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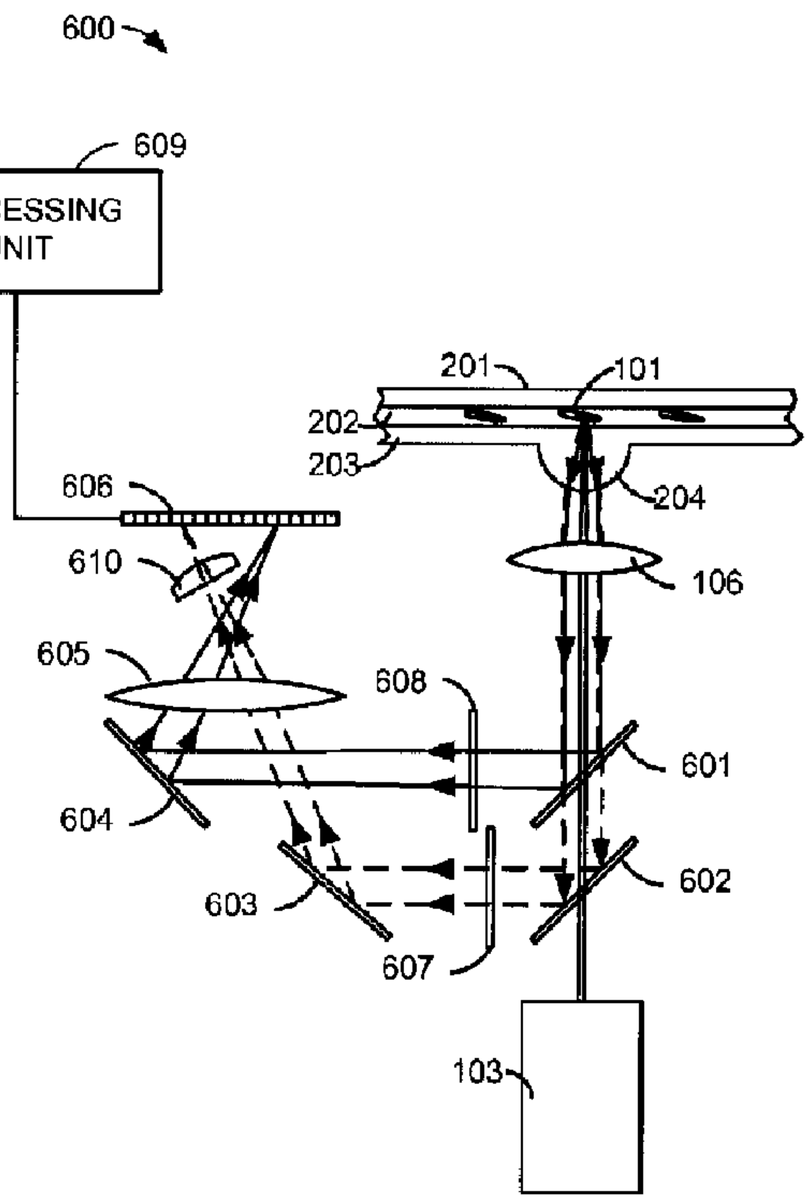
(54) Titre : SYSTEME DE CYTOMETRIE AVEC LENTILLE SOLIDE A ACCROISSEMENT D'OUVERTURE NUMERIQUE
(54) Title: CYTOMETRY SYSTEM WITH SOLID NUMERICAL-APERTURE-INCREASING LENS



(57) Abrégé/Abstract:
Flow cytometry system includes a flow element through which a cell is transported in a flowing fluid. Flow element includes a bore bounded by a wall. Light source is configured to illuminate the cell. Optical system receives light emanating from the cell and directs at least some of received light to a light sensor. The optical system includes a numerical-aperture-increasing lens at a wall of the flow element. At least some of the received light passes through the numerical-aperture-increasing lens. The flow cytometry system may also include a beam splitter that directs two wavelength bands of emanating light such that light in two wavelength band preferentially reach different sensing locations via different paths. The system may also include an optical element placed in one of the paths, shifting a focal location of the affected path to compensate for chromatic aberration of the numerical-aperture-increasing lens.

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(54) **Title**: CYTOMETRY SYSTEM WITH SOLID NUMERICAL-APERTURE-INCREASING LENS

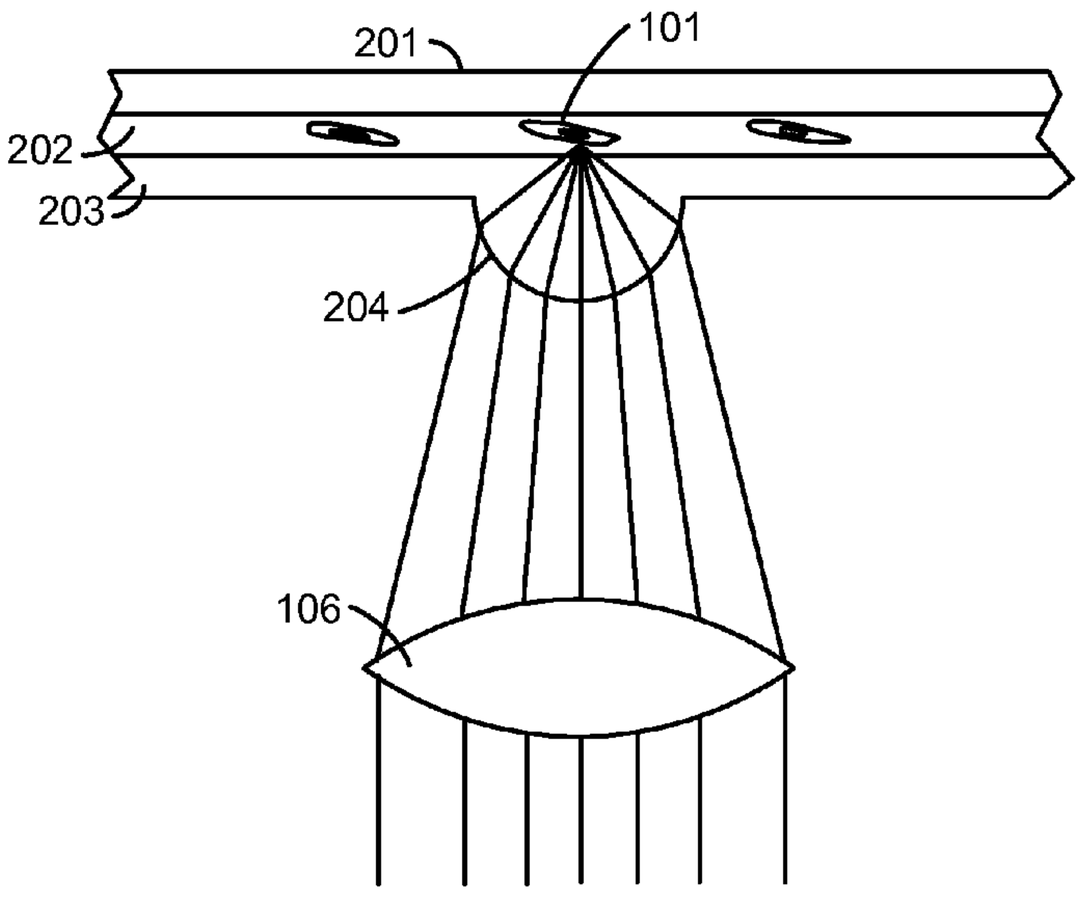

FIG. 3

(57) **Abstract**: Flow cytometry system includes a flow element through which a cell is transported in a flowing fluid. Flow element includes a bore bounded by a wall. Light source is configured to illuminate the cell. Optical system receives light emanating from the cell and directs at least some of received light to a light sensor. The optical system includes a numerical-aperture-increasing lens at a wall of the flow element. At least some of the received light passes through the numerical-aperture-increasing lens. The flow cytometry system may also include a beam splitter that directs two wavelength bands of emanating light such that light in two wavelength band preferentially reach different sensing locations via different paths. The system may also include an optical element placed in one of the paths, shifting a focal location of the affected path to compensate for chromatic aberration of the numerical-aperture-increasing lens.

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CYTOMETRY SYSTEM WITH SOLID NUMERICAL-APERTURE-INCREASING LENS

BACKGROUND OF THE INVENTION

Cytometry is a technical specialty concerned with the counting and characterization of biological cells. **Figure 1** shows a simplified diagram of a system for performing a technique known as imaging flow cytometry. In a basic form of imaging flow cytometry, cells **101** are suspended in a fluid and entrained single-file in a narrow transparent tube **102**. The entrainment can be accomplished by any of several methods, including hydrodynamic focusing. A light source **103** illuminates each cell **101** as it passes a measurement location. Light source **103** may be, for example, a laser. Light from light source **103** is scattered by the cell **101** being measured. Some light **105** is gathered by an objective lens **106** and redirected to form an image at a light sensor **107**. Light sensor **107** may be, for example, a component of a microscope or camera. Various optical components may cooperate with objective lens **106** in directing light **105** to sensor **107**, including, for example, partially reflective mirror **108** and an additional lens **109**. Output signals from sensor **107** are sent to a processing unit **110**, which may store and analyze the signals to discern information about each cell, for example its size and some information about its internal structure.

BRIEF SUMMARY OF THE INVENTION

In some embodiments, a flow cytometry system comprises a flow element through which a cell is transported in a flowing fluid. The flow element comprises a bore bounded by a wall, and at least a portion of the wall is substantially transparent. The flow cytometry system also

comprises a light source configured to illuminate the cell, a light sensor, and an optical system that receives light emanating from the illuminated cell and directs at least some of the received light to the light sensor. The optical system comprises a numerical-aperture-increasing lens at the wall of the flow element, and at least some of the received light passes through the numerical-aperture-increasing lens. In some embodiments, the numerical-aperture-increasing lens is a solid numerical-aperture-increasing lens. The optical system may receive and direct light emanating by reflection from the cell. The optical system may receive and direct light emanating by fluorescence from the cell. The numerical-aperture-increasing lens may be integrally formed with the wall of the flow element. The light sensor may comprise an electronic light sensor. The light sensor may comprise a linear electronic light sensor. The flow cytometry system may perform cross section imaging of the cell. The light source may comprise a laser.

In some embodiments, the light sensor comprises a first light sensing location, and the flow cytometry system further comprises a beam splitter that directs two wavelength bands of the emanating light such that light in one wavelength band preferentially reaches the first light sensing location via a first path, and that light in the other wavelength band preferentially reaches a second light sensing location via a second path. The first and second light sensing locations may be coplanar. The first and second light sensing locations may comprise separate locations on the light sensor. In some embodiments, the flow cytometry system comprises an optical element placed in either the first or second path, the optical element configured to compensate for chromatic aberration of the numerical-aperture-increasing lens by shifting a focal location of one of the paths. The optical element may be a transmissive flat plate. The optical element may be a lens.

In other embodiments, a flow element for flow cytometry comprises a wall defining a bore through the flow element, at least a portion of the wall being substantially transparent, and a numerical-aperture-increasing lens at the wall. The numerical-aperture-increasing lens may be integrally formed with the wall. The bore may be substantially cylindrical. The bore may comprise at least one substantially flat side. The numerical-aperture-increasing lens may comprise a semi-spherical protrusion from the wall. The numerical-aperture-increasing lens may be configured such that an inner surface of the flow element substantially corresponds with an aplanatic surface of the numerical-aperture-increasing lens.

In other embodiments, a method of performing flow cytometry comprises providing a flow element, the flow element comprising a bore bounded by a wall, transporting a cell through the flow element, illuminating the cell using a light source, and receiving, using an optical

system, light emanating from the illuminated cell, the optical system including a numerical-aperture-increasing lens at the wall of the flow element, and the received light passing through the numerical-aperture-increasing lens. In these embodiments, the method further comprises directing the received light to a light sensor. In some embodiments, the method further comprises receiving, at a processing unit, signals from the light sensor representing an intensity of light falling on the light sensor. The method may further comprise interpreting the signals to discern information about the cell. The method may further comprise providing a beam splitter that splits the received light into at least two wavelength bands, the light in the two wavelengths bands preferentially reaching different sensing locations via different paths. The method may further comprise inserting an optical element into one of the paths to shift a focal location of the path, to compensate for chromatic aberration introduced by the numerical-aperture-increasing lens.

According to other embodiments, a system for performing cytometry includes a mechanism that generates relative motion between a cell and a sensing location, a light source configured to illuminate the cell, a light sensor, and an optical system that receives light emanating from the illuminated cell and directs at least some of the received light to the light sensor. The optical system further includes a numerical-aperture-increasing lens, and at least some of the received light passes through the numerical-aperture-increasing lens. In some embodiments, the mechanism that generates relative motion between the cell and the scanning location includes a flow element through which the cell moves, the cell suspended in a flowing fluid. In some embodiments, the mechanism that generates relative motion between the cell and the scanning location includes a plate that carries the cell. The plate may include a disk. The system may further include a coupling liquid between the numerical-aperture-increasing lens and the plate.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a simplified diagram of a system for performing a technique known as imaging flow cytometry.

Figure 2 illustrates a cytometry system in accordance with one embodiment of the invention.

Figure 3 illustrates a partial section view of the cytometry system of Figure 2.

Figure 4 illustrates one example arrangement for a numerical-aperture-increasing lens.

Figures 5A and 5B illustrate actual images of clusters of fluorescent beads having a diameter of 2.5 μm, taken without and with the benefit of a numerical-aperture-increasing lens.

Figure 6 illustrates a cytometry system in accordance with another embodiment of the invention.

Figure 7 illustrates a flow element in accordance with another embodiment.

Figure 8 illustrates a portion of a system for performing cytometry, in accordance with other embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

In research applications, it is desirable that a cytometry system produce images of very high resolution and magnification. For example, a researcher studying virus trafficking in cell cytoplasm may need to image extremely small biological objects. The resolution of a microscope or other imaging device is fundamentally limited by the diffraction or Rayleigh limit, related to the numerical aperture (NA) of the objective lens and the wavelength of light being gathered by the lens. Accordingly, a very high NA is desirable, in order to achieve high resolution.

In some applications, more than one light wavelength is of interest. For example, in fluorescence cytometry, cell structures may be tagged with fluorophores that emanate light by fluorescence upon excitation by a light source. Different fluorophores may emanate light in different wavelength ranges, and an imaging objective lens should accordingly be corrected for chromatic aberration, so that detailed images may be collected simultaneously in more than one light wavelength.

These imaging requirements for magnification, resolution, and chromatic correction may have traditionally necessitated a sophisticated and expensive objective lens having a very short working distance. For example, a front surface of the objective lens may need to be within 1 millimeter or less of the subject being studied. This limited working distance is especially troublesome in flow cytometry, in which the structure required for cell handling may not readily fit within the working distance of the objective lens.

A lens with a longer working distance may be used, but at the expense of resolution, as a longer working distance may necessitate a smaller NA. Without sufficient resolution, a cytometry system may not be able to recognize sub-cellular structures.

Figure 2 illustrates a cytometry system **200** in accordance with one embodiment of the invention. Cytometry system **200** includes a flow element **201**, through which cells **101** are transported in a flowing fluid. At least a portion of flow element **201** is substantially

transparent, so that illumination light can reach cells **101**, and so that light emanating from cells **201** can be detected outside flow element **201**. Example flow element **201** comprises a bore **202** bounded by a wall **203**. In example flow element **201**, bore **202** comprises flat sides, but other shapes are possible. For example, bore **202** may be substantially cylindrical. Cytometry system **200** also includes a numerical-aperture-increasing lens, in this example a solid numerical-aperture-increasing lens (SNAIL) **204**. SNAIL **204** is a semi-spherical protrusion integrally formed with wall **203**, for example by molding. SNAIL **204** may also be formed separately from flow element **201** and affixed to wall **203**, or otherwise placed in position at the wall of flow element **201**.

Cytometry system **200** illuminates cells **101** and captures light emanating from cells **101** from the same direction. Light from light source **103** passes through partially reflective mirror **108**, objective lens **106**, and SNAIL **104** to reach cells **101**. Light emanating from cells **101** passes through SNAIL **104** and objective lens **106**, and is substantially redirected by mirror **108** toward second lens **109** and light sensor **107**. Mirror **108** may be also filter the light. For example, if cytometry system **200** is intended image cells in light wavelengths emitted from the cells by fluorescence, mirror **108** may preferentially reflect light emanated by fluorescence while preferentially passing light reflected from the cells. One of skill in the art will recognize that other arrangements are possible within the scope of the appended claims. For example, light source **103** may be positioned to illuminate cells **101** from a different direction, not aligned with the optical axis of objective lens **106**.

The function of SNAIL **204** is to effectively increase the NA of the system including objective lens **106**, thereby enabling use of an objective lens with a longer working distance than would otherwise be feasible while still providing very high resolution imaging.

Figure 3 illustrates a partial section view of cytometry system **200**, as seen from the Z direction shown in Figure 2, and positioned so that objective lens **106** is at the bottom of the view and flow element **201** is at the top. Figure 3 illustrates the function of SNAIL **204**. SNAIL **204** is an example of a solid immersion lens (SIL). The NA, and therefore also the achievable resolution, of an optical system can be effectively increased by immersing the object to be studied in a medium having a higher refractive index than the medium in which the rest of the optical system operates. In Figure 3, objective lens **106** is in air having a refractive index of essentially 1.0. Flow element **201** and SNAIL **204** may be made of a material or materials having a higher refractive index, for example BK7 glass with a nominal refractive index of about 1.518, or polycarbonate with a nominal refractive index of about 1.584, or SF11 glass with a nominal refractive index of about 1.785. (As will be discussed in

more detail below, due to the dispersion inherent in optical materials, the actual refractive index a material is wavelength dependent.) While it is preferable that SNAIL **204** and wall **203** of flow element **201** be matched in refractive index, this is not a necessity. In flow cytometry, cells **101** are also immersed in a medium having a refractive index higher than that of air, for example water having a nominal refractive index of about 1.333. Other liquid media may be used. While it is preferable that the liquid medium and wall **203** of flow element **201** be relatively closely matched in refractive index, this is also not a necessity.

As can be seen in Figure 3, SNAIL **204** enables a much larger cone of light emanating from cell **101** to be captured by objective lens **106** than would be the case if cell **101** were immersed in air. In fact, a SIL having a refractive index n can increase the NA of an optical system by as much as a factor of n^2. For example, if SNAIL **204** is made of SF11 glass with a refractive index n of 1.785 and objective lens **106** operates at an NA of 0.3, then the effective NA of the system may be as high as $(1.785)^2 * 0.3 = 0.95$, which may be higher than even a very high quality, high magnification objective lens operating without the benefit of a SNAIL.

Preferably, the dimensions of SNAIL **204** are selected to such that SNAIL **204** does not introduce excessive aberration into the optical system. **Figure 4** illustrates one example arrangement for a SNAIL **204** that is semi-spherical, having a surface radius R. The distance T indicates the distance from the apex of SNAIL **204** to inner surface **401** of wall **203**. If distance T is selected such that $T = R(1 + 1/n)$, where n is the refractive index of SNAIL **204** and wall **203**, then inner surface **401** corresponds to the so-called aplanatic surface of SNAIL **204**, and SNAIL **204** introduces very little if any geometric aberration for imaging objects such as cells **101** that are essentially at surface **401** and near the optical axis of the system. While SNAIL **204** is illustrated in Figure 4 as being semi-spherical, aspheric shapes may alternatively be used.

The benefits of including SNAIL **204** in the system are significant. For example, without the use of SNAIL **204**, a 60X objective may be required to achieve satisfactory system resolution, but the 60X objective may not have adequate working distance for flow cytometry. The introduction of SNAIL **204** may enable the use of a 10X objective with a much longer working distance, at a fraction of the cost of the 60X objective. The increased NA not only improves the system resolution, but also results in the capture of more photons from the test sample than in a system with lower NA, which can be a significant advantage for fluorescence cytometry and other low-light applications. Additionally, the magnification of the system is increased, also by a factor of about n^2. **Figures 5A and 5B** illustrate actual

images of clusters of fluorescent beads having a diameter of 2.5 μm each. Both images were taken using a 10X objective lens having a nominal NA of 0.3. Figure 5A was taken without the benefit of a SNAIL, while the system used to take the image of Figure 5B included a SNAIL. The increases in both magnification and resolution are readily apparent.

Referring again to Figure 2, light sensor **107** may be any kind of light sensor suitable for a particular application. For example, light sensor **107** may be an electronic light sensor comprising an array of photosensitive sites referred to as pixels, and may produce electrical signals representing the intensity of light falling on the pixels, from which a digital image of a cell may be produced. Light sensor **107** may comprise a two-dimensional array of pixels, a linear array of pixels, multiple linear arrays of pixels, or only a single photosensitive detector.

A optical system utilizing a SNAIL such as SNAIL **204** may be especially suited to line-scan or cross section cytometry systems such as those described in provisional U.S. patent applications 61/162,072 filed March 20, 2009 and titled "Line-Scan Camera Based Multi-color Fluorescent Imaging and Imaging Flow Cytometry", 61/232,113 filed August 7, 2009 and titled "Serial-Line-Scan Encoded Multi-color Fluorescence Microscopy and Imaging Flow Cytometry", and 61/235,608 filed August 20, 2009 and titled "High-Speed Cellular Cross Sectional Imaging".

Line-scan and cross section imaging techniques may use a smaller field of view than systems employing two-dimensional sensors. For example, a full imaging cytometry system may have a field of view 200 μm X 200 μm. While many different kinds and sizes of cells may be studied by a system such as cytometry system **200**, a typical cell may be about 10 μm across. Line-scan and cross section imaging techniques may image a cell only when it is near the center of the field of view, for example within an area of about 50 μm X 50 μm centered on the system optical axis. As such, any aberrations introduced by SNAIL **204** or by any refractive index mismatches between SNAIL **204**, wall **203** of flow element **201**, and the liquid in which the cells are suspended may be especially tolerably small.

While geometrical aberrations introduced by SNAIL **204** may be made acceptably small, SNAIL **204** may also introduce chromatic aberration into the optical system. Because the refractive index of any optical material is inherently wavelength dependent, light of different wavelengths will not necessarily be focused at the same location by a particular optical system. This wavelength dependent effect on image quality is called chromatic aberration. Sophisticated lenses are designed to reduce chromatic aberration using multiple optical elements of differing materials (having differing dispersion characteristics) and selected

powers to at least partially counter the effects of chromatic aberration. For example, lenses **106** and **109** shown in Figure 2 may be chromatically corrected. The introduction of SNAIL **204**, a simple monolithic element, may re-introduce some chromatic aberration into the system. For applications in which multiple color imaging is to be performed, this chromatic aberration may significantly reduce the ability of the system to obtain sufficient resolution in all of the colors of interest unless some other form of correction is applied.

Multi-color imaging may be especially useful in applications that detect light emanating from the cells of interest by fluorescence. For example, different cells or cell features in a test sample may be tagged by different fluorophore markers. The different markers may be excited by the same or different sources, but emit light by fluorescence in different wavelength ranges. The markers may be, for example, Cy3 and Cy5 cyanine dyes. Cy3 is excited maximally at 550 nm and emits maximally at 570 nm. Cy5 is excited maximally at 649 nm and emits maximally at 670 nm.

One approach to imaging a test sample with multiple wavelength ranges of interest is to image the different colors on different cameras, each camera adjusted to properly focus its respective color range.

Figure 6 illustrates a cytometry system **600** in accordance with another embodiment of the invention. In example cytometry system **600**, light source **103** illuminates cell **101** being transported through flow element **201**. Light source **103** may be a laser or another kind of light source. As depicted, light source **103** directs a beam through objective lens **106**, through SNAIL **204**, and to cell **101**. The beam may pass through other elements as well, or any other suitable illumination arrangement may be used. As a result of illumination by light source **103**, light emanates from cell **101**, for example by reflection, fluorescence, or both. Light containing multiple wavelength ranges may emanate, indicated in Figure 6 by solid and broken lines. For example, if light source **103** is a broadband source, then broadband light may reflect from cell **101**. Even if light source **103** is a narrow band or essentially monochromatic source such as a laser, multiple light colors may emanate from cell **101** by fluorescence of different kinds of fluorescent markers.

The emanating light is redirected by SNAIL **204** and collected by objective lens **106**, to be eventually refocused by second lens **605** onto light sensor **606**. Objective lens **106** and second lens **605** may be comprised in an infinity-corrected optical system, allowing for the insertion of various other optical components between them. Light sensor **606** may be an electronic light sensor comprising an array of photosensitive sites referred to as pixels, and

may produce electrical signals representing the intensity of light falling on the pixel. The signals are passed to a processing unit **609**, which may produce a digital image a cell. Light sensor **606** may comprise a two-dimensional array of pixels, a linear array of pixels, multiple linear arrays of pixels, or discrete photosensitive sites. Light sensor **606** may be, for example, a complementary metal oxide semiconductor (CMOS) sensor, a charge coupled device (CCD) sensor, one or more photomultiplier tubes (PMT), or another kind of sensor.

An arrangement of mirrors and filters makes up an exemplary beam splitter that directs two wavelength bands of the emanating light such that light in one wavelength band preferentially reaches a first light sensing location via a first path, and that light in the other wavelength band preferentially reaches a second light sensing location via a second path. For example, mirror **601** may be a dichroic mirror configured to preferentially reflect light in a particular wavelength band (depicted in solid lines in Figure 6) and to preferentially transmit light not in the particular wavelength band. Mirror **602** may be a simple partially reflective mirror, or may also have filter characteristics, but in any event substantially reflects light in the second wavelength band (depicted in broken lines). The light emanating from cell **101** is thus split, with some wavelengths mainly following one path and other wavelengths mainly following a different path.

Optional additional filters **607** and **608** may further condition the spectral content of the light following the two different paths, for example to reduce crosstalk between the two sensing channels. Mirrors **603** and **604** may direct the light through second lens **605** to light sensor **606**. In the example shown in Figure 6, the two light paths reach different sensing locations on the same light sensor **606**. Signals generated by light sensor **606** will then represent two images, formed in light of different colors and shifted spatially by the beamsplitter comprising mirrors **601** and **602**. Alternatively, the different sensing locations may be on different sensors provided to receive the two different images.

Because light sensor **606** is substantially planar, and because of chromatic aberration in the system, the two images may not both focus at light sensor **606** without some form of correction. In system **600**, the correction is provided by inserting an additional optical element **611** in one of the paths. The optical element **610** is configured to compensate for chromatic aberration of SNAIL **204** by shifting a focal location of light in one of the wavelength bands. As shown in Figure 6, optical element **610** is a positive lens inserted into the path having the longest focal distance, so that the affected path is shortened. Other kinds of optical elements may be used. For example, optical element **610** could be a simple flat transmissive plate, or a negative lens could be placed into the other optical path to lengthen it.

Figure 7 illustrates and alternative embodiment for flow element **201**. In this embodiment, flow element **201A** has a generally cylindrical bore **202A** bounded by a wall **203A**. A flow element suitable for use in embodiments of the invention may be formed in any of a number ways. Merely by way of example, a flow element such as flow element **201** or **201A** could be molded as an integrated unit from a clear material such as a glass or polymer, including SNAIL **204** or **204A**. Alternatively, the wall and bore of the flow element could be formed by extrusion, and the SNAIL formed separately and attached later using an adhesive. Preferably, the adhesive would be index matched to the wall and SNAIL being joined. These or other fabrication methods may result in a low-cost device that may be an interchangeable or even disposable component of a flow cytometry system. A flow element such as element **201** or **201A** may also include features for facilitating connection to other parts of a flow cytometry system, for example mounting surfaces or lugs, bolt holes, hose connectors, or other features.

Figure 8 illustrates a portion of a system **800** for performing cytometry, in accordance with other embodiments of the invention. System **800** comprises a mechanism that generates relative motion between a cell **101** and a sensing location **801**. Sensing location **801** may be, for example, near a focal point of an objective lens such as lens **806**, operating in concert with a SNAIL **802**. Preferably, objective lens **806** and SNAIL **802** are held in fixed relationship. A light source and light sensor (not shown) illuminate cell **101** and receive light emanating from cell **101**. Cell **101** and other cells may be adhered to or otherwise carried by a plate **803**. Plate **803** may be, for example, a microscope slide or a disk. The relative motion between cell **101** and sensing location **801** may be generated by moving plate **803**, by moving objective lens **806** and SNAIL **802**, or by moving both at different velocities. In one embodiment, objective lens **806** and SNAIL **802** are held stationary, while plate **803** in the form of a rotating disk is moved. In another example arrangement, lens **806** and SNAIL **802** may move radially in relation to a rotating disk on which cell **101** and other cells are adhered or otherwise carried.

Cell **101** may be suspended in a fluid, for example in a fluid chamber **804**. Preferably, a coupling liquid **805** also resides between SNAIL **802** and plate **803** to maintain the immersion of cell **101** in a high-index environment. Ideally, the refractive indices of the materials involved in the immersion are matched, for example, the material of which plate **803** and SNAIL **802** are made, the fluid in which cell **101** is suspended, if any, and coupling liquid **805**. However, in practice perfect index matching is not generally needed to achieve benefits.

While system **800** is shown with SNAIL **802** and objective lens **103** below plate **803**, the system could also be inverted, so that SNAIL **802** and objective lens **103** are above plate **803**. Other arrangements may be possible as well. A system according to embodiments of the invention may utilized a lower cost objective lens **806** than would otherwise be needed to achieve comparable image quality without SNAIL **802**, and may also have relaxed requirements for axial registration and focus adjustment.

While embodiments of the invention have been illustrated as scanning cells confined in a linear tube or carried by a plate, one of skill in the art will recognize that embodiments of the invention may be utilized in systems using any of a wide range of cell delivery techniques, including electrophoresis, pressure driven flow, optical tweezers, motorized translation stage, and others. Cells may be conveyed as a payload in an oil emulsion, in an electrowetting-actuated droplet, or via magnetic transport assisted by magnetic bead tagging. It is intended that the claims not be limited by the cell delivery method utilized.

In the claims appended hereto, the term "a" or "an" is intended to mean "one or more." The term "comprise" and variations thereof such as "comprises" and " comprising," when preceding the recitation of a step or an element, are intended to mean that the addition of further steps or elements is optional and not excluded. The invention has now been described in detail for the purposes of clarity and understanding. However, those skilled in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. An imaging flow cytometry system, comprising:

a flow element through which a cell is transported in a flowing fluid, the flow element comprising a bore bounded by a wall, at least a portion of the wall being substantially transparent;

a light source configured to illuminate the cell;

an array light sensor having a plurality of pixels; and

an optical system that receives light emanating from the illuminated cell and directs at least some of the received light to the light sensor, the optical system comprising an objective lens and a numerical-aperture-increasing lens at the wall of the flow element, at least some of the received light passing through the numerical-aperture-increasing lens, wherein the optical system forms an image of at least a portion of the cell on the light sensor.

2. The flow cytometry system of claim 1, wherein the numerical-aperture-increasing lens is a solid numerical-aperture-increasing lens.

3. The flow cytometry system of claim 1, wherein the optical system receives and directs light emanating by reflection from the cell.

4. The flow cytometry system of claim 1, wherein the optical system receives and directs light emanating by fluorescence from the cell.

5. The flow cytometry system of claim 1, wherein the numerical-aperture-increasing lens is integrally formed with the wall of the flow element.

6. The flow cytometry system of claim 1, wherein the light sensor comprises an electronic light sensor.

7. The flow cytometry system of claim 1, wherein the light sensor comprises a linear electronic light sensor.

8. The flow cytometry system of claim 1, wherein the flow cytometry system performs cross section imaging of the cell.

9. The flow cytometry system of claim 1, wherein the light source comprises a laser.

10. The flow cytometry system of claim 1, wherein the light sensor comprises a first light sensing location, the flow cytometry system further comprising:

a beam splitter that directs two wavelength bands of the emanating light such that light in one wavelength band preferentially reaches the first light sensing location via a first path, and that light in the other wavelength band preferentially reaches a second light sensing location via a second path.

11. The flow cytometry system of claim 10, wherein the first and second light sensing locations are coplanar.

12. The flow cytometry system of claim 10, wherein the first and second light sensing locations comprise separate locations on the light sensor.

13. The flow cytometry system of claim 10, further comprising:

an optical element placed in either the first or second path, the optical element configured to compensate for chromatic aberration of the numerical-aperture-increasing lens by shifting a focal location of one of the paths.

14. The flow cytometry system of claim 13, wherein the optical element is a transmissive flat plate.

15. The flow cytometry system of claim 13, wherein the optical element is a lens.

16. A flow element for flow cytometry, the flow element comprising:

a wall defining a bore through the flow element, at least a portion of the wall being substantially transparent; and

a numerical-aperture-increasing lens at the wall;

wherein the numerical-aperture-increasing lens is configured such that an inner surface of the flow element substantially corresponds with an aplanatic surface of the numerical-aperture-increasing lens.

17. The flow element of claim 16, wherein the numerical-aperture-increasing lens is integrally formed with the wall.

18. The flow element of claim 16, wherein the bore is substantially cylindrical.

19. The flow element of claim 16, wherein the bore comprises at least one substantially flat side.

20. The flow element of claim 16, wherein the numerical-aperture-increasing lens comprises a semi-spherical protrusion from the wall.

21. A method of performing imaging flow cytometry, the method comprising:

providing a flow element, the flow element comprising a bore bounded by a wall;

transporting a cell through the flow element;

illuminating the cell using a light source;

receiving, using an optical system, light emanating from the illuminated cell, the optical system including a numerical-aperture-increasing lens at the wall of the flow element and an objective lens, the received light passing through the numerical-aperture-increasing lens; and

directing the received light using the objective lens to an array light sensor having a plurality of pixels, forming an image of at least part of the cell on the light sensor.

22. The method of claim 21, further comprising receiving, at a processing unit, signals from the light sensor representing an intensity of light falling on the light sensor.

23. The method of claim 22, further comprising interpreting the signals to discern information about the cell.

24. The method of claim 21, further comprising providing a beam splitter that splits the received light into at least two wavelength bands, the light in the two wavelengths bands preferentially reaching different sensing locations via different paths.

25. The method of claim 24, further comprising inserting an optical element into one of the paths to shift a focal location of the path, to compensate for chromatic aberration introduced by the numerical-aperture-increasing lens.

26. A system for performing imaging cytometry, the system comprising:

a mechanism that generates relative motion between a cell and a sensing location;

a light source configured to illuminate the cell;

an array light sensor having a plurality of pixels; and

an optical system that receives light emanating from the illuminated cell and directs at least some of the received light to the light sensor, the optical system comprising a numerical-aperture-increasing lens and an objective lens, at least some of the received light passing through the numerical-aperture-increasing lens and the objective lens, which forms an image of at least part of the cell on the light sensor.

27. The system of claim 26, wherein the mechanism that generates relative motion between the cell and the sensing location comprises a flow element through which the cell moves, the cell suspended in a flowing fluid.

28. The system of claim 26, wherein the mechanism that generates relative motion between the cell and the sensing location comprises a plate that carries the cell.

29. The system of claim 28, wherein the plate comprises a disk.

30. The system of claim 28, wherein the system further comprises a coupling liquid between the numerical-aperture-increasing lens and the plate.

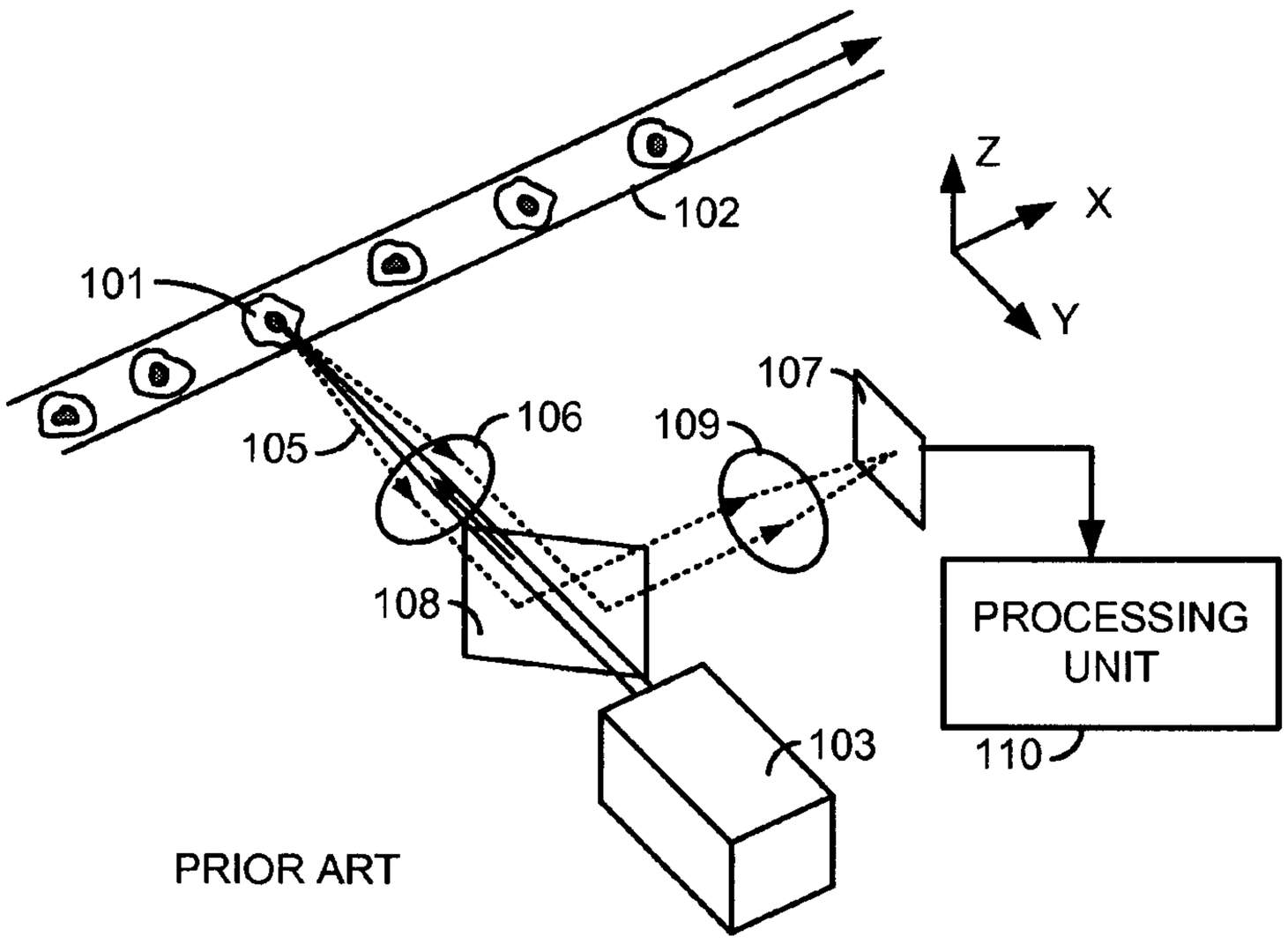
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FIG. 1

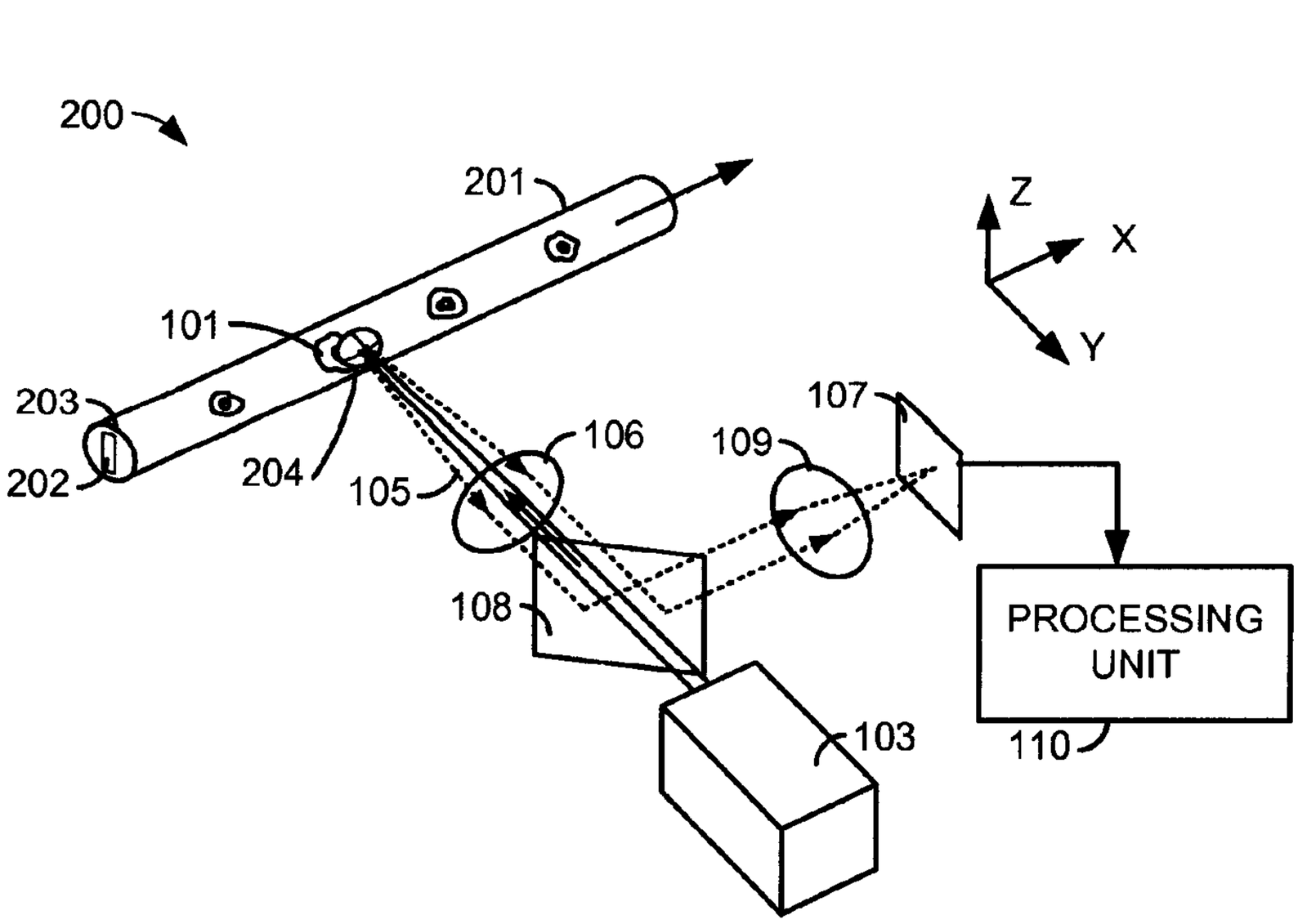
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FIG. 2

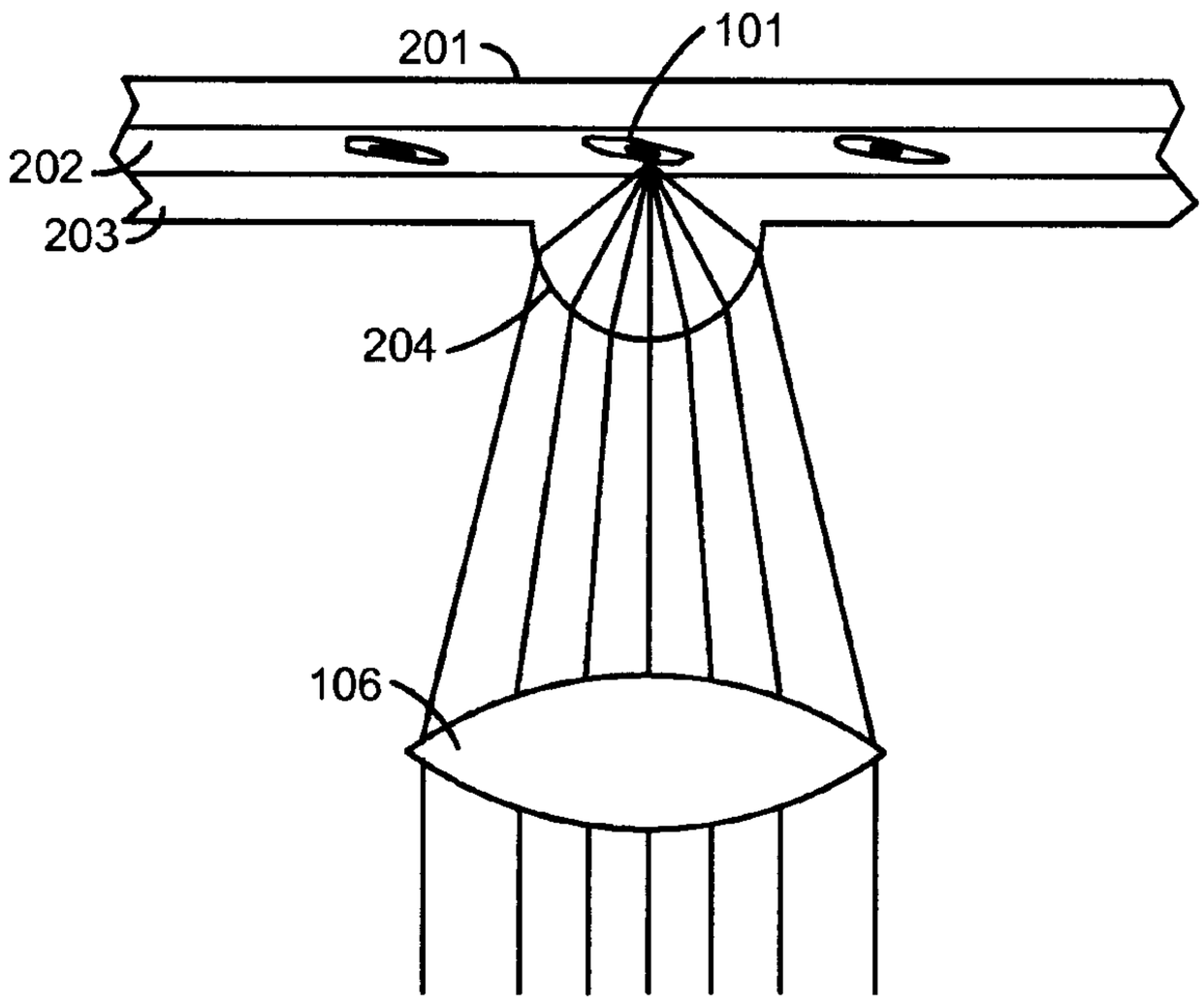


FIG. 3

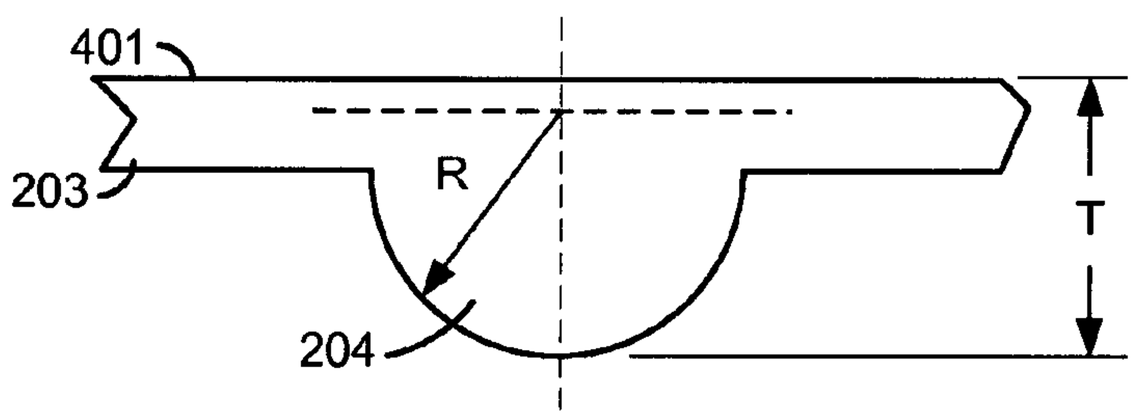
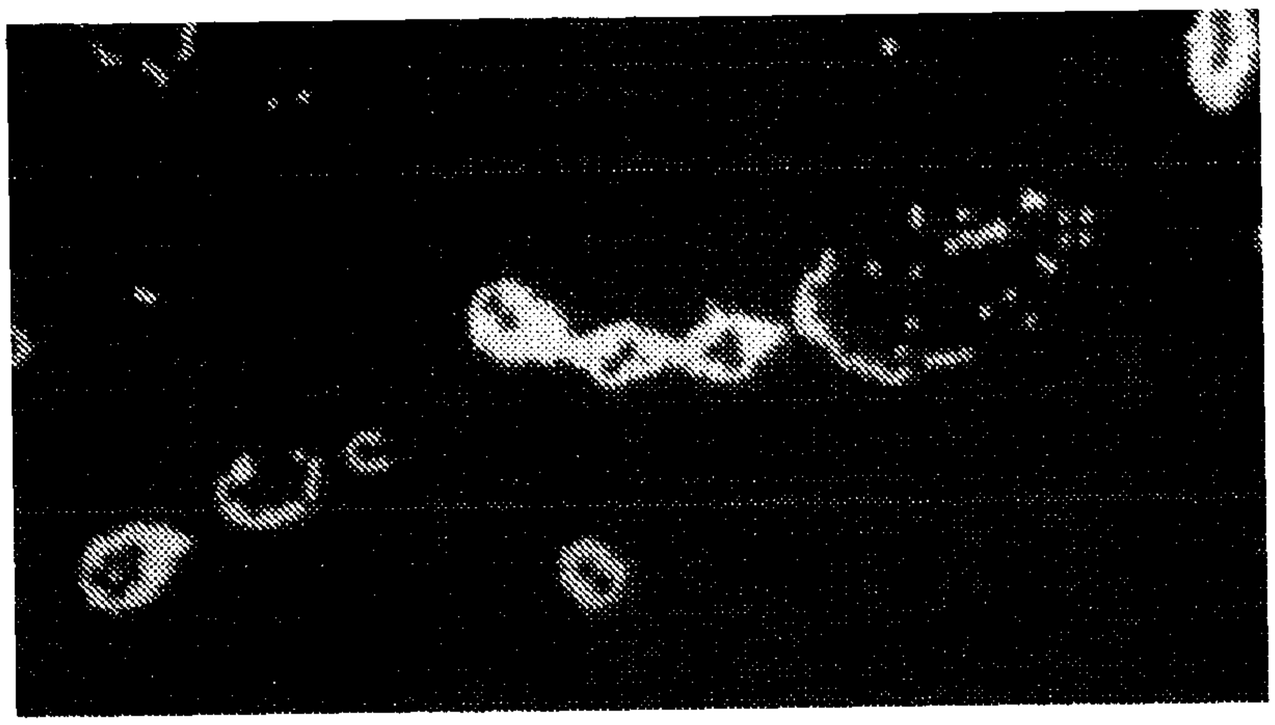


FIG. 4



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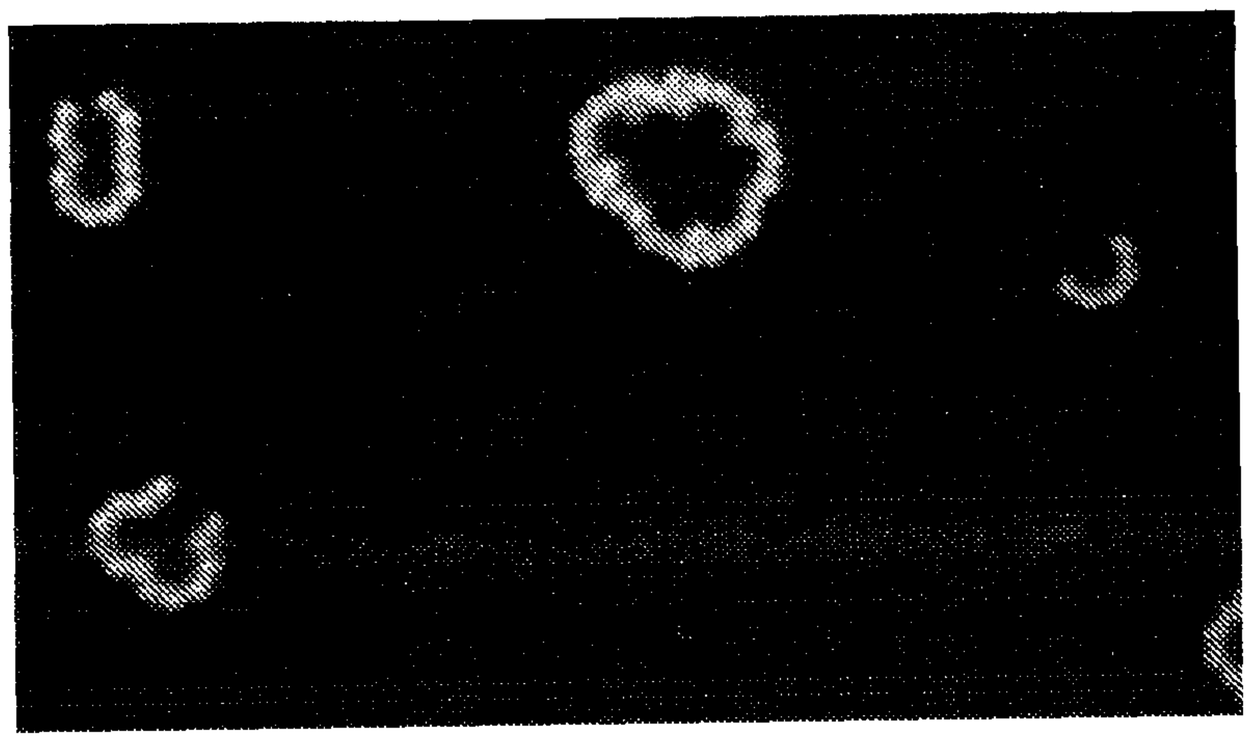
NO SNAIL

FIG. 5A



10X OBJECTIVE
NA = 0.3
WITH SNAIL

FIG. 5B

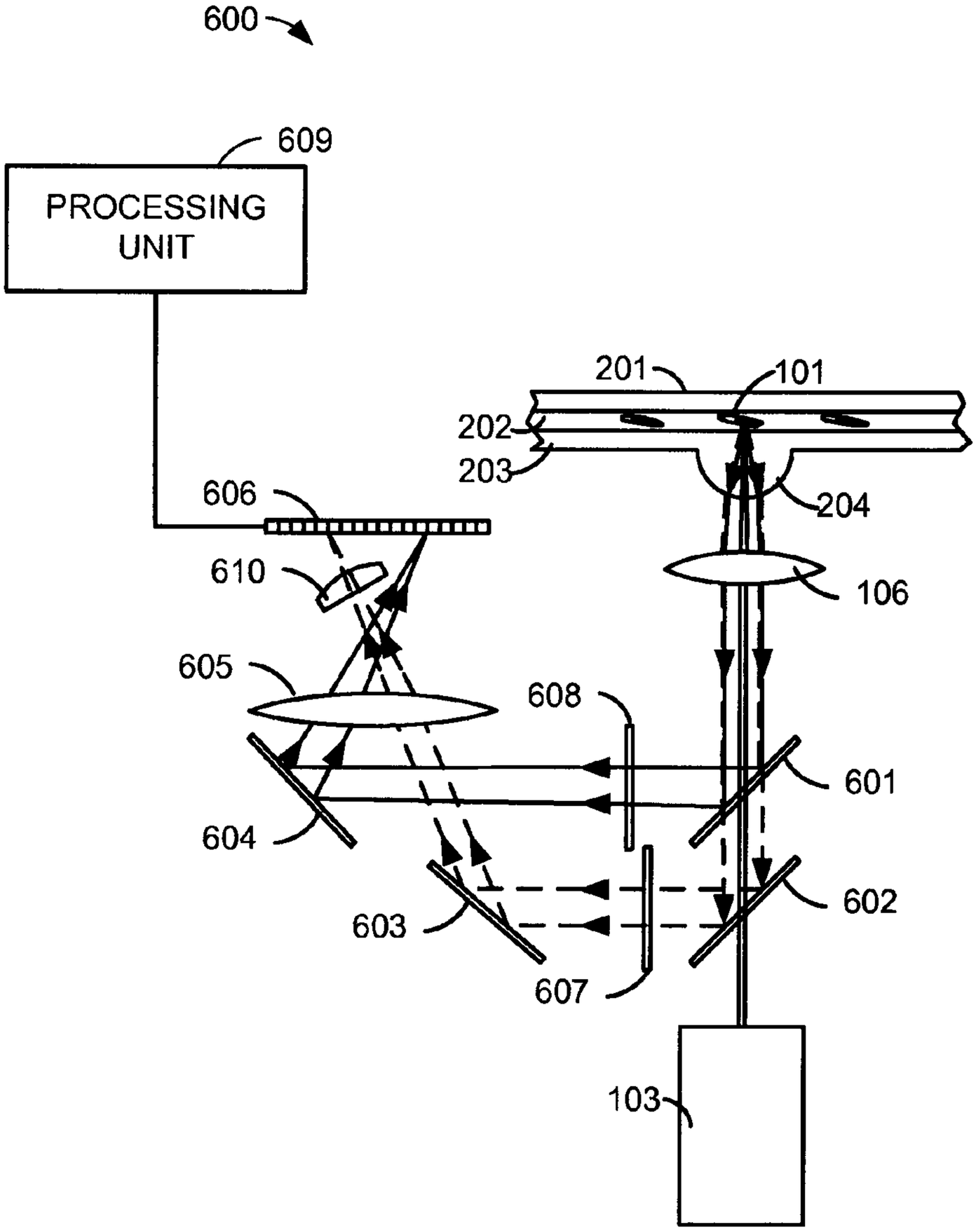

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FIG. 6

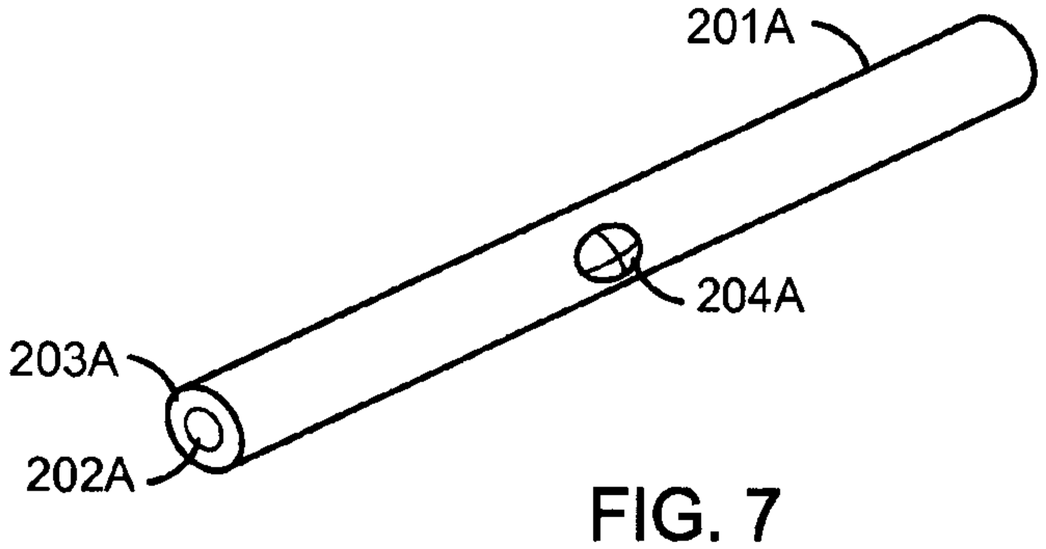


FIG. 7

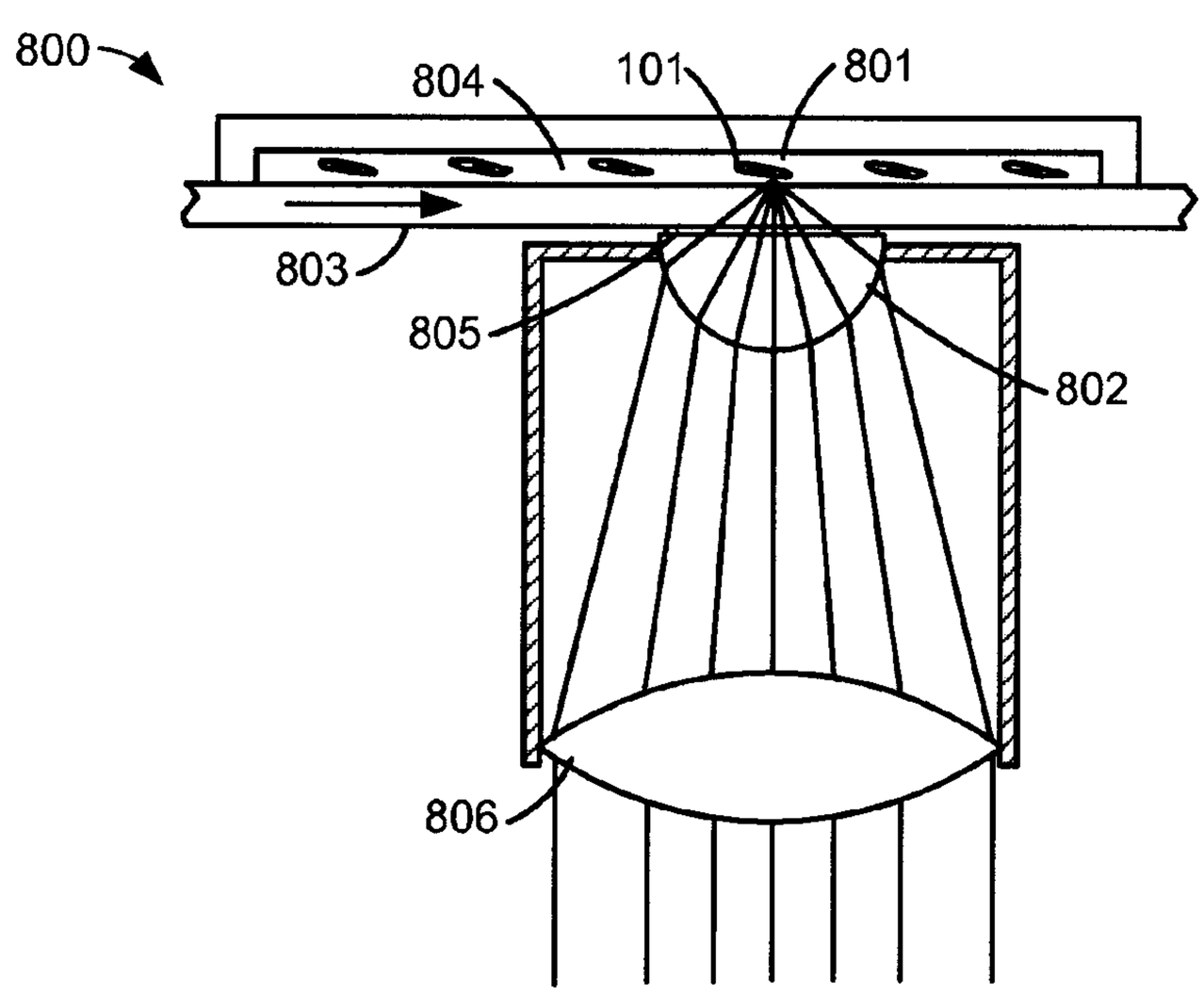
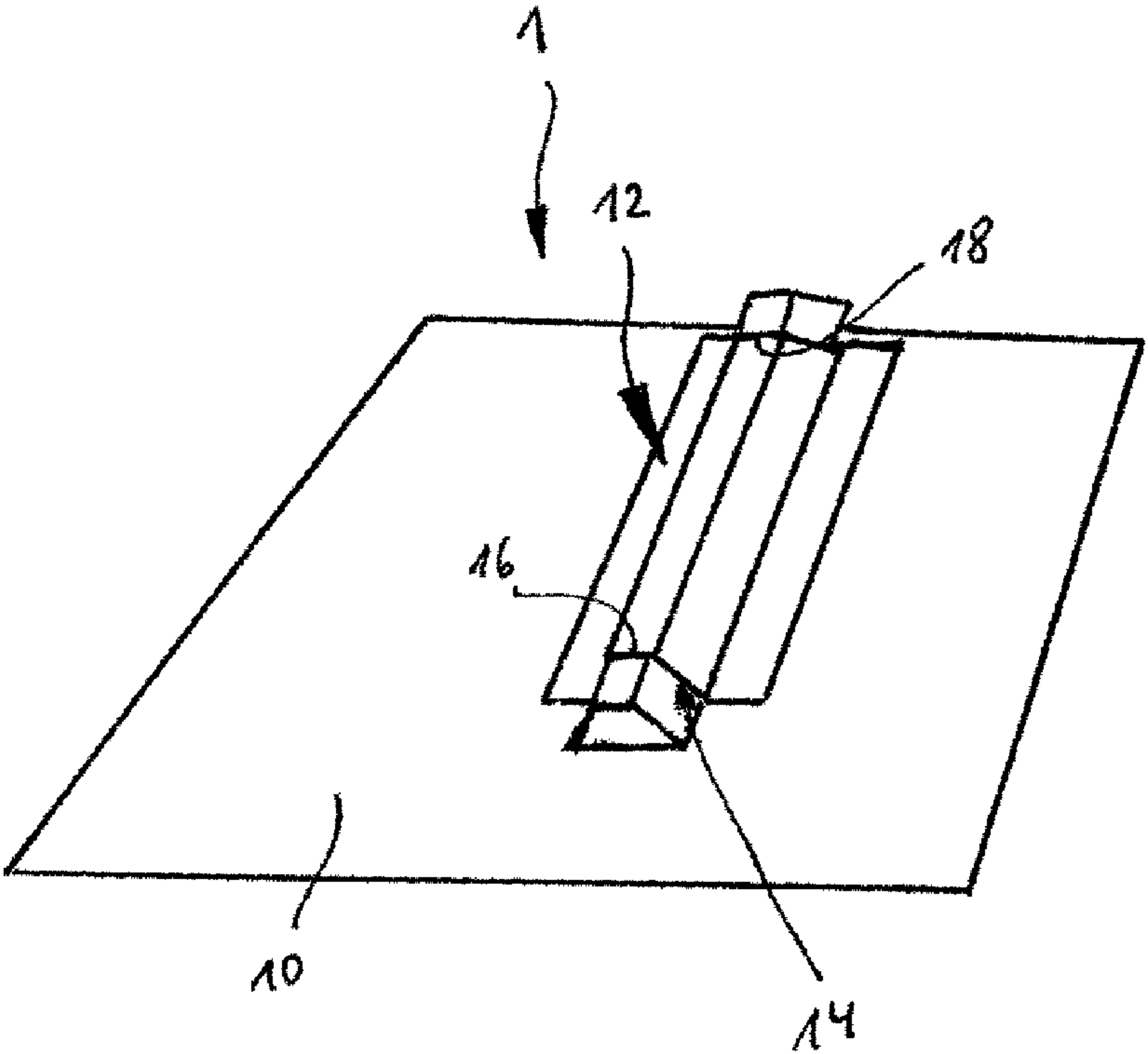


FIG. 8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