United States Patent [19]

Kamentsky et al.

[11] **3,827,555**

[45] **Aug. 6, 1974**

[54] **PARTICLE SORTER WITH SEGREGATION INDICATOR**

[75] Inventors: **Louis A. Kamentsky,** Briarcliff Manor; **Isaac Klinger,** Yorktown Heights, both of N.Y.

[73] Assignee: **Bio/Physics Systems, Inc.,** Mohapac, N.Y.

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[21] Appl. No.: **338,215**

[52] **U.S. Cl.** ..... **209/111.7,** 137/81.5, 210/85, 250/222 CP, 324/71 CP, 356/39

[51] **Int. Cl.** **B07c 5/342**

[58] **Field of Search** ..... 209/4, 3, 74, 111.6, 111.7, 209/111.8; 324/34, 61, 71 CP; 137/81.5; 356/39; 210/65, 85; 250/222 CP; 235/92 V, 92 PC

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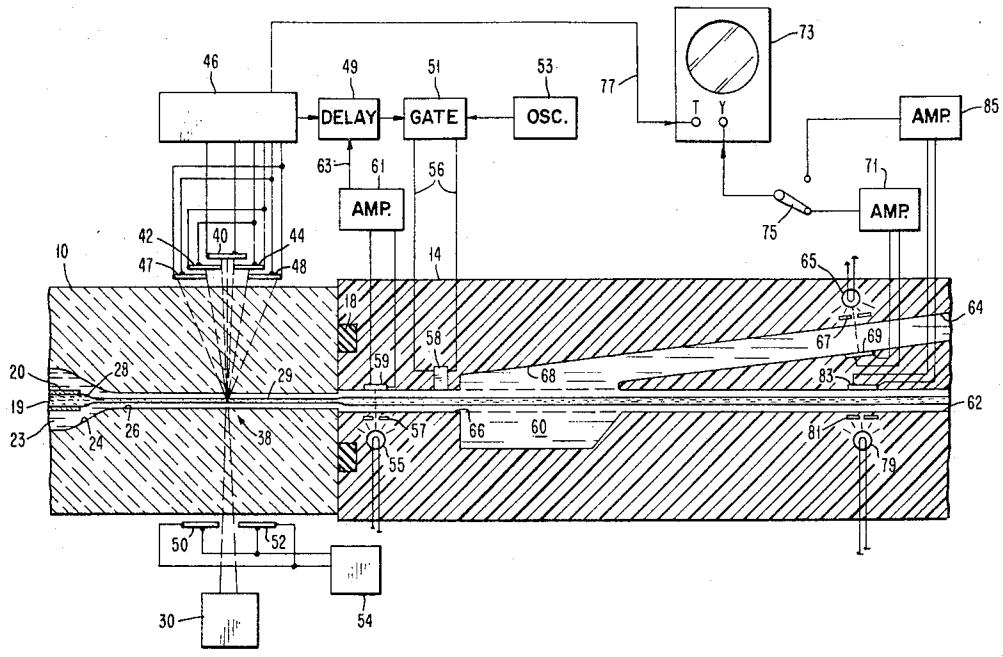
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Primary Examiner—Lloyd L. King
Assistant Examiner—Gene A. Church
Attorney, Agent, or Firm—Curtis Ailes

[57] **ABSTRACT**

Small particles to be sorted are entrained in a stream of fluid and particle differences are detected to control a sorting means located downstream. The sorting means is effective to switch the particle carrying fluid to two different paths determined by the particle differences to thereby accomplish the sort. A photoelectric particle detector is positioned to detect the passage of particles through one of said paths in order to verify that the sorting operation has occurred.

13 Claims, 4 Drawing Figures



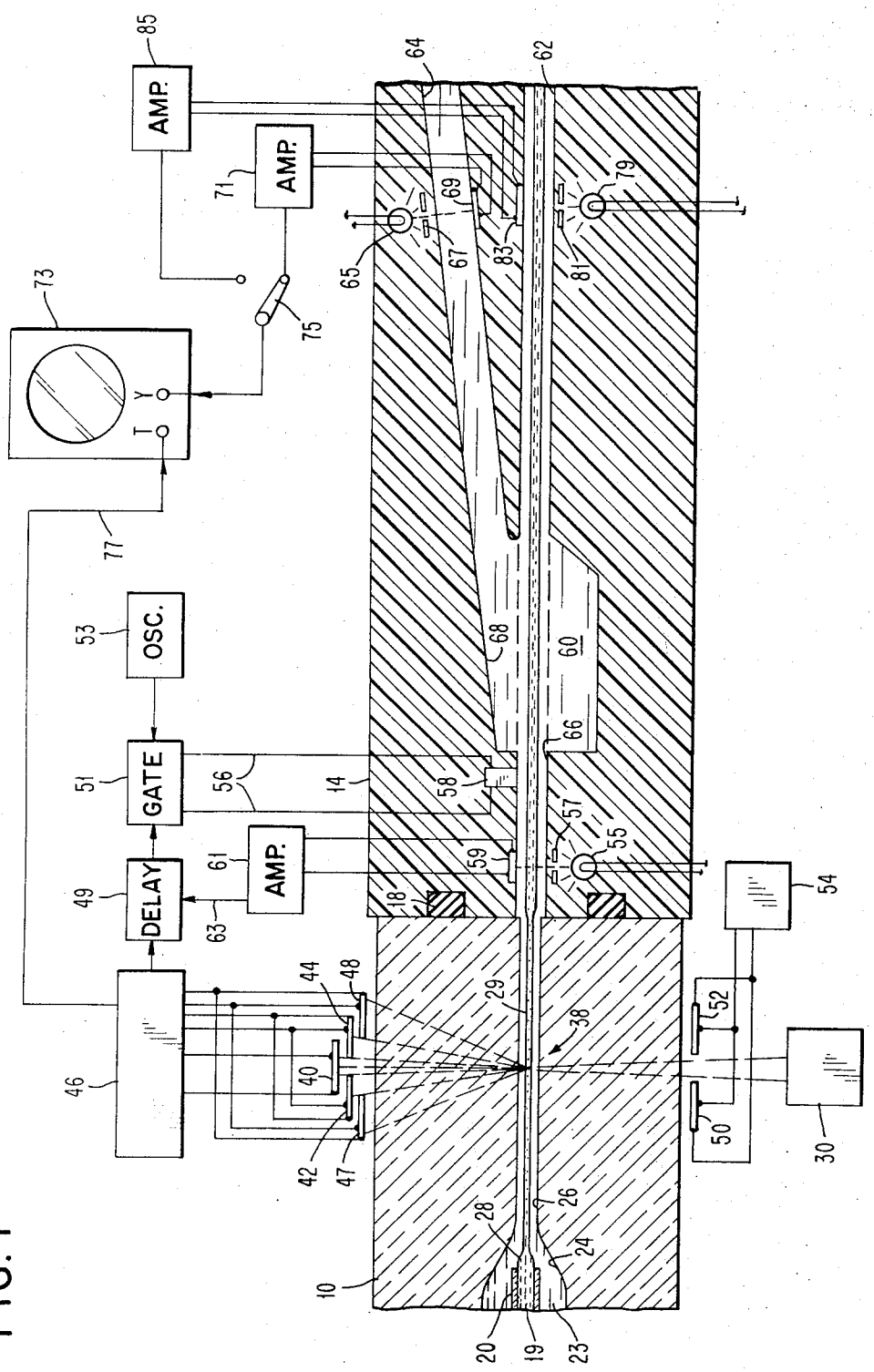

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FIG. 1

FIG. 2

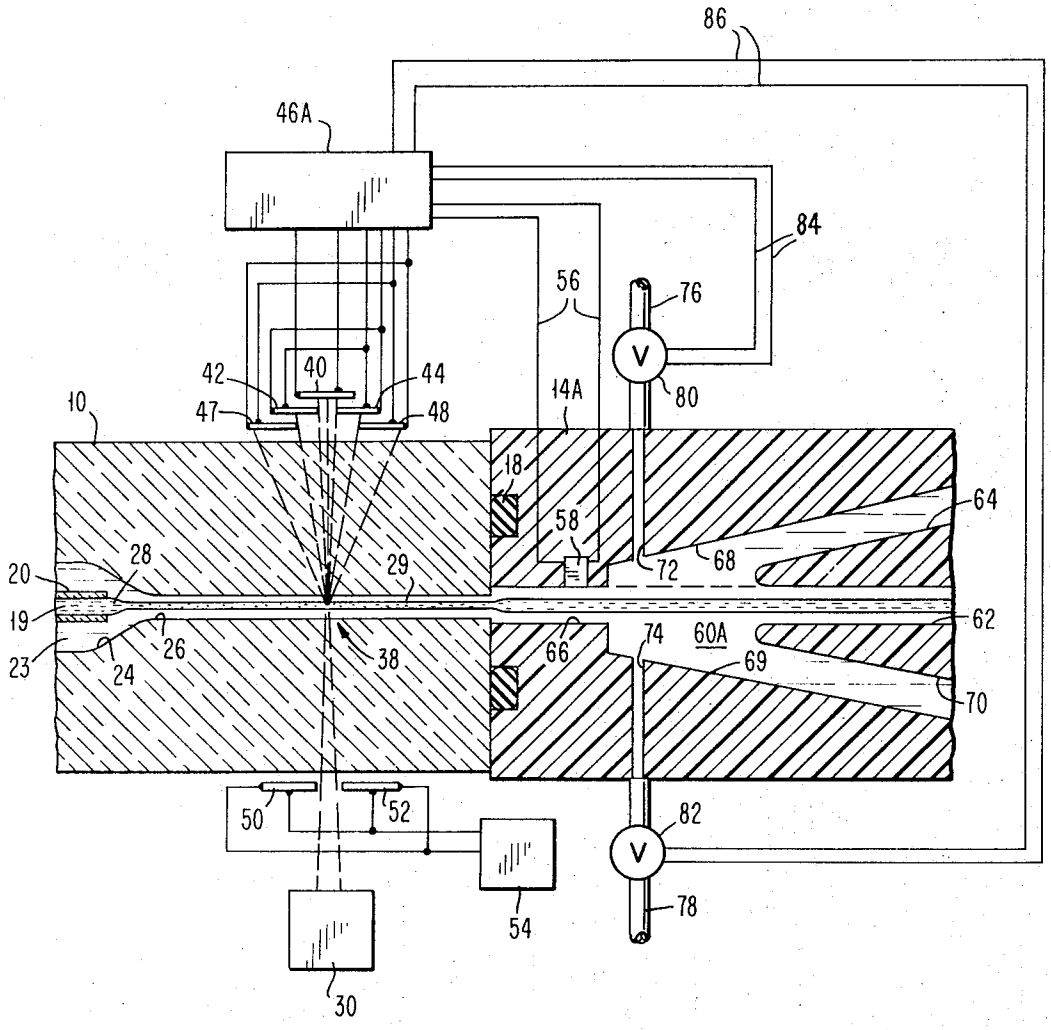

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FIG. 3

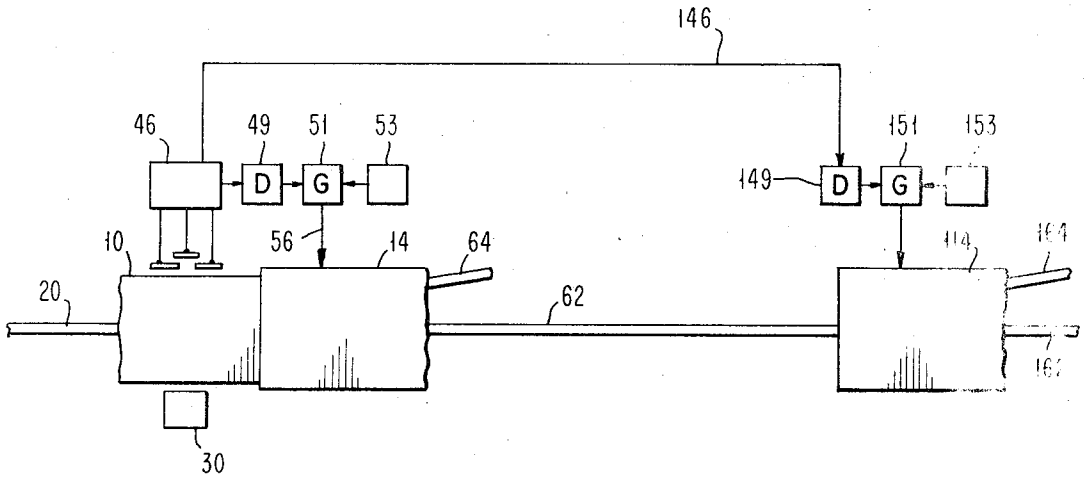
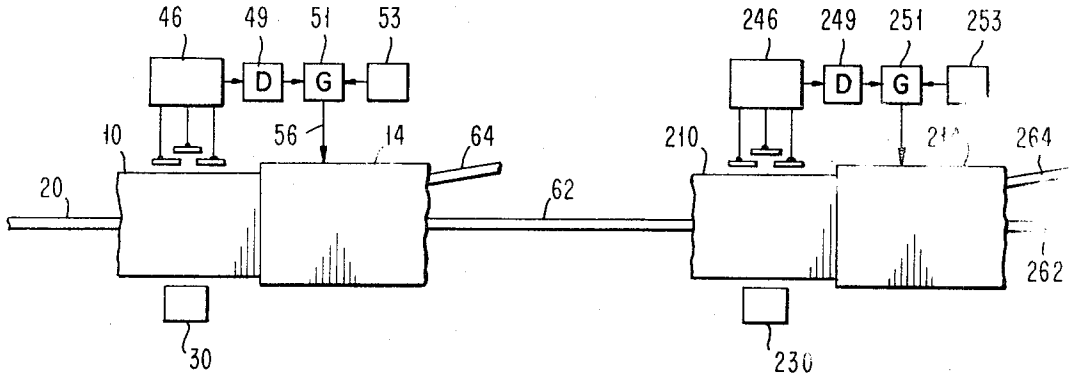

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FIG. 4


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PARTICLE SORTER WITH SEGREGATION INDICATOR

This invention relates to apparatus for sorting small particles such as biological cells which may be microscopic in size. More particularly, the apparatus is capable of sorting such particles having different characteristics into different containers or receptacles with a high degree of accuracy.

In recent years, accurate high speed machines have been devised for measuring and indicating various characteristics of small particles such as biological cells. One such machine is described and claimed, for instance, in U.S. Pat. No. 3,705,771 dated Dec. 12, 1972 for a PHOTOANALYSIS APPARATUS, and assigned to the same assignee as the present application. However, there is a continuing important need for a machine which will very accurately and very rapidly sort such particles into two or more groups having different characteristics. This sorting function is particularly needed for purposes of medical diagnosis, and for medical research. There are many different particle characteristics which can be the basis for the sorting or segregation. The sorting is particularly valuable in instances where the particles or cells having the unique characteristics are present in a very small proportion to the total, making it difficult to obtain information about the unique particles without physically separating those particles from the main body of particles in which they occur.

The present invention is particularly useful in conjunction with apparatus disclosed in patent application Ser. No. 338,216 filed concurrently with the present application by Mitchell Friedman, now U.S. Pat. No. 3,791,517 issued Feb. 12, 1974, for a DIGITAL FLUIDIC AMPLIFIER PARTICLE SORTER and assigned to the same assignee as the present application. The present invention is disclosed in combination with the apparatus of the above-mentioned copending application, but it is understood that the present invention is also useful in combination in other sorting apparatus.

One of the most serious problems in particle sorters for very small particles is the difficulty in determining whether or not the apparatus is operating correctly to provide the desired segregation of sorted particles. This problem is particularly serious with particle sorters capable of vary rapid operation.

Accordingly, it is one object of the present invention to provide an improved particle sorter which incorporates means for verifying that the sorting operation has taken place.

In particle sorting apparatus, the mode of operation may include the entrainment of the particles to be sorted in a stream of fluid, detection of differences in particle characteristics as the stream passes a detection station, and then transmission of the resultant detection signals to a sorting means located downstream of the detection station. The precise timing of the signals to the sorting means from the detection station is vital to the accurate operation of the apparatus. The required timing is dependent upon the velocity of the particle carrying fluid stream.

Accordingly, it is another object of the present invention to provide a means for indicating the duration of the interval for the passage of a particle from the detection station to the sorting means in order to determine

the exact timing for the operation of the sorting means.

Further objects and advantages of the invention will be apparent from the following description and the accompanying drawings.

In carrying out the invention there is provided an improved particle sorting apparatus for sorting very small particles comprising a housing defining a detection chamber with means for moving a fluid in which the particles are suspended through said housing in a stream. A detection means is associated with said detection chamber for detecting differences in particle characteristics and operable to provide electrical signals which vary in accordance with said differences in particle characteristics. A sorting means is positioned downstream from said detection chamber housing, said sorting means being connected to said detection means and being operable in response to said electrical signals from said detection means to segregate particles having predetermined differences in particle characteristics from the stream of particles. Said particle sorting means defines at least two alternate paths of egress of particles therefrom, one of said paths representing particles segregated thereby and the other of said paths representing particles not to be segregated from the stream. The apparatus includes the combination of a light source and a photoelectric detector associated with one of said paths to determine the passage of particles therethrough in order to verify the sorting operation of the apparatus.

In the accompanying drawings:

FIG. **1** is a schematic side view, partly in section, illustrating a preferred embodiment of the invention.

FIG. **2** is a representation corresponding to FIG. **1**, but showing an alternative embodiment of the invention.

FIG. **3** is a simplified schematic diagram illustrating a modification of the invention employing a plurality of fluidic amplifiers.

FIG. **4** is a simplified schematic diagram illustrating a modification of the invention employing a plurality of combinations of detection chambers and digital fluidic amplifiers connected in tandem.

Referring more particularly to FIG. **1**, there is shown an optical chamber formed by a glass tube member **10** which is clamped by means not shown to a digital fluidic switch chamber housing member **14**, the two members being sealed together by a liquid-tight annular seal **18**. The liquid **19** containing the particles to be observed enters the apparatus through a tube **20** centrally disposed within the funnel-shaped entrance portion **24** of the cylindrical central bore **26** of the member **10**. Another liquid **23** also enters the mouth **24** of the central bore **26** and forms a sheath of liquid for the liquid **19** containing the particles.

The velocity and volume of flow of the particle-bearing liquid **19** and the sheath liquid **23** entering the mouth **24** of the central bore **26** are such as to cause the stream of particle-bearing liquid to be narrowed down, as shown at **28**, into a very narrow stream **29** having a maximum dimension of the same order of magnitude as the maximum dimension of the particles being carried by the stream. For instance, this dimension may be in the order of 25 microns. The particles of greatest interest are often somewhat smaller than this, being in the range from 1 to 10 microns in diameter. The funnel-shaped entrance portion **24** of the cy-

lindrical member 10 is preferably provided with an exponential function shape to provide for smooth non-turbulent flow of the liquids at the critical position 28 where the particle-carrying liquid is narrowed down. Typically, the particle-carrying liquid may be an aqueous solution and the sheath liquid 23 may be water.

The stream 29 of particles is illuminated by a beam of light emitted by a light source 30 which preferably consists of a laser together with an appropriate system of lenses as described more fully in the above-mentioned patent. One satisfactory type of laser, for instance, is a helium-neon laser. The laser and the associated lenses provided a very narrow beam in which the pattern of the illumination of the beam at point 38 where it strikes the particles is preferably a very narrow ellipse which appears to be a thin line of light transverse to the stream of particles.

Electrical photoresponsive pick-up elements are arranged around the outside of cylindrical chamber member 10 to detect different optical reactions of each particle to illumination from the beam. These elements are illustrated at 40, 42, 44, 47, and 48 which are all connected to provide signals to an apparatus 46, and elements 50 and 52 connected to provide signals to apparatus 54. The apparatus 54 may be combined with the apparatus of 46, but is separately shown to simplify the drawing. The apparatus 46 may include amplifiers, logic circuitry, digital counters, and electronic display devices. The circuits within the apparatus 46 may be carried out in accordance with the teachings of a prior U.S. Pat. No. 3,662,176 issued May 9, 1972 on an invention of Louis A. Kamentsky and Isaac Klinger for A PHOTO-OPTICAL PARTICLE ANALYSIS METHOD AND APPARATUS which is assigned to the same assignee as the present application. The apparatus 46 is sometimes referred to hereinafter as "circuits 46."

When a unique particle characteristic is detected which signifies the presence of a unique particle which is to be segregated from the other particles, the detection circuits 46 send out an electrical signal through a delay circuit 49, a gate circuit 51, and connections 56 to an electrical transducer 58 which is mounted within the fluidic switch housing 14. This causes a switching of the particle-carrying stream from one outlet port to another.

The fluidic amplifier housing 14 defines a switching chamber 60 having a first outlet port 62, and a second outlet port 64. The flow of liquid through the optical chamber 10 is in a laminar (non-turbulent) mode. In the absence of a signal at the transducer 58, the stream of fluid emanating from the bore 26 of the chamber 10 continues to flow in a laminar mode into the inlet 66 of the fluidic amplifier housing 14, and continues in the laminar mode through the switching chamber 60, and out through the first outlet port 62, which is in direct axial alignment with the inlet 66. However, when the transducer 58 is energized, it induces turbulence into the liquid stream. In the presence of turbulence, the stream tends to attach itself to the nearest side wall 68. This "wall attachment" effect causes the stream to follow the side wall 68 to the second outlet port 64.

The wall attachment effect is sometimes referred to as the "Coanda effect" in honor of the Rumanian engineer, Henry Coanda, who discovered it. This effect is well recognized in the literature as the basis for many fluidic digital switching devices. The wall attachment effect is caused by a "bubble" of low pressure adjacent to the exit of the nozzle formed by the inlet 66 at the beginning of the near side wall 68. This low pressure bubble causes the stream of liquid to bend towards the wall 68 and to become stable in this deflected course of travel. Thus, as long as the stream remains turbulent, by reason of the application of a signal to the transducer 58, the stream remains deflected to the second outlet port 64. However, upon the discontinuance of the signal to transducer 58, laminar flow is reestablished, the wall attachment effect disappears, and the stream returns to the first outlet port 62.

The speed of operation of the circuits 46 in providing a signal to the transducer 58 is properly correlated with the speed of the liquid stream of particles and the dimension between the optical detection point 38 and the transducer 58 to provide for switching of the desired particles from port 62 to port 64. The dynamic response in the speed of operation of the fluidic switch is also a factor. For this purpose, the delay circuit 49 is provided between the circuits 46 and transducer 58. The delay circuit 49 may be adjustable to properly correlate the timing of the signal to transducer 58 with the arrival of the particle to be switched by the transducer. One of the important advantages of this preferred embodiment of the invention is that the response of the system is extremely rapid since the transmission of signals is accomplished entirely electrically to the very point in the inlet 66 of the fluidic switch where turbulence must be induced. This is in contrast to other fluidic switches in which a signal is transmitted through a column of fluid to the control point.

The transducer 58 is preferably a piezoelectric crystal which is capable of physical deformation in response to an applied voltage. The excitation signal applied to the crystal 58 is preferably an alternating current at a frequency corresponding to the natural resonant frequency of the crystal 58 and its surrounding fluid so as to provide maximum mechanical output in response to the available electrical input energy. Thus, the individual signals applied to the transducer 58 are usually in the form of bursts of alternating current gated by gate 51 from an oscillator 53. The resultant alternating mechanical changes in the piezoelectric crystal 58 are very efficient in inducing turbulence in the liquid stream so as to assure immediate initiation of the wall attachment effect.

While the transducer is shown as embedded in a side wall of the inlet nozzle 66 of the fluidic amplifier on the same side as the wall 68, it will be understood that the transducer may be effective also in other locations communicating with the inlet 66, or in the switching chamber 60 in close proximity to inlet 66. The piezoelectric crystal is preferred as the transducer for this purpose. However, other types of transducers, such as electromagnetically energized acoustic vibration transducers may be employed.

The optical chamber member 10 is a glass tube having a cylindrical inner bore 26. However, the interior cavities of the digital fluidic amplifier defined by the housing 14 may be circular or non-circular in cross-section, or essentially two-dimensional in nature. Thus, the inlet 66 may include a transition from a circular shape to a rectangular shape, or the inlet 66 may simply be rectangular in shape throughout its length, having a minimum cross-sectional dimension which is at least as great as the diameter of the bore 26 of the optical

chamber **10.** The transition of the stream of liquid from the circular cross-section bore **26** to the rectangular inlet **66** of the fluidic amplifier does not disturb the flow sufficiently to create turbulence. Thus, the stream retains its laminar-characteristic until it is made turbulent by the transducer **58.** The interior cavities of the housing **14** can be rounded at the corners, and the inlet **66** and the outlet ports **62** and **64** can actually be circular in cross-section without interfering with the operation of the device as described above.

The ports **62** and **64** are connected to suitable collectors or containers, not shown. Either, or both, of the separate collected cell bearing liquids can be run through the apparatus again to accomplish an additional refinement in the sorting operation by again sorting for the same characteristic, or for still another characteristic. After a run is completed, the apparatus may be flushed with a saline solution or water. To assure complete collection of all of the unique cells sorted at port **64,** flushing liquid may be applied at the inlet **23** while outlet port **62** is blocked so that all of the flushing liquid is necessarily directed through the outlet port **64,** carrying any sorted particles which remained in the port **64** and the associated passage to the collector or container associated with that port. The apparatus is then preferably completely flushed to prevent contamination of a new sample with the remains of a completed sample.

A number of different characteristics of the particles may be optically detected in the chamber **10** and used as a basis for the sorting of the particles. For instance, the electrical photoresponsive pick-up element **40** is arranged in direct line with the beam to measure the degree of extinction of illumination by each particle. In the absence of a particle at the intersection of the beam, or in the absence of any substantial extinction, the beam strikes the element **40** without any substantial diminution.

As illustrated in the drawing, the beam diverges to a certain extent after having been converged at the center of the chamber at **38.** The effective divergence in a practical embodiment has been limited to approximately one degree on each side of the center line of the beam as measured from the particle scanning point **38** at the center of the chamber. Thus, photoresponsive pick-up elements **42** and **44** are arranged on opposite sides of the direct beam and can be used to measure illumination scattered out of the direct beam by the particles over a selected range of angles from 1° up to a predetermined angular limit. For instance, this range of angles may be from 1° to 9°. As shown in the drawing, the photoresponsive pick-up elements **42** and **44** may be electrically connected in parallel so that electrical signals resulting from illumination scattered on either side of the beam and detected by elements **42** and **44** will be registered at the electrical apparatus **46.** Additional pairs of photoresponsive pick-up elements for detecting scattered light at other ranges of angles may be provided as shown at **47** and **48.** For instance, this additional pair of pick-up elements may detect scatter over the scatter angle range from 9° to 22°.

Scattering of illumination from the particles in the reverse direction, called "back scattering" can also be detected by photoresponsive elements **50** and **52** arranged on the same side of the chamber as the light source **30** and connected in parallel to an electrical pick-up and recording apparatus **54.** Apparatus **54** may be combined with the apparatus **46,** but it is shown separately here to simplify the drawing.

The portion of the apparatus for detecting different particle characteristics as just described above may preferably be carried out in accordance with the teachings of the patent first mentioned above. In addition to detecting different particle characteristics by extinction and by scatter, distinctive particle characteristics may also be determined on the basis of fluorescent radiation reactions from the particles to illumination of the particles as taught in that prior patent. When fluorescent radiation reactions are desired, an argon ion laser may be used as the source of illumination. Furthermore, sophisticated combinations of particle measurement characteristics may be employed for controlling the particle sorting operation. For instance, electrical summations or differences of different signals may be employed at selected threshold values for determining when a particle should be segregated from the main stream. Such circuits are described in the aforementioned U.S. Pat. No. 3,662,176.

The features described above in connection with FIG. **1** are common to the above-mentioned concurrently filed patent application, now U.S. Pat. No. 3,791,517. The remaining features described immediately below in connection with FIG. **1** are particularly important and unique with respect to the present invention.

A source of illumination such as a small incandescent lamp is provided, as indicated at **55,** which directs a beam through a central slit in an optical mask **57** and thus through the particle carrying stream to an optical pick-up element, or photocell, **59.** The optical pick-up element **59** is connected to an amplifier **61** which may be connected at **63** to control the variable delay circuit **49.** The illumination from the lamp **55** traversing the particle stream to the photoelectric pick-up element **59** is effective to detect the passage of particles in the particle stream. Since this combination including pick-up **59** is located near the transducer **58,** it is in a position to measure the arrival of the particle upon which the transducer **58** is intended to be effective, and to thus measure the travel time of the particle from the initial detection point **38** to the transducer **58.**

While the pick-up element **59** is not located at the identical position of the transducer **58,** the travel time of particles from point **38** to pick-up element **59** is proportional to the travel time from point **38** to the transducer **58** so that the interval until the arrival of particles at pick-up element **59** is a measure of the travel time to the transducer **58.** Thus, the signals from pick-up element **59** amplified by the amplifier **61** may be used to control the delay circuit **49** to provide an exact match of the operation of the electrical circuits energizing transducer **58** with the velocity of the particle-carrying liquid. This provides an important enhancement in the precision and accuracy of operation of the sorter.

In accordance with another feature, another light source in the form of an incandescent lamp **65** provides a beam of light through a slit in an optical mask **67** which crosses the passage for port **64** to a photoelectric pick-up element **69** which is connected to an amplifier **71.** By means of this apparatus associated with the photoelectric pick-up **69,** the passage of a particle through the port **64** can be detected so as to positively indicate that the sorting operation has been successfully accom-

plished with respect to that particle. A very useful means for indicating this success is a cathode ray oscilloscope 73 which is connected through a switch 75 to receive the amplified sort indication signal from the amplifier 71, preferably as a vertical deflection on the oscilloscope.

In order to provide a correlated horizontal sweep, the scope 73 is preferably connected through a connection 77 to receive from the circuits 46 an indication of the passage of the particle at the original detection point 38, the signal on 77 being used to trigger the initiation of the horizontal sweep on the scope 73. Thus, the vertical deflection caused by the signal from amplifier 71 will occur at a predictable horizontal position on the scope 73 which is related to the velocity of the particle-carrying liquid through the apparatus.

Alternatively, a similar detection of the passage of particles to the port 62 may be accomplished by the combination of a lamp 79, an apertured mask 81, a photoresponsive pick-up element 83, and an amplifier 85 connected thereto. The switch 75 is arranged to select the output from amplifier 71 or from amplifier 85 for indication on the oscilloscope 73.

The pick-up 83 for port 62 may be used to indicate that the particles passing through the port 62 have not been selected to be segregated into port 64. For instance, the apparatus may be checked for proper sorting operation by introducing a sample in which all particles are of a class which should be segregated into the port 64. With such a sample, whenever the sorting operation is begun, vertical deflections on the oscilloscope 73 derived from the pick-up element 83 for port 62 should disappear completely.

The signal from the pick-up element 83 may also be employed in place of the signal from pick-up element 59 for controlling the delay circuit 49. Assuming that the main body of particles in the initial liquid stream continues on through the discharge port 62, the time interval of travel of an individual particle from the initial detection point 38 to the vicinity of the pick-up element 83 will be a predictable function of the interval for the travel of an individual particle from point 38 to the transducer 58. Accordingly, the measurement available from pick-up element 83 is an appropriate signal for controlling the delay circuit 49 in order to properly time the gating of the signals to the transducer 58. The pick-up element 59 and the associated apparatus may be omitted from the system if the signal from pick-up element 83 is used to control the delay circuit 49.

It is not absolutely necessary, in order to obtain the advantages of these features to have a direct connection, such as connection 63, from one of the pick-up amplifiers to control the delay circuit 49. In other words, an open loop system may be employed in which the delay interval is measured, such as by the indication on the oscilloscope 73, and that measurement is then used to manually set the delay on the variable delay circuit 49. However, the direct connection 63 from the amplifier 61 to the delay circuit 49 provides the advantage of continuous and automatic adjustment of the delay to compensate for any fluctuation in the velocity of the particle-carrying stream.

In accomplishing the purposes of the pick-ups 69 and 83 in indicating the accomplishment of the sort function, it may also be useful to have counters attached for actuation from the amplifiers 71 and 85 for indicating and storing a registration of the numbers of the particles which have been sorted into the respective ports 62 and 64. It is contemplated that the circuits 47 may include counters for counting the total number of particles and also for counting particles having unique characteristics to be detected and upon which the sort is to be based. Accordingly, the counters attached to the amplifiers 71 and 85 which indicate the numbers of particles sorted into the two channels can be compared with the counts registered by the counters within the apparatus 46 to accurately determine the efficiency of the sorting operation.

It will be understood that the pick-up elements 59, 69, and 83, and the associated apparatus, are shown schematically in order to simplify and clarify the drawing. In a preferred embodiment of the invention, each of these combinations of apparatus is preferably rotated 90° about the axis of the associated liquid channel so that the direction of the light beam in each instance is directly perpendicular to the plane of the section shown in the drawing. Thus, in such a preferred arrangement, the pick-up element 59, for instance, would appear on the wall of the inlet 66 directly behind the liquid stream. In such a preferred physical embodiment, the lamp 55 and the pick-up 59 can be arranged and positioned exactly at the axial position of the transducer 58 within the inlet 66 so as to provide an exact measurement of the interval until the arrival of a particular particle at the transducer 58.

The switching chamber 70, and the ports 62, 64, and 66 may preferably be formed by providing the chamber housing 14 in two parts, one part containing cavities to provide the chamber and ports, and the other part constituting a cover which is attached over the other part to enclose the cavities. Thus, the part of the housing 14 containing the cavities may contain the pick-up elements 59, 69, and 83 in the back walls thereof, and the light sources 55, 65, and 79, together with their associated optical masks, may be attached to, or be a part of, the cover member. These positions may, of course, be reversed.

Other modifications are also possible. For instance, fiber optics may be employed to carry the illumination from a lamp, such as 55, to the channel, such as 66, where it is needed. Instead, or in addition, fiber optics may be used to convey the light beam from the channel 66 to the photoelectric pick-up 59. The use of fiber optics may be particularly advantageous because of the space limitations in the vicinity of the channels being monitored, the optical fibers requiring much less space than the lamp and photoelectric pick-up elements. Also, light sources other than incandescent lamps may be employed.

In order to simplify the drawings and descriptions of the modifications of the invention illustrated in FIGS. 2, 3, and 4, the pick-up elements 59, 69, and 83, and the associated apparatus, are not illustrated or described in connection with these other figures. However, it will be understood that the principles of the features associated with these pick-up elements are equally applicable to these modifications. For instance, in FIG. 2, three outlet ports are provided from the switching chamber and it will be understood that photoelectric sort detectors, such as elements 69 and 83, may be employed for each of those three outlet ports.

FIG. 2 illustrates an alternative embodiment of the invention in which the switching chamber 60 is modified as shown at 60A, in a modified fluidic amplifier housing 14A, to provide an additional outlet port 70 and added control ports 72 and 74. A control fluid under pressure may be supplied to the switching chamber 60A through the control ports 72 and 74 through the respective supply lines 76 and 78 under the control of electromagnetically operated valves 80 and 82. These valves may be controlled from the apparatus 46 through the electrical connections respectively indicated at 84 and 86.

As illustrated in the drawing, the opposite walls 68 and 69 of the switching chamber 60A are essentially equidistant from the nozzle formed by the inlet 66. Accordingly, they are equally capable of displaying the wall attachment effect in the presence of turbulence in the liquid stream, as previously described above. Thus, just as the wall attachment effect to wall 68 directs the liquid stream to outlet port 64, the wall attachment effect at wall 69 leads the fluid stream to the outlet port 70. Once established at one wall, the wall attachment effect will be maintained and will hold the stream to one of these two walls, and thus direct the stream to one of these two outlet ports, as long as turbulence continues. In order to determine which direction the stream will take, a signal must be supplied from one of the control ports 72 or 74. If the signal takes the form of a supply of control fluid under pressure, it has the effect of shifting the stream away from the wall adjacent to the control port and over to the opposite wall. Thus, if control fluid is supplied to the switching chamber 68 through the control port 74, the supply of fluid destroys the low pressure bubble at the wall 69, causing the stream to shift to the opposite wall 68. A similar, but opposite effect is available if a vacuum is applied at the control port 74. This reduces the pressure at the wall 69, tending to increase the wall attachment at the wall 69 and to switch the device so that the liquid stream is pulled away from the wall 68 and to the wall 69 and to the port 70.

The embodiment of FIG. 2 is capable of several different alternative modes of operation. For instance, if the switching chamber 60A is fabricated in an asymmetrical form such that the wall 68 is substantially closer to the nozzle formed by the inlet 66 than the wall 69, then without any control signals at the control ports 72 and 74, the switching action will be identical to that described above for the embodiment of FIG. 1. Thus, if a signal is supplied to the transducer 58, the resulting turbulence will cause the stream to attach to the wall 68 and to be directed to port 64. In the absence of a signal at transducer 58, the laminar flow will continue, and the stream will be directed through the outlet port 62.

However, with the asymmetrical configuration, if a fluid pressure control signal is applied at the control port 72 while the turbulent condition exists by reason of the operation of the transducer 58, then the wall attachment effect at wall 68 will be discontinued, and the stream will attach to wall 69, even though that wall is more distant from the nozzle formed by inlet 66. Thus, in such an arrangement, with an asymmetrical configuration, the second control port 74 is not necessary to provide a three way switching effect to the three outlet ports 62, 64, and 70. Summarizing the operation of such an asymmetrical form of the invention: with neither the transducer 58 nor the control port 72 being effective, laminar flow continues, and the stream exits through the center port 62. With only the turbulence transducer 58 energized, the resultant turbulence causes the stream to attach to wall 68 and to discharge through port 64. With both the turbulence transducer 58 and the control port 72 in operation, the stream is directed to the far wall 69 and to the outlet port 70. Since the wall attachment effect is self-sustaining in the presence of continued turbulence, the signal from control port 72 need not be continued to maintain the discharge at port 70.

In the symmetrical form actually illustrated in FIG. 2, a signal must be supplied from one of the control ports substantially concurrently with the signal to the transducer 58 in order to make it certain that the stream is directed to the correct outlet port. When no cells are selected to be segregated from the stream, no signals are supplied to the transducer 58 or to the valves 80 and 82. In these circumstances, the flow remains laminar, and the liquid is discharged through the center port 62. However, upon the detection of a cell or particle of a first type to be segregated, signals are supplied substantially concurrently to the transducer 58 and to open the valve 82, respectively causing the stream to become turbulent, and providing a control port signal at 74 causing the stream to be switched to the wall 68 and the outlet port 64. Upon the detection of a particle of a second category to be segregated, signals are supplied to the transducer 58 to initiate or maintain turbulence, and to open valve 80 to the control port 72, causing the stream to switch to the wall 69 and the outlet port 70. Thus, in this embodiment, there is the capability of sorting the particles into three categories in a single pass through the apparatus.

In another alternative mode of operation, the transducer 58 remains on at all times, the stream is always turbulent, and switching of the stream is always exclusively controlled by the control ports 72 and 74 so that the stream is always emitted either from the port 64 or the port 70. The center port 62 is not used. Also, with the versatility provided by the modification of FIG. 2, there is presented the possibility of achieving a faster response of the fluidic amplifier in terminating the turbulent flow to one of the nonaxial outlet ports, such as 64, when the transducer is turned off, by concurrently providing a short signal from the associated control port 72. This sharply terminates the "wall attachment" at wall 68 while laminar flow is being re-established.

In the broader sense, the valves 80 and 82 may also be referred to as electrical transducers. They perform the function of transducers in that they convert electrical signals to fluidic control signals which cause the switching of the liquid stream from one outlet port to another. The switching fluid used at the ports 72 and 74 should be compatible which the liquid in the main stream, but it need not be identical to the liquid. Thus, where the liquid in the main stream is water, the switching fluid may be water, or air, or some other compatible fluid.

For the sake of simplicity in the drawing, the valves 80 and 82 are shown only schematically. However, it will be understood that they may be electromagnetically operated valves, or they may operate on some other principle. For instance, they may be piezoelectric crystal actuated valves in which crystal movement in response to a voltage serves to open the valve. While

not so illustrated, the valves **80** and **82** are preferably built into the housing **14A**, as close as possible to the exits of the associated control ports **72** and **74**. By this means, the transit time of signals initiated through the valves is substantially reduced since the signals are transmitted substantially the entire distance to the point of use by electrical means rather than by means of a column of fluid.

It is possible to modify the embodiment of FIG. **2** to provide for at least two more side ports corresponding to ports **64** and **70** by arranging such ports in a circular pattern around the central port **62**. Thus, another side port (not shown) can be arranged behind the central port **62**, and another one can be arranged in front of the central port **62**. Such an arrangement requires the addition of appropriate valves and control ports corresponding to the valves **80** and **82** and the control ports **72** and **74**.

While not illustrated in the drawings of either of the FIGS. **1** or **2**, the side outlet ports **64** and **70** may be provided with vent passages to reduce the pressure in the outlet ports to enhance the wall attachment effect and to reduce any possible impairment of the switching action which might be caused by a build-up of pressure in the receptacles to which the respective outlet ports are attached.

The embodiment of FIG. **2** provides greater versatility than the embodiment of FIG. **1**, but the FIG. **1** embodiment is definitely preferred. One of the major advantages is that the control ports **72** and **74** are not required, and the problem of purging the switching chamber when different samples are to be used, and when cleaning is required, is greatly simplified by the elimination of these control ports.

In the embodiments of both FIGS. **1** and **2**, the optical detection chamber **10** is preferably composed of glass, and the switching chamber housing **14** or **14A** may preferably be composed of a transparent synthetic resin material. While illustrated as separate housings which can be disassembled from one another, it is obvious that these housings can be combined in a unitary structure.

As illustrated in the simplified schematic diagram of FIG. **3**, additional fluidic amplifier switches may be employed downstream from the fluidic amplifier switch of the system of FIG. **1**, or in that of FIG. **2**. This provides the possibility of still further sorting and segregation of particles on a single pass through the apparatus. The downstream fluidic amplifiers may also be connected to receive control signals from circuits **46**.

FIG. **3**, at the left side, illustrates in simplified schematic form an apparatus corresponding to the apparatus of FIG. **1**, with corresponding parts correspondingly numbered. The main stream outlet port **62** is connected to a second fluidic amplifier switch housing **114** which may correspond exactly in structure and operation with the fluidic switch contained within the housing **14** and described above in connection with FIG. **1**. The fliudic switch **114** responds to a signal from circuits **46** on a connection indicated at **146** through a delay circuit **149** and a gate circuit **151** to control a signal from an oscillator **153** to a transducer within the switch housing **114**. By this means, particles which were not sorted and segregated in the first fluidic amplifier within housing **14**, and diverted to the outlet port **64**, continue on through the port connection **62**, through the switch **114**, and may be sorted and segregated according to a second particle characteristic into an outlet port **164**. If the particles are not so segregated, they continue on in the main stream outlet port **162** from the housing **114**.

Thus, FIG. **3** illustrates the principle that a plurality of fluidic amplifier switches may be controlled to accomplish several sorting operations based on signals obtained from a single optical chamber **10**. In the operation of the system of FIG. **3**, it will be understood that the delay interval provided by the delay circuit **149** is appropriately lengthened to accommodate for the additional interval required for the particles to travel from the chamber **10** to the digital fluidic amplifier **114**.

FIG. **4** is a simplified schematic diagram illustrating the principle that two sets of the apparatus shown and described in connection with FIG. **1** above can be connected in tandem to accomplish successive detection and sorting operations by two independent optical detections of particle characteristics accompanied by associated sorting operations. Thus, in FIG. **4**, the combination of apparatus at the left side of the figure corresponds precisely with the apparatus illustrated and described above in connection with FIG. **1**. The apparatus on the right of the figure again duplicates the apparatus shown and described above in connection with FIG. **1**, all of the parts being numbered with corresponding part numbers, but with a prefix digit **2** added to each number. Thus, FIG. **4** illustrates the principle that a plurality of the apparatus combinations of FIG. **1** may be connected in tandem to accomplish successive sorts on the same sample.

While the larger combinations illustrated in FIG. **3** and FIG. **4** are shown and described as being related to the apparatus of FIG. **1**, it will be quite obvious that the principle of the use of multiple digital fluidic amplifiers and multiple combinations of sorting apparatus connected in tandem may be applied as well to the apparatus of FIG. **2**.

The invention has been described above entirely in terms of a liquid particle carrying stream. While a liquid handling apparatus is preferred, it will be understood that the principles of the invention can be employed with a gaseous fluid particle carrying stream using a gas such as air.

While this invention has been shown and described in connection with particular preferred embodiments, various alterations and modifications will occur to those skilled in the art. Accordingly, the following claims are intended to define the valid scope of this invention over the prior art, and to cover all changes and modifications falling within the true spirit and valid scope of this invention.

We claim:

1. An improved particle sorting apparatus for sorting very small particles comprising

a housing defining a detection chamber,

means for moving a fluid in which the particles are suspended through said housing in a stream,

a detection means associated with said detection chamber for detecting differences in particle characteristics and operable to provide electrical signals which vary in accordance with said differences in particle characteristics,

sorting means positioned downstream from said detection chamber housing,

said sorting means being connected to said detection means and being operable in response to said elec-

trical signals from said detection means to segregate particles having predetermined differences in particle characteristics from the stream of particles,

said particle sorting means defining at least two alternate paths of egress of particles therefrom,

one of said paths representing particles segregated thereby and the other of said paths representing particles not to be segregated from the stream,

an indicating means coupled to receive signals from said particle characteristic detection means indicative of the presence of particles to be sorted,

the combination of a light source and a photoelectric detector associated with one of said paths to determine the passage of particles therethrough,

said indicating means being coupled to said photoelectric detector to receive a signal therefrom in response to the passage of a particle through the path with which said photoelectric detector is associated,

said indicating means being operable in response to said last-mentioned signal in correlation with the corresponding signal for that particle from said particle characteristic detection means to register the passage of that particle through said path in order to verify the sorting operation of the apparatus.

2. A particle sorting apparatus as claimed in claim **1** wherein

said combination of a light source and a photoelectric detector is associated with the path of particles segregated by said particle sorting means.

3. A particle sorting apparatus as claimed in claim **1** wherein

said combination of a light source and a photoelectric detector is associated with the path representing particles not to be segregated from the stream.

4. A particle sorting apparatus as claimed in claim **2** wherein

a second combination of a light source and a photoelectric detector is associated with the path representing particles not to be segregated from the stream so that both paths are monitored to indicate which path each particle takes.

5. Apparatus as claimed in claim **1** wherein

said indicating means comprises a cathode ray oscilloscope.

6. An improved particle sorting apparatus for sorting very small particles comprising

a housing defining a detection chamber,

means for moving a fluid in which the particles are suspended through said housing in a stream,

a detection means associated with said detection chamber for detecting differences in particle characteristics and operable to provide electrical signals which vary in accordance with said differences in particle characteristics,

sorting means positioned downstream from said detection chamber housing,

said sorting means being connected to said detection means and being operable in response to said electrical signals from said detection means to segregate particles having predetermined differences in particle characteristics from the stream of particles,

said particle sorting means defining at least two alternate paths of egress of particles therefrom,

one of said paths representing particles segregated thereby and the other of said paths representing particles not to be segregated from the stream,

the combination of a light source and a photoelectric detector associated with one of said paths to determine the passage of particles therethrough in order to verify the sorting operation of the apparatus,

an indicating means coupled to said photoelectric detector for registering the passage of a particle through the path with which said photoelectric detector is associated,

said indicating means comprising a cathode ray oscilloscope,

said first mentioned detection means being connected to said cathode ray oscilloscope to provide a signal to initiate the operation of an oscilloscope sweep circuit in response to the passage of a particle at said first mentioned detection means,

and said oscilloscope being coupled to provide a visual indication of the signal from said last mentioned photoelectric detector on an axis perpendicular to the axis of the sweep obtained from said sweep circuit.

7. An improved particle sorting apparatus for sorting very small particles comprising

a housing defining a detection chamber,

means for moving a fluid in which the particles are suspended through said housing in a stream,

a detection means associated with said detection chamber for detecting differences in particle characteristics and operable to provide electrical signals which vary in accordance with said differences in particle characteristics,

sorting means positioned downstream from said detection chamber housing,

said sorting means being connected to said detection means and being operable in response to said electrical signals from said detection means to segregate particles having predetermined differences in particle characteristics from the stream of particles,

said particle sorting means defining at least two alternate paths of egress of particles therefrom,

one of said paths representing particles segregated thereby and the other of said paths representing particles not to be segregated from the stream,

the combination of a light source and a photoelectric detector associated with one of said paths to determine the passage of particles therethrough in order to verify the sorting operation of the apparatus,

said sorting means comprising a digital fluidic amplifier having an inlet connected to the outlet of said detection chamber to receive the particle stream,

said fluidic amplifier including a switching chamber communicating with said inlet and at least two different outlet ports communicating with said switching chamber and defining said alternate paths of egress of particles therefrom,

said sorting means including an electrical transducer coupled to receive electrical signals from said detection means,

said fluidic amplifier being operable in response to signals received from said detection means through said electrical transducer to switch the fluid parti-

cle carrying stream entering the inlet thereof from a first outlet port representing one of said alternate paths to a second selected outlet port representing the other of said alternate paths.

8. Apparatus as claimed in claim **7** wherein said housing defining said detection chamber is operable to provide for a laminar flow of the particle-suspending fluid therethrough, said electrical transducer being operable to convert the laminar flow to turbulent flow within said fluidic amplifier switching chamber for selectively inducing turbulence in the stream of fluid in response to electrical signals from said detection means, said fluidic amplifier being operable in response to the conversion of the stream of fluid from laminar flow to turbulent flow to switch the stream in said switching chamber from said first outlet port to said second outlet port.

9. An improved particle sorting apparatus for sorting very small particles comprising

a housing defining a detection chamber,

means for moving a fluid in which the particles are suspended through said housing in a stream,

a detection means associated with said detection chamber for detecting differences in particle characteristics and operable to provide electrical signals which vary in accordance with said differences in particle characteristics,

sorting means positioned downstream from said detection chamber housing,

said sorting means being connected to said detection means and being operable in response to said electrical signals from said detection means to segregate particles having predetermined differences in particle characteristics from the stream of particles,

said particle sorting means defining at least two alternate paths of egress of particles therefrom,

one of said paths representing particles segregated thereby and the other of said paths representing particles not to be segregated from the stream,

an indicating means coupled to receive signals from said particle characteristic detection means indicative of the presence of particles to be sorted,

the combination of a light source and a photoelectric detector associated with said stream of particle carrying fluid down stream from said detection means for providing an indication of the passage of a particle therethrough,

said indicating means being coupled to said photoelectric detector to receive a signal therefrom in response to the passage of a particle through the path with which said photoelectric detector is associated,

said indicating means being operable in response to said last mentioned signal in correlation with the corresponding signal for that particle from said particle characteristic detection means,

and said indicating means being operable to measure the interval between the signal from said particle characteristic detection means and the corresponding signal from said photoelectric detector to thereby measure the speed of a particle to be sorted as a basis for determining the timing of the operation of said sorting means.

10. Apparatus as claimed in claim **9** wherein said combination of said light source and said photoelectric detector is positioned in the vicinity of said sorting means.

11. An improved particle sorting apparatus for sorting very small particles comprising

a housing defining a detection chamber,

means for moving a fluid in which the particles are suspended through said housing in a stream,

a detection means associated with said detection chamber for detecting differences in particle characteristics and operable to provide electrical signals which vary in accordance with said differences in particle characteristics,

sorting means positioned downstream from said detection chamber housing,

said sorting means being connected to said detection means and being operable in response to said electrical signals from said detection means to segregate particles having predetermined differences in particle characteristics from the stream of particles,

said particle sorting means defining at least two alternate paths of egress of particles therefrom,

one of said paths representing particles segregated thereby and the other of said paths representing particles not to be segregated from the stream,

the combination of a light source and a photoelectric detector associated with said stream of particle carrying fluid down stream from said detection means for providing an indication of the speed of a particle to be sorted as a basis for determining the timing of the operation of said sorting means,

an adjustable delay means connected between said detection means and said sorting means for providing an adjustment in the timing between the actuation of said detection means and the resulting signal to said sorting means,

said delay being adjustable in accordance with the time interval determined by said last mentioned photoelectric detector.

12. Apparatus as claimed in claim **11** wherein the signal from said last mentioned photoelectric detector is coupled to said delay means to directly control the operation of said delay means to provide for operation of said sorting means after the correct interval of time.

13. An improved particle sorting apparatus for sorting very small particles comprising

a housing defining a detection chamber,

means for moving a fluid in which the particles are suspended through said housing in a stream,

a detection means associated with said detection chamber for detecting differences in particle characteristics and operable to provide electrical signals which vary in accordance with said differences in particle characteristics,

sorting means positioned downstream from said detection chamber housing,

said sorting means being connected to said detection means and being operable in response to said electrical signals from said detection means to segregate particles having predetermined differences in particle characteristics from the stream of particles,

said particle sorting means defining at least two alternate paths of egress of particles therefrom,

one of said paths representing particles segregated thereby and the other of said paths representing particles not to be segregated from the stream,

the combination of a light source and a photoelectric detector associated with said stream of particle carrying fluid down stream from said detection means for providing an indication of the speed of a particle to be sorted as a basis for determining the timing of the operation of said sorting means,

said sorting means comprising a digital fluidic amplifier having an inlet connected to the outlet of said detection chamber to receive the particle stream,

said fluidic amplifier including a switching chamber communicating with said inlet and at least two different outlet ports communicating with said switching chamber and defining said alternate paths of egress of particles therefrom,

said sorting means including an electrical transducer coupled to receive electrical signals from said detection means,

said fluidic amplifier being operable in response to signals received from said detection means through said electrical transducer to switch the fluid particle carrying stream entering the inlet thereof from a first outlet port representing one of said alternate paths to a second selected outlet port representing the other of said alternate paths.

* * * * *

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,827,555 Dated August 6, 1974

Inventor(s) LOUIS A. KAMENTSKY and ISAAC KLINGER

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 1. line 48, "vary" should read --very--.

Column 3, line 13, "provided" should read --provide--.

Column 8, line 3, "circuits 47" should read --circuits 46--;
line 30, "chamber 70" should read --chamber 60--.

Column 10, line 56, "which" should read --with--;
line 57, "the" should read --that--.

Signed and sealed this 5th day of November 1974.

(SEAL)
Attest:

McCOY M. GIBSON JR.
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents