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[Continued on next page]

(54) Title: MOVING MENISCUS RINSING AND MIXING IN CELL STAINING

(57) Abstract: An automated cell staining apparatus comprises a translatable head and at least one mixing extension. The translatable head is positionable over a slide and has a lower surface. A portion of the lower surface is spaced apart from the slide by a first gap sufficiently small to allow a meniscus of liquid to form from liquid on the slide during translation of the slide. A mixing extension extends from the lower surface of the translatable head, defines a second gap smaller than the first gap between the mixing extension and the slide, and has a lateral dimension less than the width of the slide and sufficient to generate lateral movement in the liquid on the slide during translation of the head in a direction generally extending from the second gap to the first gap.

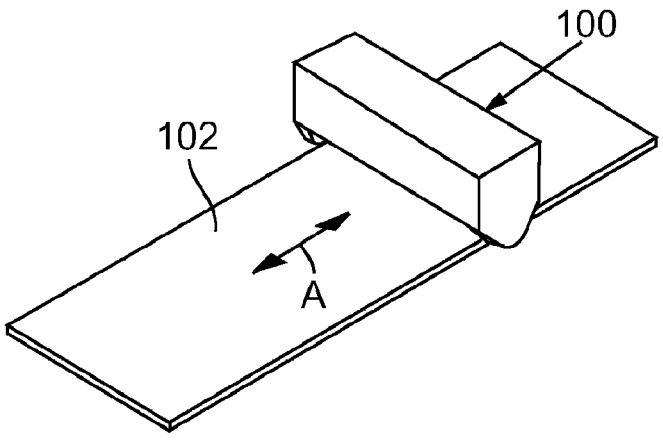


FIG. 1

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Published:

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MOVING MENISCUS RINSING AND MIXING IN CELL STAINING

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Applications No. 61/331,335, filed May 4, 2010, and 61/469,661, filed on March 30, 2011, which are incorporated herein by this reference.

FIELD

This application relates to cell staining technology, and in particular to automated cell staining equipment and methods.

BACKGROUND

One known type of automated slide staining system relies on moving a member (commonly called a "head") back and forth across a microscope slide on which a specimen to be tested is provided. The moving or translating head is kept at a desired gap above the slide that is sufficiently small to allow a meniscus of fluid to form across the gap between the slide and the lower surface of the head. As the head translates back and forth relative to the slide, the meniscus is dragged by the head, thus facilitating the mixing of the fluid on the slide. The translating head has a width corresponding to the width or narrow dimension of a standard microscope slide. Guide surfaces assist in keeping the head aligned with the slide during movement. This technology, sometimes referred to as the "translating gap" approach, is described in the present assignee's U.S. Patent No. 7,820,381, which is incorporated herein by reference.

Although the current translating gap technology provides a workable solution, even better mixing of the reagents on the slide can decrease the required processing time and also allow use of less reagent in some circumstances. Thus, achieving better mixing can help reduce costs.

It would be advantageous to improve the mixing over the level that can be carried out with the use of current translating gap technology. Providing for enhanced rinsing of the slide surface, e.g., between steps in a cell staining sequence, would also be advantageous.

SUMMARY

Described below are various embodiments and methods that use a moving meniscus to improve mixing in cell staining.

According to one implementation, an automated cell staining apparatus comprises a translatable head and at least one mixing extension. The translatable head is positionable over a slide. The head has a lower surface with a lateral dimension transverse to a direction of translation at least as great as a width of the slide. A portion of the lower surface is spaced apart from the slide by a first gap sufficiently small to allow a meniscus of liquid to form from liquid on the slide during translation of the slide. The mixing extension extends from the lower surface of the translatable head. The mixing extension defines a second gap smaller than the first gap between the mixing extension and the slide. The mixing extension has a lateral dimension less than the width of the slide. During translation of the head, the lateral dimension of the mixing extension is sufficient to generate lateral movement in the liquid on the slide in a direction generally extending from the second gap to the first gap.

The translatable head can comprise rail surfaces extending from the lower surface of the head and dimensioned to contact a surface to keep the mixing extension spaced from the slide by the second gap and keep the portion spaced from the slide by the first gap.

In one implementation, the mixing extension can be dimensioned relative to the rail surfaces to produce a second gap between the mixing extension and the slide of about 80 microns. The mixing extension can be approximately centered relative to the lower surface of the head. The first gap between the lower surface and the slide can be about 400 microns. The lateral dimension of the mixing extension can be about 25% of the lateral dimension of the lower surface.

The apparatus can comprise a linear slide coupled to the translatable head, wherein the linear slide is controllable to cause the translatable head to translate relative to the slide.

The translatable head can have at least one opening through which suction can be applied sufficient to remove liquid from a slide by vacuum aspiration through

the opening. The apparatus can comprise a source of vacuum pressure connected to the at least one opening.

The translatable head can include a rinse outlet gap, and the head can be configurable to controllably expel rinse liquid in a direction away from the head and toward the slide to rinse the slide and other surfaces. The apparatus can comprise a source of rinse liquid connected to the rinse outlet gap.

According to another implementation, an automated cell staining apparatus comprises a rockable cap positionable over a slide, the rockable cap having a curved surface dimensioned at least as large as a working area of the slide, the curved surface being spaced apart from the slide by a desired gap sufficiently small to allow a meniscus of liquid to form by capillary action from liquid on the slide, the cap being rockable back and forth to contact and mix the liquid on the slide.

The rockable cap comprises at least one surface extending from the curved surface of the cap and dimensioned to contact the slide while keeping at least a portion of the curved surface spaced apart from the slide by the desired gap. In one implementation, the desired gap is about 50 microns. The curved surface of the rockable cap has a longitudinal axis, and the cap can be positionable relative to the slide such that the longitudinal axis of the cap is substantially parallel with a longer side of the slide.

These and other features and advantages will become more apparent from the following detailed description, which proceeds with reference to the accompanying drawings.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 is a perspective view of a translating head that drags reagent across the slide through capillary action at a gap between the head and an upper surface of the slide.

Fig. 2 is a perspective view of a shaped cap having a curved under surface positioned in contact with liquid on the slide and rockable back and forth to mix the liquid.

Fig. 3(a) is a transparent perspective view of a specific embodiment of the head shown in Fig. 1 that also shows the internal structure of the head.

Fig. 3(b) is a front elevation view of the head of Fig. 3(a).

Fig. 3(c) is a top plan view of the head of Fig. 3(a).

Fig. 3(d) is a bottom plan view of the head of Fig. 3(a).

Fig. 3(e) is a side elevation view of the head of Fig. 3(a).

Fig. 3(f) is a side elevation view in section taken at the line 3(f)-3(f) in Fig. 3(b).

Fig. 3(g) is a front elevation view in section taken at the line 3(g)-3(g) in Fig. 3(e).

Fig. 4(a) is a front perspective view of a translating gap head in position over a microscope slide.

Fig. 4(b) is an enlarged cross-sectional view in elevation showing the gap between the translating gap head and the microscope slide at a point spaced away from the mixing projection.

Fig. 4(c) is an enlarged cross-sectional view in elevation showing the smaller gap between the mixing extension on the translating gap head and the microscope slide.

Figs. 5(a)-5(g) are various views of a two-piece translating gap head according to an alternative embodiment.

Figs. 6(a)-6(c) are various views of the cap piece of the translating gap head of Figs. 5(a)-5(g).

Figs. 7(a)-7(f) are various views of the base piece of the translating gap head of Figs. 5(a)-5(g).

Fig. 8 is a perspective view of a linear guide screw powered by a stepper motor for moving the translating gap head.

Figs. 9(a) and 9(b) are elevation views of the linear guide screw and translating gap head in operation.

DETAILED DESCRIPTION

Referring to Fig. 1, an embodiment of the translating gap head 100 is shown in relation to a conventional microscope slide 102 or other similar surface having a specimen and over which it is desired to apply a layer of reagent or other liquid. After reagent is dispensed onto the slide 102, the translating gap head makes contact

with the reagent while maintaining a physical gap, such as, e.g., about 400 microns (about 0.003 inch) between the surface of the translating gap head 100 and the top surface of the microscope slide, as shown in Fig. 4(a). The translating gap head 100 then moves back and forth across the slide 102, typically in the longitudinal direction A of the slide parallel to its longer sides (Fig. 1), dragging along with it the reagent through capillary attraction. As a result, the entire working area of the slide 102 is covered with reagent. Using this method, reagent volumes as low as 25 microliters are sufficient for complete coverage of the slide 102.

It has been found that promoting even greater mixing of the liquids on the slide 102, which may be reagents or other liquids, while the translating gap head 100 is translating along the direction A, would be advantageous. Better mixing can allow use of less reagent, which saves on costs and in some circumstances, saves on processing time, too.

It has been discovered that mixing is improved if a portion of the available gap G1 is reduced. One or more mixing extensions 104 or projections, as shown, e.g., in Figs. 3(b), 4(a) and 4(c), can be added to the bottom surface of the translating gap head 100, thus placing structure closer to the surface of the slide. A resulting second gap G2 between a distal end of the mixing extension 104 and the slide 102, e.g., of about 80 microns (Fig. 4(c)), is smaller than the first gap G1 of about 400 microns (Fig. 4(b)) over the rest of the lower surface of the head 102. When the head 100 is caused to translate, liquid L on the slide 102 at a level above the first gap will be pushed by the approaching mixing extension, causing some of it to deflect laterally. The deflected liquid seeks a path of least resistance and tends to flow laterally along the advancing head 100 until it encounters a part of its leading edge that is separated from the slide 102 by the greater first gap G1. Thus, the mixing extension 104 promotes lateral movement and mixing of the liquid(s) on the slide 102 even when the primary motion of the head 100 is translation in the direction A.

As shown in the illustrated embodiment, e.g., in Fig. 3(b), the mixing extension 104 is typically narrower than the width of the head 100. In one embodiment, the mixing extension 104 is about 25% of the width of the head 100. In other embodiments, the mixing extension 104 can have a greater or lesser lateral

dimension, provided it is sufficient to generate lateral movement of the liquid and to promote mixing.

The mixing extension 104 can be positioned centrally as shown in the illustrated embodiment, thus defining portions 105 of the lower surface on either side of the mixing extension 104. Alternatively, the mixing extension 104 could be positioned at an off-center location.

As shown, e.g., in Fig. 3(b) and 4(a), the head 100 can have rail surfaces 112 on either side that project downwardly from the lower surface of the head and are dimensioned to contact a surface so as to assist in guiding the head when it is translated and to maintain the first and second gaps G1, G2 relative to the slide 102. In the illustrated embodiment, the rail surfaces 112 are spaced farther apart than the width of the slide and are positioned to contact a support surface upon which the slide 102 rests.

Cell staining procedures typically require complete coverage of the microscope slide with one or more reagents, and nearly constant interaction between these reagents and the tissue sample. The procedures typically involve multiple steps, so the reagent(s) used in each step usually need to be removed from the slide after the step is completed. New reagent(s) is then applied to the slide for use in subsequent steps. In addition to spreading and mixing reagent as discussed above, it has been discovered that configuring the translatable head 100 to assist in removing reagents from the slide is advantageous. For example, the illustrated embodiment of Figs. 3(a)-3(g) has a series of small openings 106 in the lower surface of the head 100 through which a suction force can be applied to remove reagent from the slide 102 by vacuum aspiration. When a cell staining step is complete, suction is applied to the head 100 as it moves back and forth across the slide 102 to enable removal of reagent on the slide. Removing reagent in this way is quick, minimizes the need for additional specialized slide cleaning equipment and lessens the chance of introducing contaminants into the system.

Referring to Fig. 3(g), which is a section view of the head 100 in elevation, the openings 106 have respective passages leading to a common manifold 108, which in turn is connected to a source of suction pressure (not shown) at an opening 110 in the upper surface of the head 100.

A translating gap head 300 according to an alternative embodiment is shown in Figs. 5(a)-5(e). Referring to Fig. 5(a), which is a perspective view, the head 300 includes a cap 320 that fits over a base 322. Fig. 5(b) is a top plan view of the head 300 showing three rinse inlet ports 324. In the head 300, in addition to removal of reagent by vacuum aspiration, there is a capability to supply rinse liquid under pressure to allow for controllably rinsing the slide, such as before each step in a staining process. Fig. 5(c) is an elevation view in section of the head 300 that shows the rinse inlet ports 324 in the cap 320 and passages 306 in the base 322 through which vacuum is applied.

Fig. 5(d) is a section view in elevation showing passageways 326 for conveying the rinse liquid to the slide. In the illustrated embodiment, the passageways are configured in the spaces between the cap 320 and the base 322.

Fig. 5(e) is a front elevation view of a magnified portion of the head 300. Specifically, Fig. 5(e) shows a lateral guide surface 330, a rail surface 312 and a lower surface of the head 305 spaced about 50 microns above the rail surface 312.

Fig. 5(f) is a perspective view similar to Fig. 5(a), except with a portion of the head 300 cut away to show the arrangement of the passages 306, the rinse liquid passageways 326 and a vacuum port 310. Fig. 5(g) is another perspective cutaway view of the head 300.

Fig. 6(a) is a bottom plan view of the body 322 showing the array of vacuum inlets and the rail surfaces 312. Fig. 6(b) is a front elevation view of the body 322. Fig. 6(c) is an elevation view in section showing the intersection between the passages 306 and the vacuum port 310.

Fig. 7(a) is a perspective view of the cap 320. Fig. 7(b) is a plan view of the bottom side of the cap showing the rinse inlet ports 324, as well as rinse bleed slots 330 and distribution channels 332 that lead from the rinse inlet ports. Fig. 7(c) is sectioned side elevation view. Fig. 7(d) is a sectioned front elevation view showing the rinse inlet ports 324 and one of the bleed slots 330. The bleed slot 330 for center rinse inlet port 324 is shown in a magnified elevation view in Fig. 7(e). Fig. 7(f) is a perspective view showing an underside of the cap 320.

As shown in Fig. 8, the back and forth translation motion of the translating gap head, such as the head 100, can be achieved using a screw-driven linear guide

500 which is powered by a two-phase stepper motor 502. The screw-driven linear guide 500 is arranged horizontally. An air actuator 504 between the translating gap head 100 and the screw-driven linear slide 500 provides up and down motion to the translating gap head 100. As shown in Fig. 9(a), the air actuator can be actuated to extend and place the head 100 close to the slide 102. As shown in Fig. 9(b), the air actuator can be retracted to withdraw the head 100 away from the slide 102, such as when a step in the staining process is complete.

The actuator 504 allows for the removal of the slide 102 by lifting the translating gap head 100 vertically away from the slide 102. The linear guide 500 then moves the translating gap head 100 horizontally, allowing enough room for removing the slide 102. The actuator 504 also applies appropriate force to the head 100 to maintain the gaps G1, G2 as the head 100 translates.

As an alternative to the translating gap approach, a cap shaped to contact and spread liquid on the slide 102 can be used instead of the translating head. Referring to Fig. 2, a cap 201 may have a curved surface dimensioned to have a length approximately as long as the working length of the slide 102. In this way, the cap 201 can be caused to rock back and forth to spread liquid reagent 40 on the slide 102, without requiring the cap 201 to translate back and forth. The rocking action of the cap 201 shifts the meniscus formed in the liquid reagent 40 on the slide 60 back and forth, thus tending to mix the reagent on the slide. In the illustrated embodiment, there are outer rails 202 provided at each end and having a height set to establish a gap between the cap 201 and the slide 102, or between the cap 201 and the liquid reagent 40 on the slide 60, as desired. In the illustrated embodiment, the rails 202 are each about 50 microns in height. The slide 102 may have a bar code identifier, such as a bar code label 290 as shown in Fig. 2.

The various functions of the translating head, including translation, vertical motion, application of vacuum force, rinsing, etc., can be controlled, such as by using a microprocessor-based control circuit, as is known by those of skill in the art.

The translating head can be used in a steam heating environment. In some implementations, it is advantageous to heat the specimen on the slide and the reagent, and to do so quickly and controllably. Providing a source of steam to a chamber that surrounds the head and the slide, and providing for quenching the

steam with ambient air to control the temperature in the chamber, produces excellent results.

In view of the many possible embodiments to which the disclosed principles may be applied, it should be recognized that the illustrated embodiments are only preferred examples and should not be taken as limiting in scope. Rather, the scope of protection is defined by the following claims.

Claims:

1. An automated cell staining apparatus, comprising:

a translatable head positionable over a slide, the head having a lower surface with a lateral dimension transverse to a direction of translation at least as great as a width of the slide, wherein a portion of the lower surface is spaced apart from the slide by a first gap sufficiently small to allow a meniscus of liquid to form from liquid on the slide during translation of the slide; and

at least one mixing extension extending from the lower surface of the translatable head, the mixing extension defining a second gap smaller than the first gap between the mixing extension and the slide, wherein the mixing extension has a lateral dimension less than the width of the slide and sufficient to generate lateral movement in the liquid on the slide during translation of the head in a direction generally extending from the second gap to the first gap.

2. The apparatus of claim 1, wherein the translatable head comprises rail surfaces extending from the lower surface of the head and dimensioned to contact a surface to keep the mixing extension spaced from the slide by the second gap and keep the portion spaced from the slide by the first gap.

3. The apparatus of claim 2, wherein the mixing extension is dimensioned relative to the rail surfaces to produce a second gap between the mixing extension and the slide of about 80 microns.

4. The apparatus of claim 1, wherein the mixing extension is approximately centered relative to the lower surface of the head.

5. The apparatus of claim 1, wherein the first gap between the lower surface and the slide is about 400 microns.

6. The apparatus of claim 1, wherein the lateral dimension of the mixing extension is about 25% of the lateral dimension of the lower surface.

7. The apparatus of claim 1, further comprising a linear slide coupled to the translatable head, wherein the linear slide is controllable to cause the translatable head to translate relative to the slide.

8. The apparatus of claim 1, wherein the translatable head includes at least one opening through which suction can be applied sufficient to remove liquid from a slide by vacuum aspiration through the opening.

9. The apparatus of claim 8, further comprising a source of vacuum pressure connected to the at least one opening.

10. The apparatus of claim 1, wherein the translatable head includes a rinse outlet gap, and wherein the head is configurable to controllably expel rinse liquid in a direction away from the head and toward the slide to rinse the slide and other surfaces.

11. The apparatus of claim 10, further comprising a source of rinse liquid connected to the rinse outlet gap.

12. An automated cell staining apparatus, comprising:

a rockable cap positionable over a slide, the rockable cap having a curved surface dimensioned at least as large as a working area of the slide, the curved surface being spaced apart from the slide by a desired gap sufficiently small to allow a meniscus of liquid to form from liquid on the slide by capillary action, the cap being rockable back and forth to contact and mix liquid on the slide.

13. The apparatus of claim 12, wherein the rockable cap

comprises at least one surface extending from the curved surface of the cap and dimensioned to contact the slide while keeping at least a portion of the curved surface spaced apart from the slide by the desired gap.

14. The apparatus of claim 12, wherein the desired gap is about 50 microns.

15. The apparatus of claim 12, wherein the curved surface of the rockable cap has a longitudinal axis, and wherein the cap is positionable relative to the slide such that the longitudinal axis of the cap is substantially parallel with a longer side of the slide.

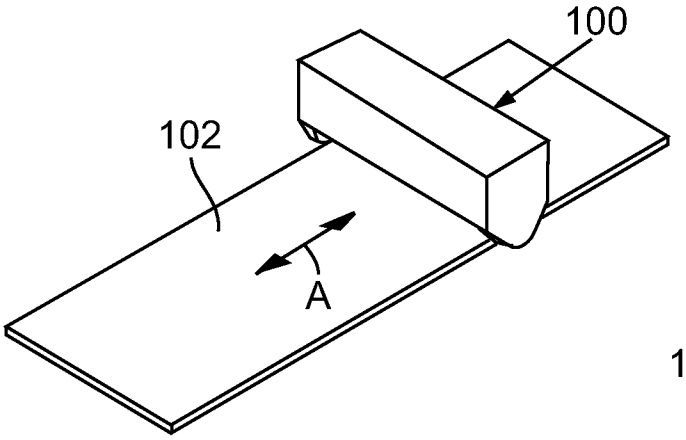


FIG. 1

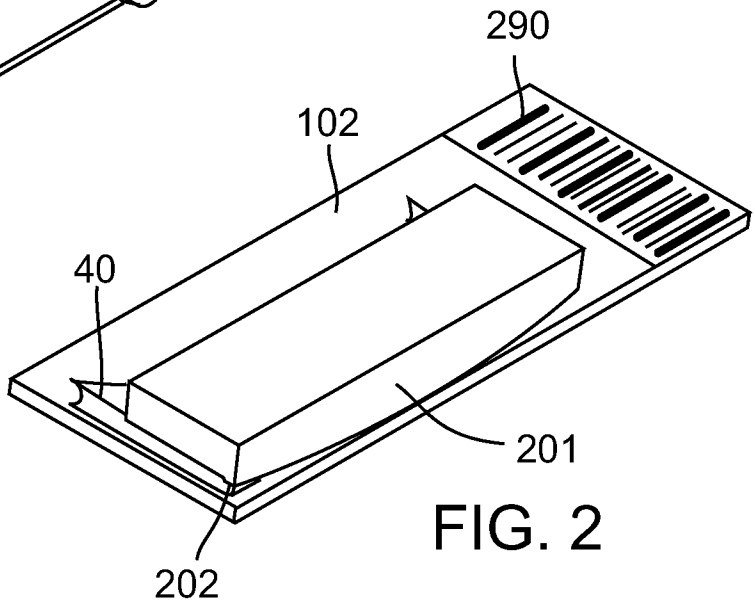


FIG. 2

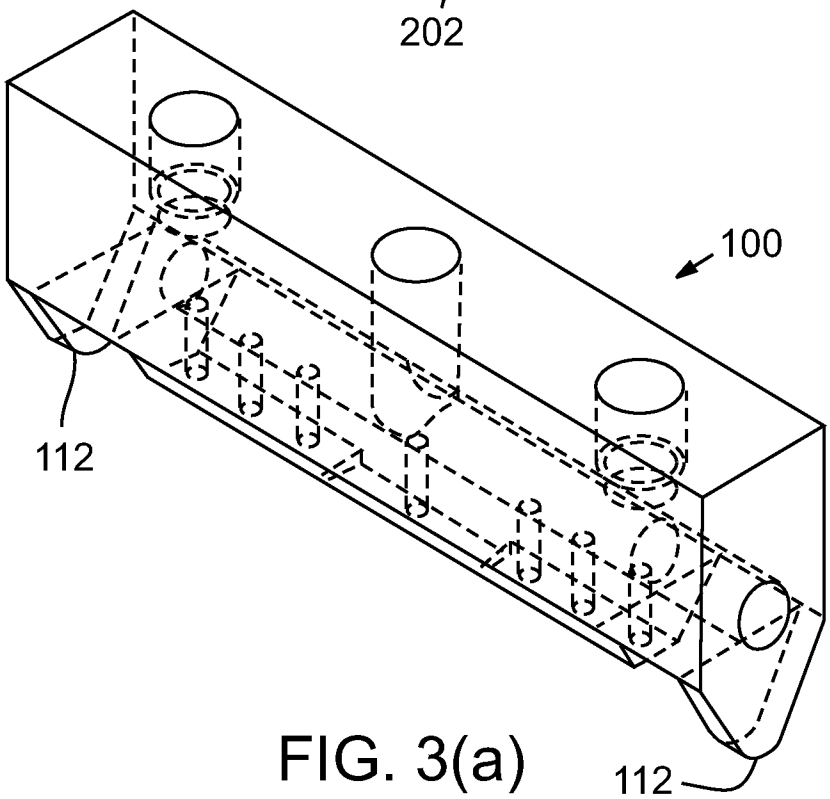


FIG. 3(a)

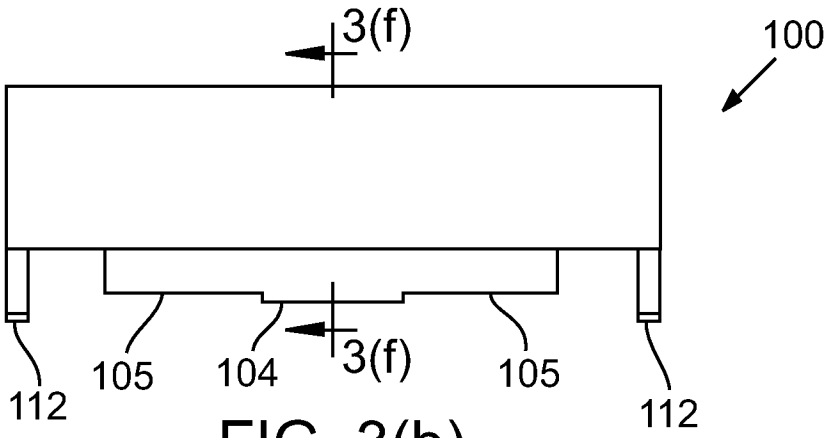


FIG. 3(b)

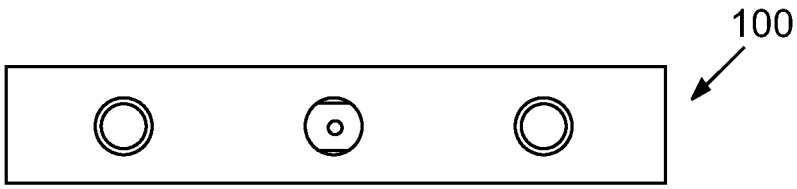


FIG. 3(c)

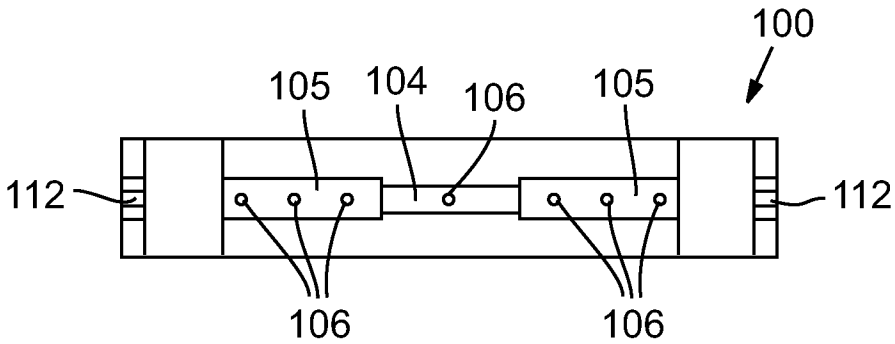


FIG. 3(d)

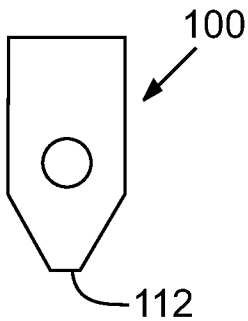


FIG. 3(e)

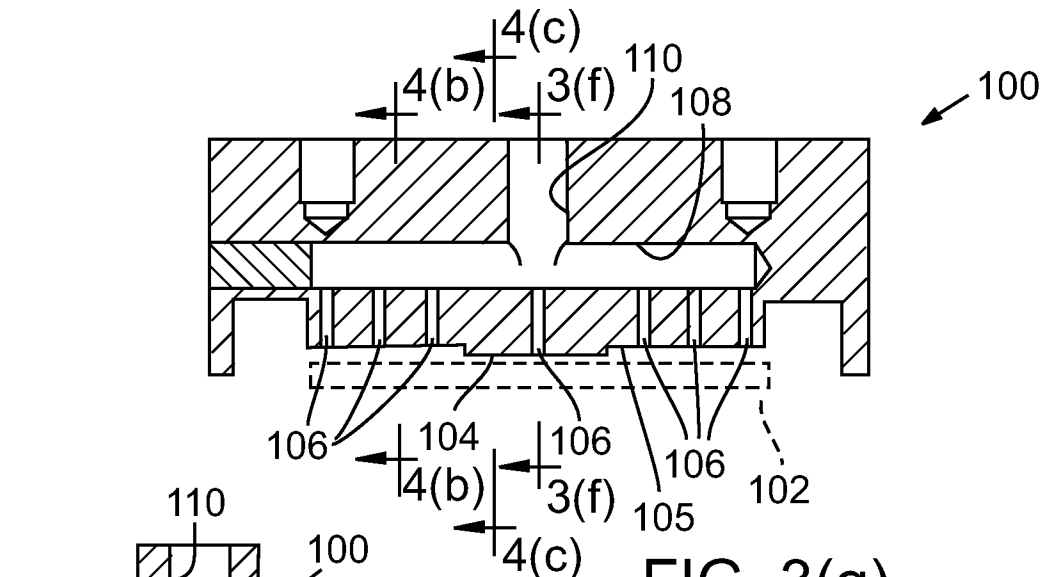


FIG. 3(g)

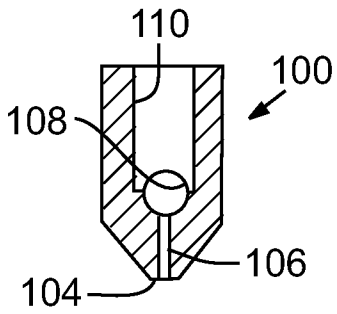


FIG. 3(f)

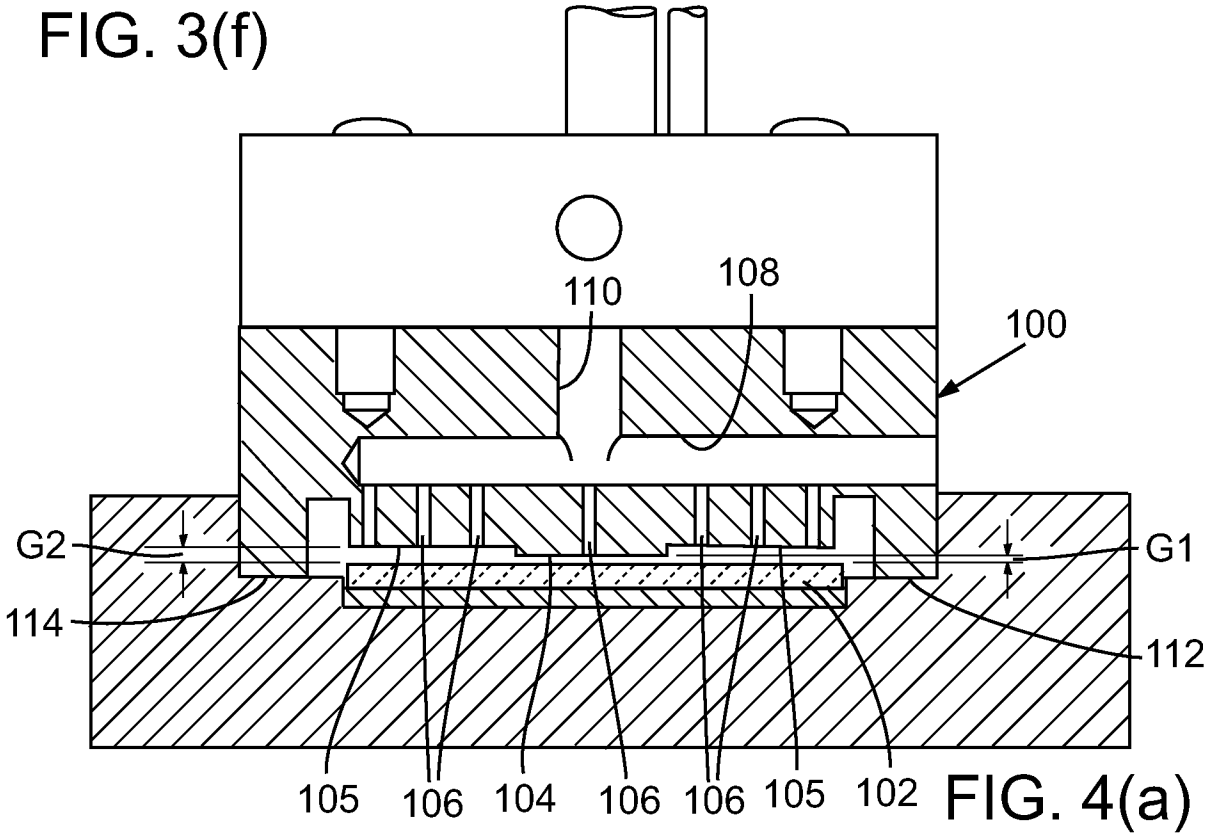


FIG. 4(a)

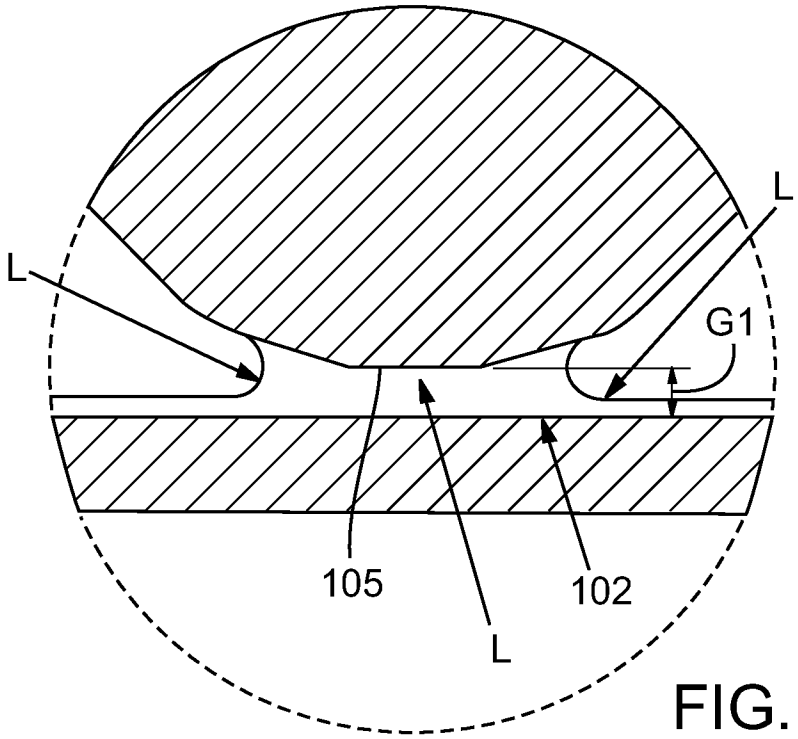


FIG. 4(b)

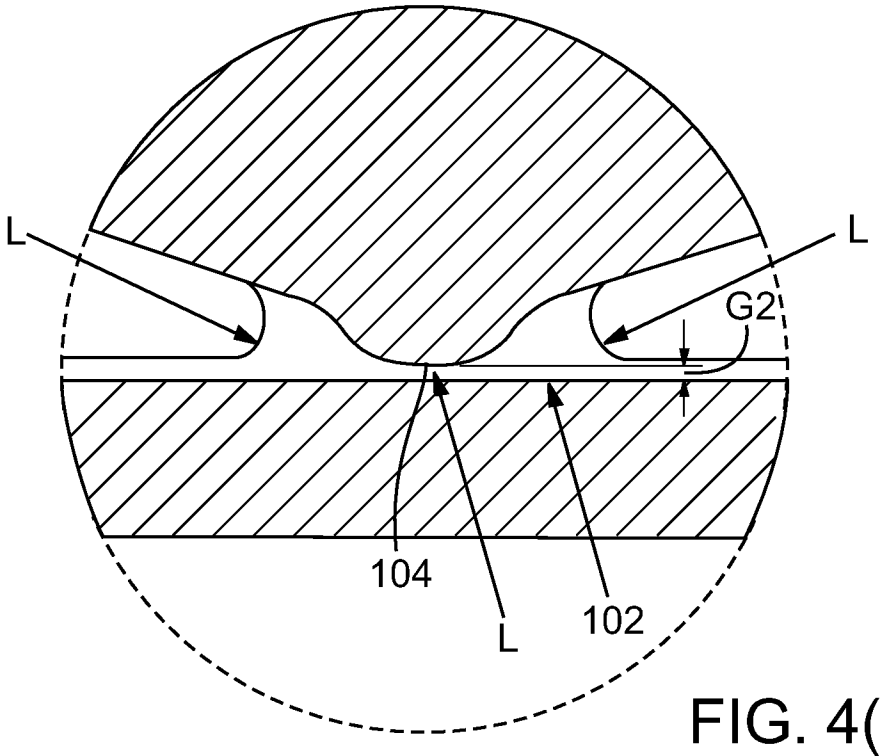


FIG. 4(c)

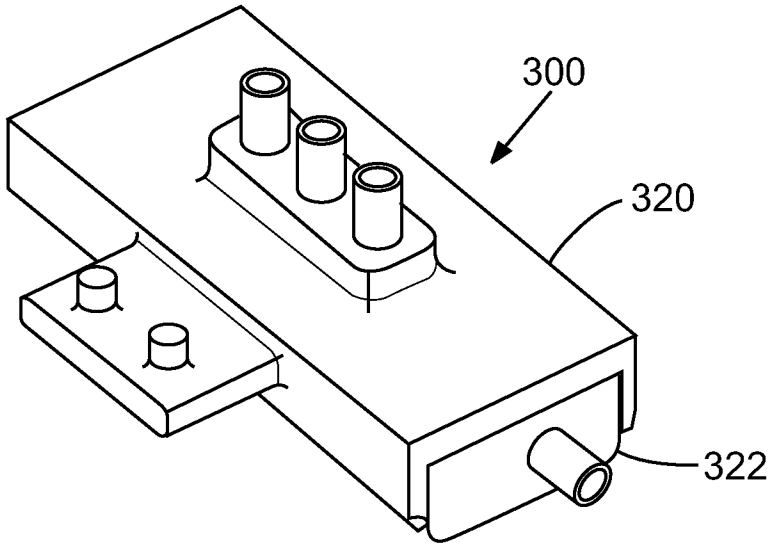


FIG. 5(a)

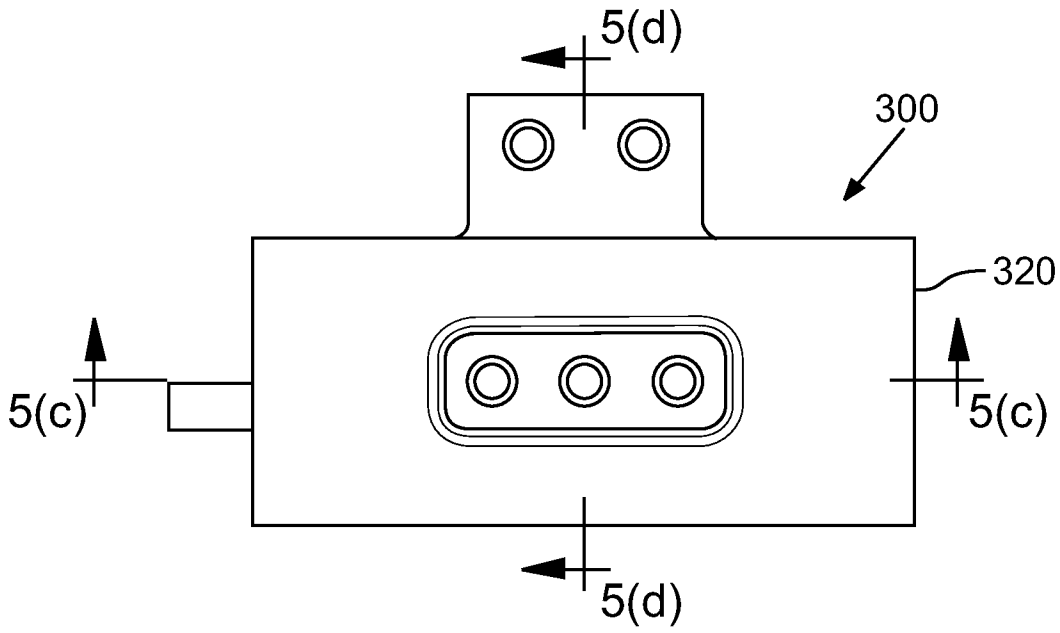


FIG. 5(b)

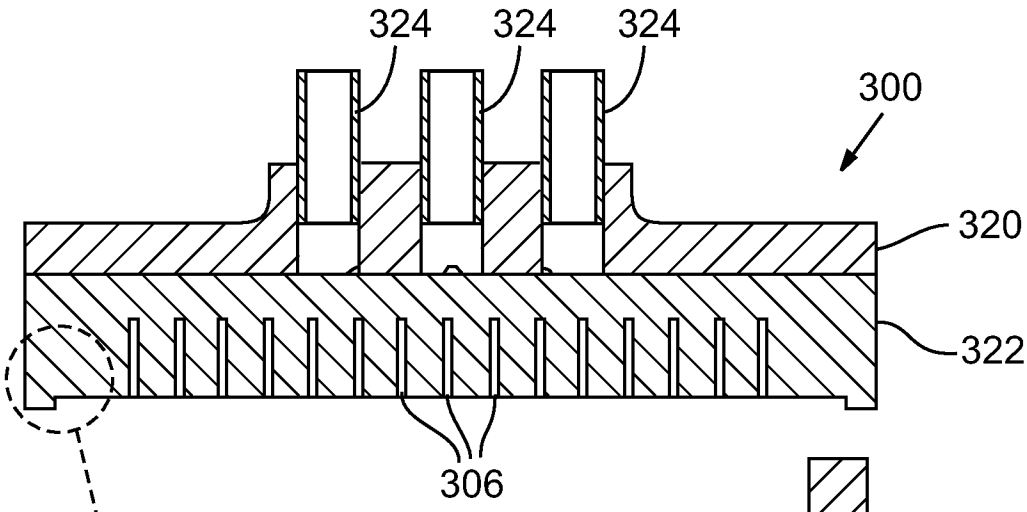


FIG. 5(e)

FIG. 5(c)

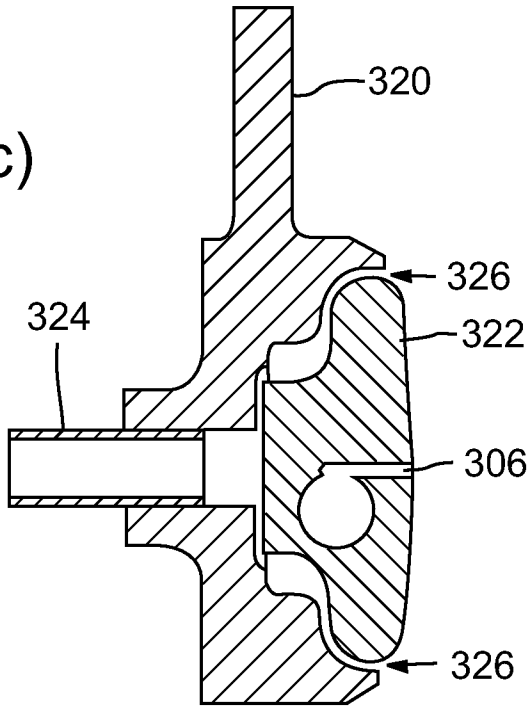


FIG. 5(d)

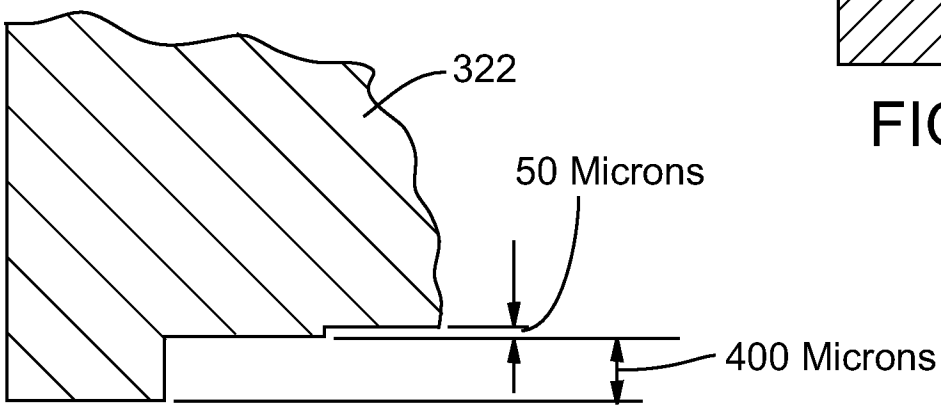


FIG. 5(e)

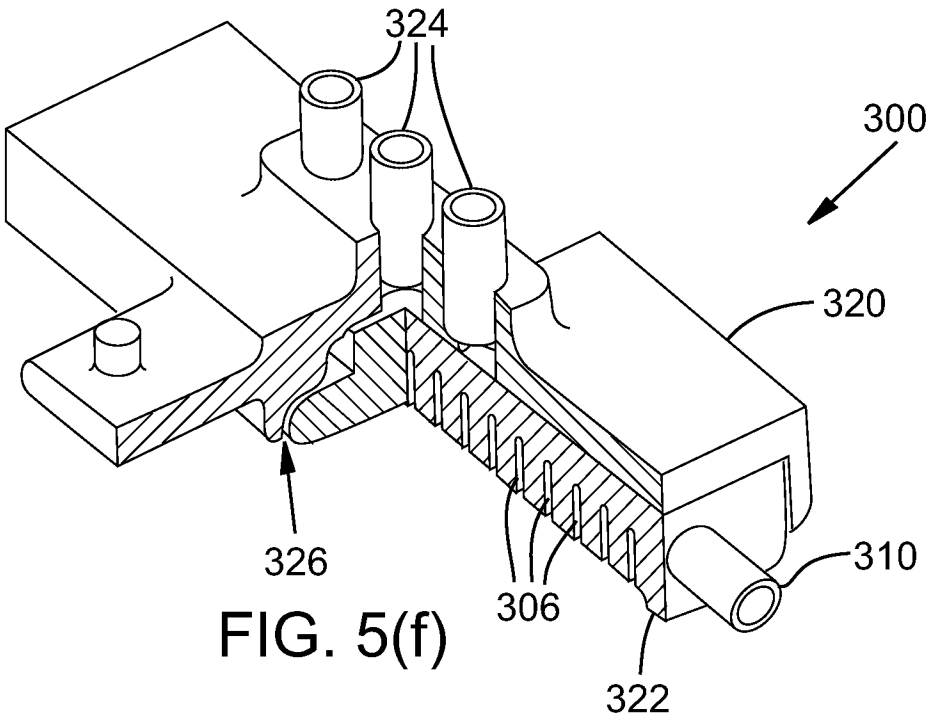


FIG. 5(f)

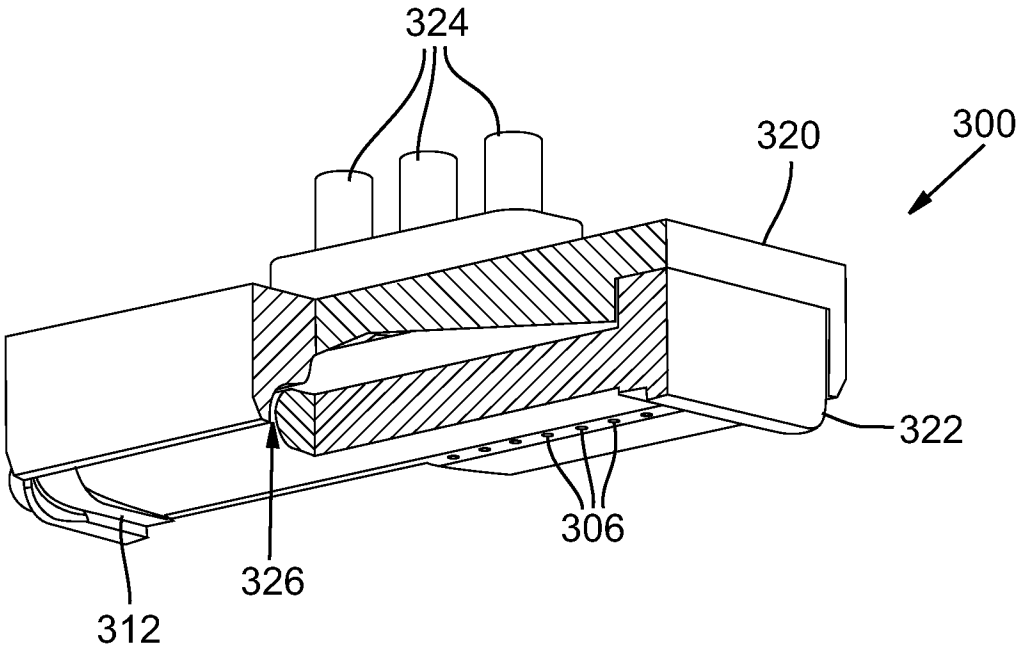


FIG. 5(g)

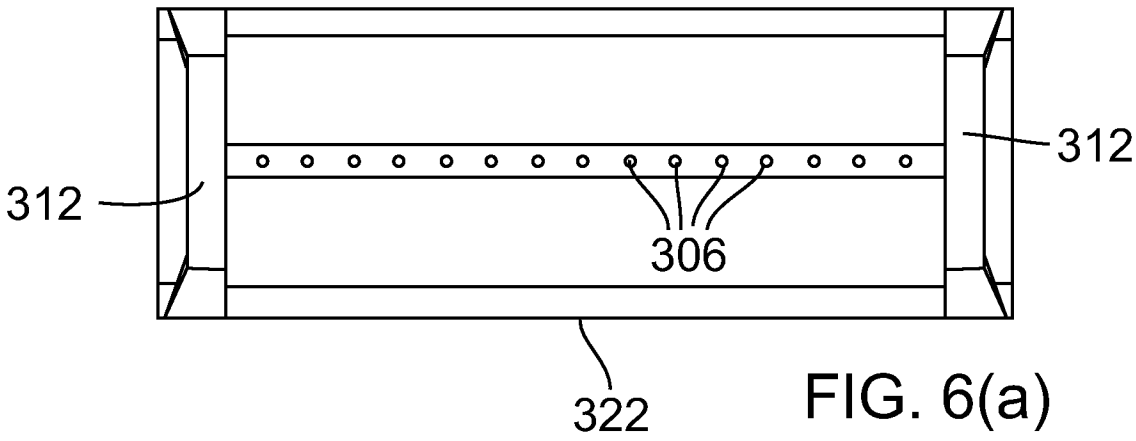


FIG. 6(a)

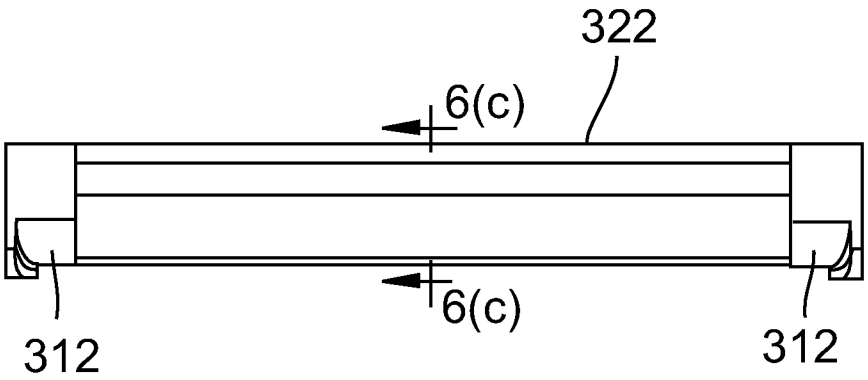


FIG. 6(b)

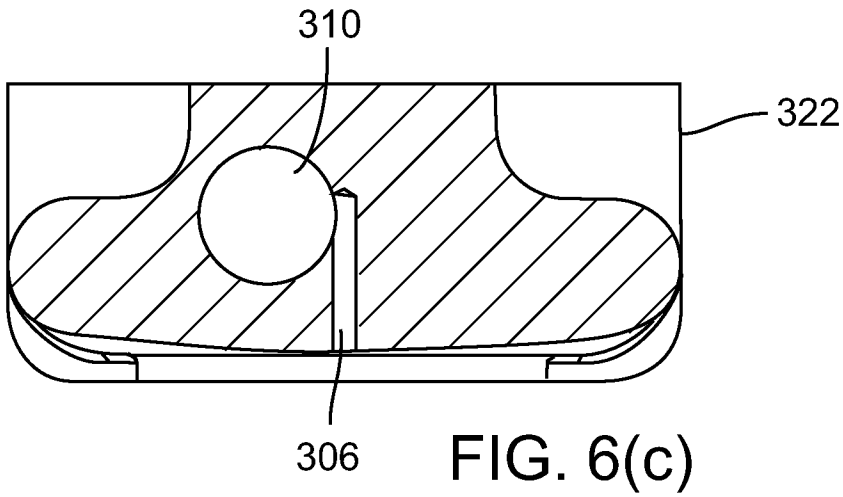


FIG. 6(c)

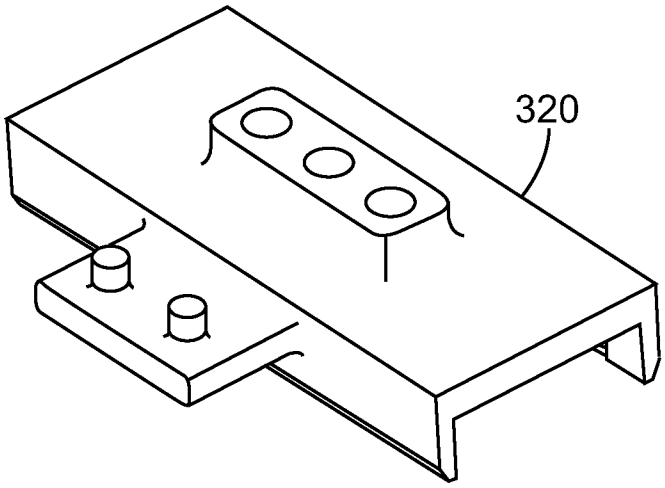


FIG. 7(a)

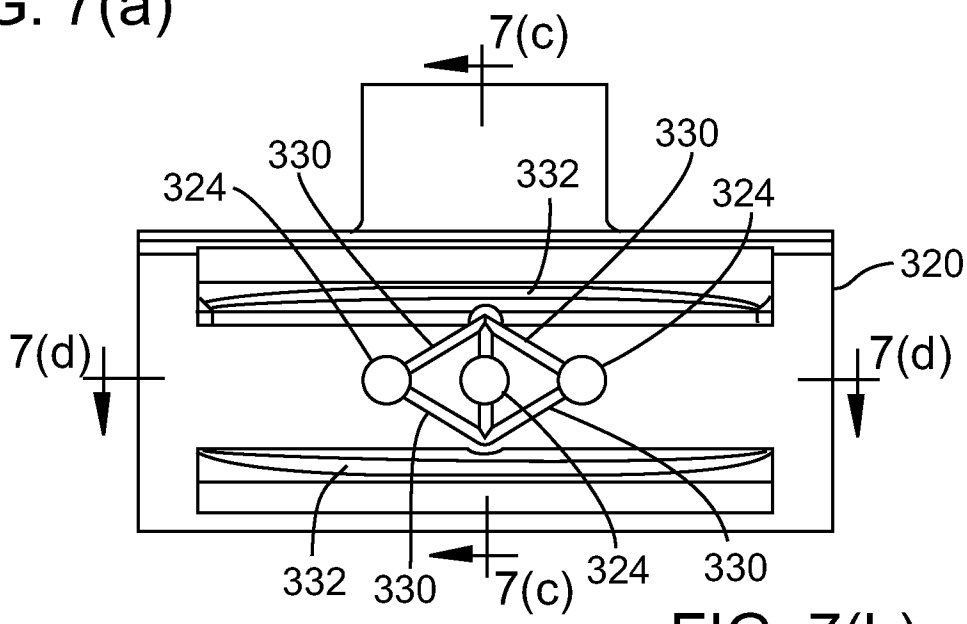


FIG. 7(b)

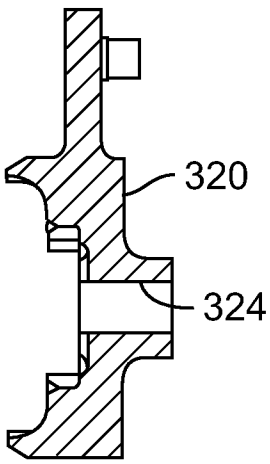


FIG. 7(c)

FIG. 7(e)

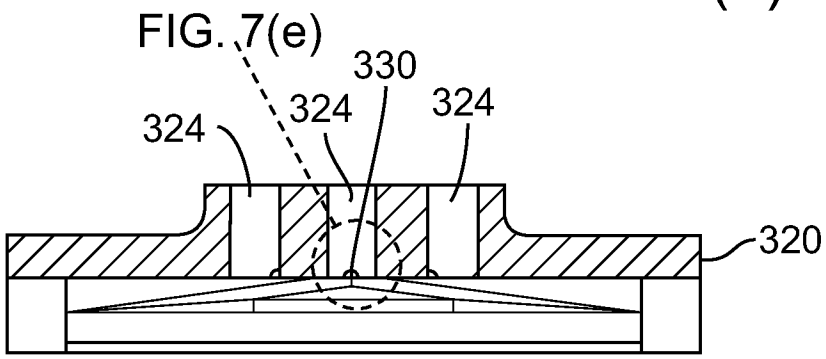


FIG. 7(d)

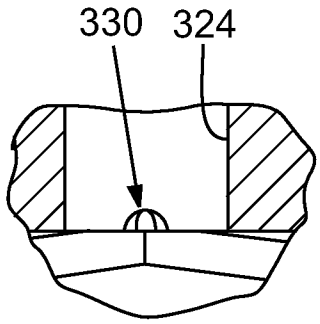


FIG. 7(e)

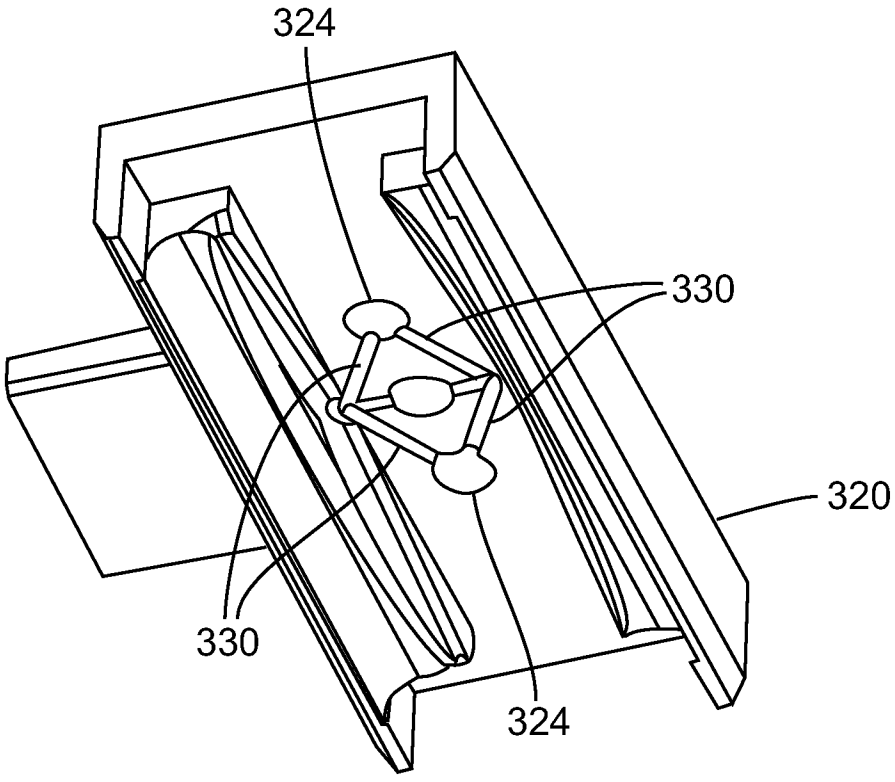


FIG. 7(f)

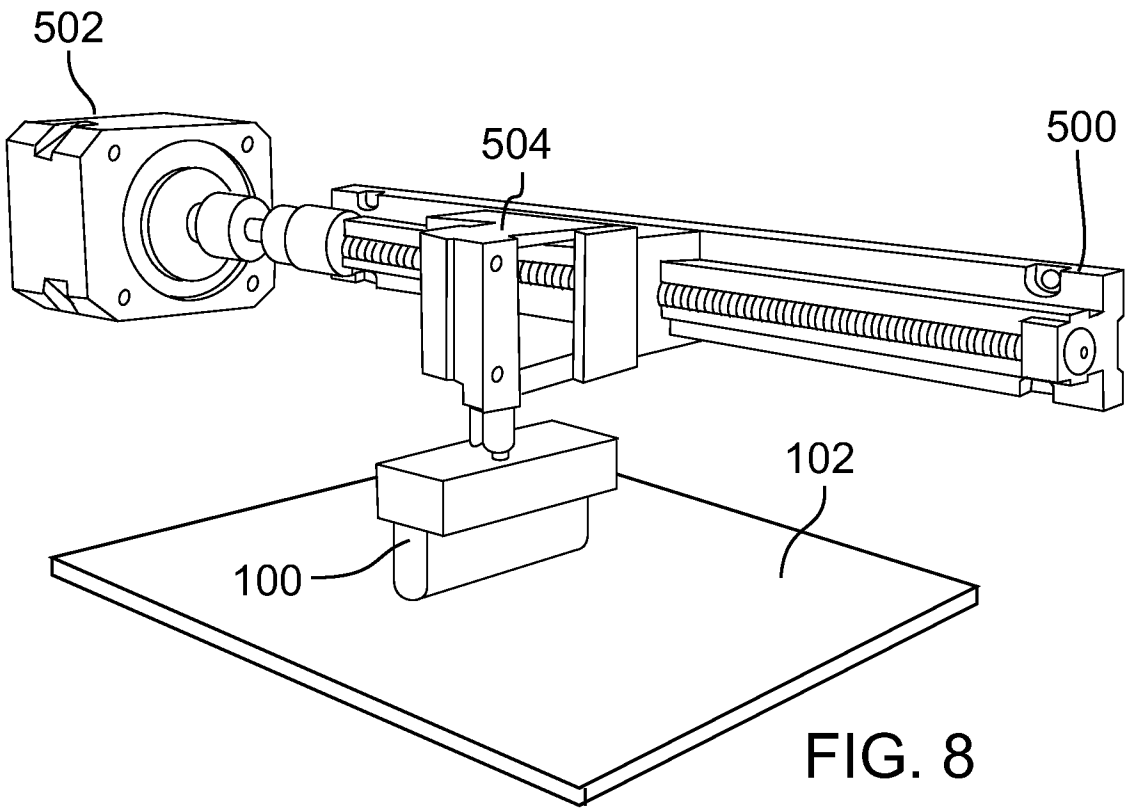


FIG. 8

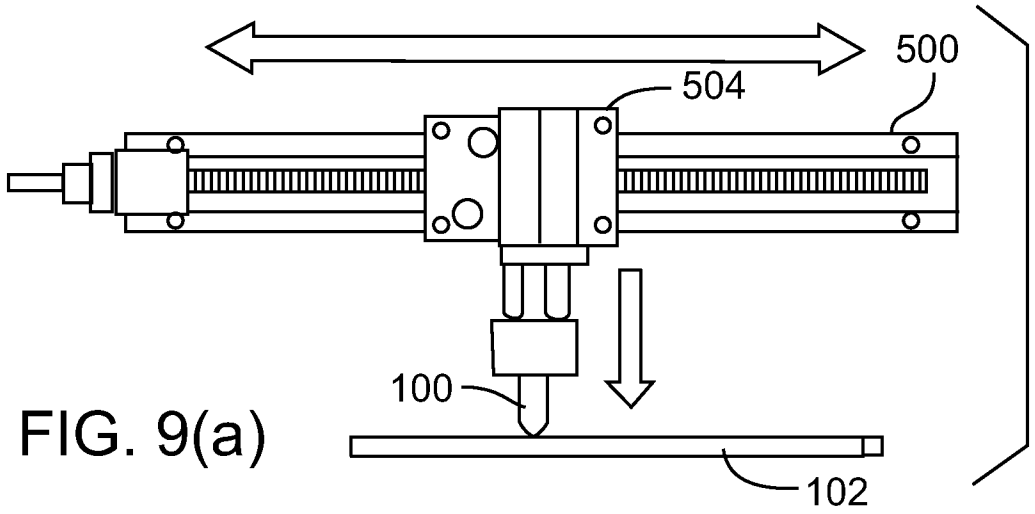


FIG. 9(a)

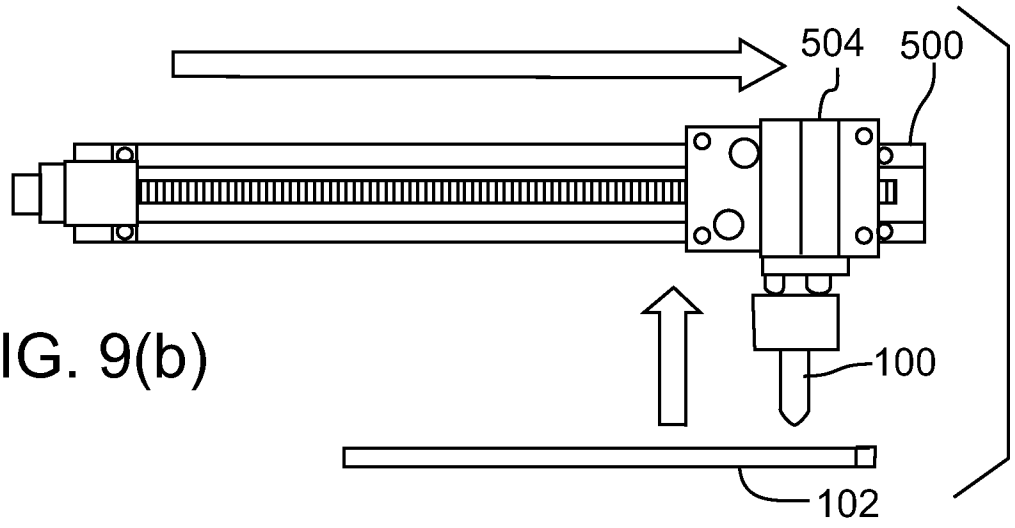


FIG. 9(b)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/34826

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 1/31, G01N 1/30, G01N 35/10 (2011.01)
USPC - 422/521, 422/509, 422/524, 422/563
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)
USPC - 422/521, 422/509, 422/524, 422/563
IPC(8) - G01N 1/31, G01N 1/30, G01N 35/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 422/521, 422/509, 422/524, 422/563
IPC(8) - IPC G01N 1/31, G01N 1/30, G01N 35/10; G01N$

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, EPAB, JPAB); Google (patents, Scholar)
Search Terms Used: Cell$2, organism$2, slide$2,Stain$4, color$4, enhanc$4, different$5, translat$4, move$5, slide$5, translation, moving, sliding gap$4, spac$5 mix$4) fluid$2, liquid, First, 1st, Second, 2nd

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X – Y	US 2006/0019302 A1 (Lemme et al.) 26 January 2006 (26.01.2006), entire document, especially Fig 5 and para [0002]-[0036]	12-15 --- 1-11
Y	US 2009/0325309 A1 (Favuzzi et al.) 31 December 2009 (31.12.2009), entire document, especially Fig 1 and para [0087]-[0108])	1-11
A	US 5,839,091 A (Rhett et al.) 17 November 1998 (17.11.1998), entire document	1-15
A	US 5,948,359 A (Kalra et al.) 07 September 1999 (07.11.1999), entire document	1-15
A	US 5,439,649 A (Tseung et al.) 08 August 1995 (08.08.1995), entire document	1-15

☐ Further documents are listed in the continuation of Box C. ☐

* 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
12 July 2011 (12.07.2011)	28 JUL 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)