A stage controller may also be adapted to control the temperature of the assay
10 plate for instance by using a Peltier-disc controlled chamber similar to that of a PCR machine. This means that the surface configuration can be measured at a range of defined temperatures and can, for instance, allow repeated measurements to be made during a rising and falling temperature ramp. This can usefully give a quantification of temperature related surface effects such as surface tension hysteresis. The
15 invention also allows surface tension to be measured at a range of defined pressures and operation is possible in a non-air atmosphere. Furthermore, the speed and repeatability of measurement allows measurements to be repeated during a reaction, for instance to follow surface tension changes following initiation of a reaction by reagent addition optionally within the reader. Thus the fact that the measurements
20 are contactless and non-destructive and repeatable makes the apparatus highly versatile.

One application of the invention is in the field of process control where it is desired to maintain a consistent product quality as measurable by surface activity, such as surface tension. In this embodiment the apparatus is adapted to take regular
25 samples of the product and subject them to measurement. The result can be fed back to the production process to control a process parameter, for instance, the proportion of some reagents. The arrayed samples thus collected can be used as a quality control archive for the production run, and because the surface tension measurements are non-contact they do not preclude any other (e.g. chemical) measurement being
30 made subsequently.

Another application of the invention lies in the determination of surface activity of an analyte in a liquid. The change in surface activity with concentration

(or with time in the case of a reaction) can be evaluated by measuring the curvature of the surface of the liquid as described above.

In the embodiments above the invention has been used to measure surface tension. However the measurements made are characteristic of the surface configuration and thus the invention is applicable to the measurement of other quantities affecting the surface. One example of this is for measuring the viscosity of samples. A stage controller may be used to used to agitate the sample, in this case to swirl them, to create a vortex in each sample well. The result of this vortex is that the liquid is forced towards the outside of the well, and thus the surface curvature increases from the rest position. The agitation can then be ceased and the rate at which the surface returns to the rest position is dependent upon the viscosity of the sample. This rate of change is measured in exactly the same way as in the embodiments above, i.e. by imaging the distortion of the pattern. Alternatively, rather than imaging the relaxation time, it is possible simply to measure the change in the curvature created by the agitation which, again, will be dependent upon the viscosity of the liquid.

In the embodiments of the invention described above, the pattern and detector have been on opposite sides of the surface of the medium being measured, and the pattern has been sensed at the detector by transmission of light through the medium. According to an alternative embodiment, the pattern can be sensed at the detector by reflection of light off the surface of the medium, resulting in similar distortion of the pattern. In this case both the pattern and detector can be provided on the same side of the surface, for example both above the surface of the medium. Although the transmission arrangement is generally more convenient optically, the reflection arrangement can be advantageous in specific circumstances such as when access to both sides of the medium is not possible, or when the medium is opaque or has scattering effects or chromatic absorption effects at certain wavelengths. The reflection arrangement does not impose any requirements on the optical properties of the container, such as the well, holding the medium. Therefore, for example, short wavelength UV light can be used as the light from the pattern, without the requirement for an expensive UV-transparent window in the base of the plate.

In the preceding description, reference was made to 96-well plates. In this

case the diameter of each well would typically be in the range of 5 to 8 mm. The invention is not limited to this type of plate. Other plates are of course commercially available, with other numbers of well per plate, such as 384 (well diameter 3 to 4 mm) or 1536 (well diameter 1 to 2 mm). Plates are also available with larger wells, for example a 24-well plate or even a 6-well plate. However, in this case, where the wells are greater than about 10 mm across, the central area of the liquid surface shows gravitational flattening. The detector or processor can be arranged to identify and exclude this area, for example by defining an annular region of interest co-axial with the well centre, using image analysis, or simply only using the output signal for a predetermined distance from the periphery of the well.

CLAIMS

1. A method of measuring the configuration of a surface of a medium comprising:
5 providing a pattern and a detector for sensing the pattern via the surface of the medium and producing an output signal;
moving the medium and pattern relative to each other; and
measuring the variation in the output signal of the detector while the medium and the pattern are in motion relative to each other to measure the distortion of the
10 pattern when sensed via the surface of the medium.
2. A method according to claim 1, wherein the step of moving the medium and pattern relative to each other comprises moving the medium while the pattern is stationary.
15
3. A method according to claim 1, wherein the step of moving the medium and pattern relative to each other comprises moving the pattern while the medium is stationary.
- 20 4. A method according to claim 1, 2 or 3, wherein the distortion of the pattern is assessed from the frequency of the output signal.
5. A method according to any one of the preceding claims, further comprising the step of comparing the frequency of the output signal with a
25 predetermined threshold value.
6. A method according to anyone of the preceding claims, wherein the detector produces two output signals from different parts of the pattern, separated in the direction of relative motion of the pattern and medium, and the measuring step
30 comprises determining the phase difference between the two output signals.

7. A method according to any one of the preceding claims, wherein the pattern is generated using an addressable array of elements.

8. A method of measuring the configuration of a surface of a medium
5 comprising:

generating a pattern and providing a detector for sensing the pattern via the surface of the medium and producing an output signal; and

using the output signal of the detector to measure the distortion of the pattern when sensed via the surface of the medium,

10 wherein the pattern is generated using an addressable array of elements.

9. A method according to any one of the preceding claims, wherein the pattern is sensed via the medium by one of: transmission of light from the pattern through the surface of the medium; and reflection of light from the pattern by the
15 surface of the medium.

10. A method according to any one of the preceding claims, wherein the pattern is a periodic pattern.

20 11. A method according to any one of the preceding claims, wherein the pattern consists of parallel lines.

12. A method according to any one of the preceding claims, wherein the surface is a meniscus of a liquid.
25

13. A method according to any one of the preceding claims, comprising generating the pattern with an initial spatial frequency, then reducing the spatial frequency of the pattern until a desired resolution of the pattern at the detector is obtained.
30

14. An apparatus for measuring the configuration of a surface of a medium comprising:

a pattern;

a detector arranged to sense the pattern via the surface of the medium and to produce an output signal;

a driver arranged to move the medium and pattern relative to each other; and

5 a processor arranged to measure the variation in the output signal of the detector while the medium and the pattern are in motion relative to each other to measure the distortion of the pattern when sensed via the surface of the medium.

15. An apparatus according to claim 14, wherein the processor comprises
10 a comparator arranged to compare the frequency of the output signal with a threshold value.

16. An apparatus according to claim 14 or 15, wherein the detector
comprises two light sensitive elements, arranged to produce an output signal from
15 different parts of the pattern, the respective parts of the pattern being separated in the direction of relative motion of the pattern and medium, and the processor is arranged to determine the phase difference between the two output signals.

17. An apparatus according to claim 14, 15 or 16, further comprising an
20 addressable array of elements for generating the pattern.

18. An apparatus for measuring the configuration of a surface of a
medium comprising:

a display device for generating a pattern;

25 a detector arranged to sense the pattern via the surface of the medium and to produce an output signal; and

a processor arranged to use the output signal of the detector to measure the distortion of the pattern when sensed via the surface of the medium,

wherein the display device comprises an addressable array of elements for
30 generating the pattern.

19. An apparatus according to claim 17 or 18, wherein the addressable array of elements comprises one selected from the group consisting of: a liquid crystal display, cathode ray tube, light emitting diode array, plasma screen, electromechanical display and e-paper.

5

20. An apparatus according to any one of claims 14 to 19, wherein the detector is arranged to sense the pattern via the medium by one of: transmission of light from the pattern through the surface of the medium; and reflection of light from the pattern by the surface of the medium.

10

21. An apparatus according to any one of claims 14 to 20, wherein the pattern is automatically changeable in response to feedback from the processor.

Fig. 1

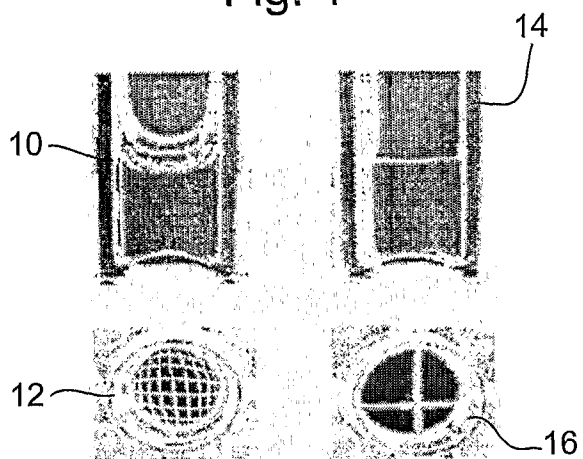


Fig. 2

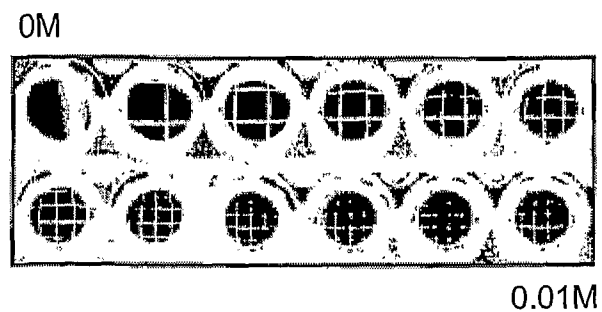


Fig. 3

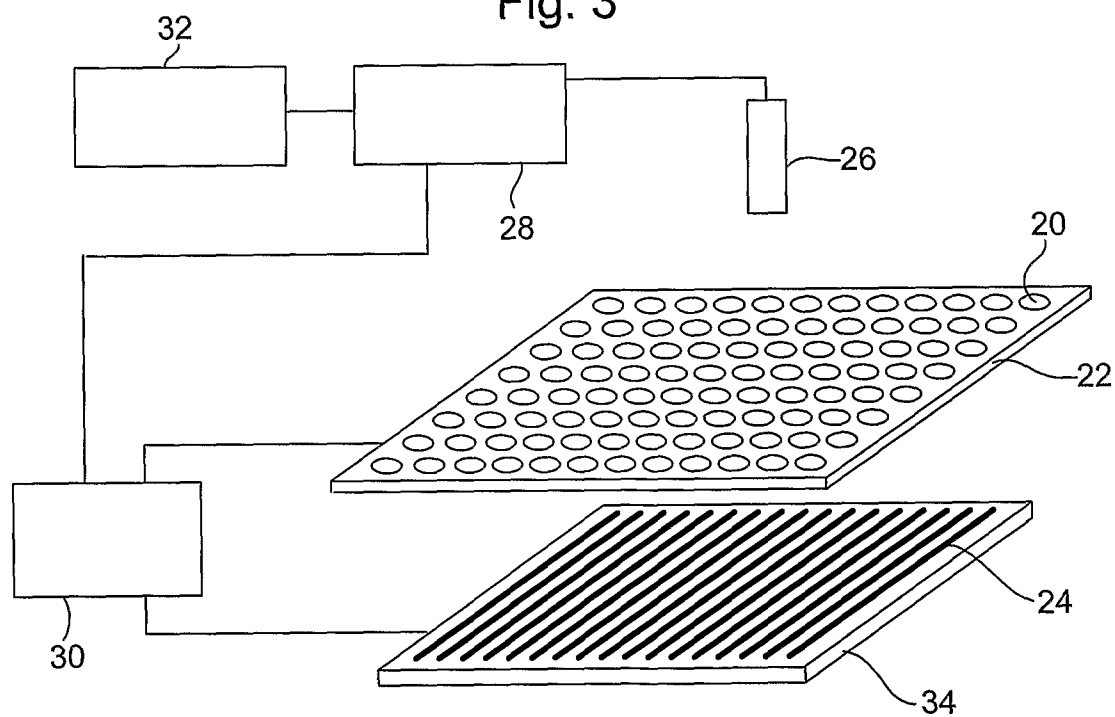
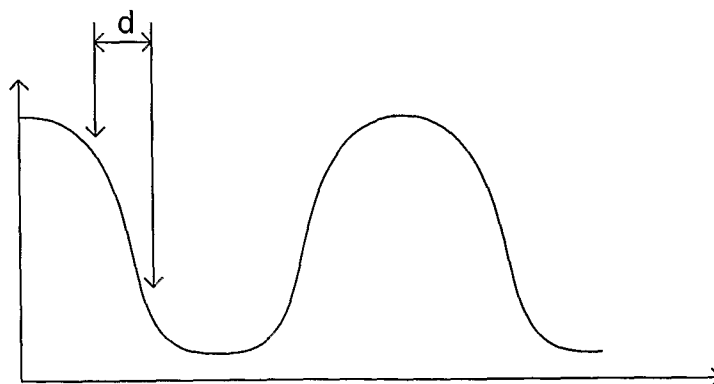


Fig. 4



INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/003674

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N13/02

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)
G01N G01B

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 practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 556 097 A1 (NIPPON SHEET GLASS CO LTD [JP]) 7 June 1985 (1985-06-07) page 2, line 28 - page 6, line 25; figures 1-6	1-21
X	GB 2 408 572 A (ISIS INNOVATION [GB]) 1 June 2005 (2005-06-01) the whole document	1,8,14, 18
X	US 2004/057046 A1 (ABBOTT MARK M [US] ET AL) 25 March 2004 (2004-03-25) paragraphs [0050] - [0054]; figures 1-12	1-21
A	US 2003/128371 A1 (VAUX DAVID JOHN [GB] ET AL) 10 July 2003 (2003-07-10) paragraphs [0029] - [0032]; figures 1-3 ----- -/--	1,8,14, 18



Further documents are listed in the continuation of Box C.



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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

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Z document member of the same patent family

Date of the actual completion of the international search

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