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(54) AUTOMATED IMAGING SYSTEM AND METHOD

(76) Inventors: **Rhett L. Affleck**, Poway, CA (US); **Robert K. Levin**, San Diego, CA (US); **John E. Lillig**, Ramona, CA (US); **Robert K. Neeper**, Ramona, CA (US)

Correspondence Address:
KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614 (US)

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Publication Classification

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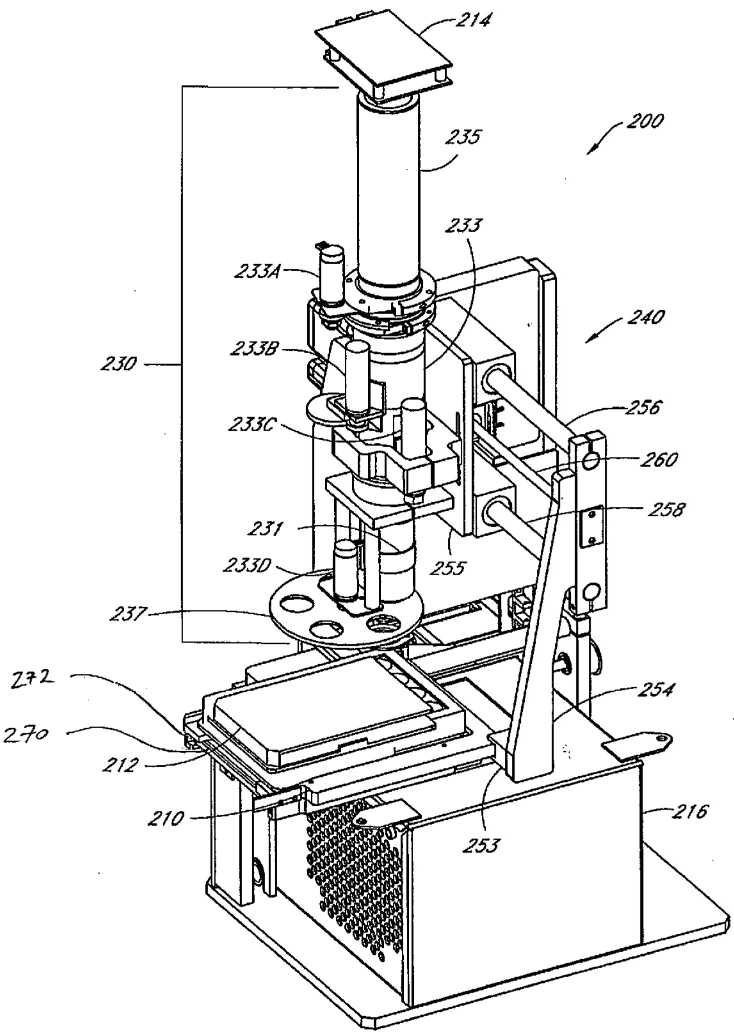
(57) ABSTRACT

An imaging system for automation of sample monitoring includes an image capture device that cooperates with a lens assembly for imaging the samples. A translator positions the lens assembly and/or a sample plate mount for acquisition of the images. Some embodiments of the system include a light source configured to provide low temperature, flash illumination of a sample plate.



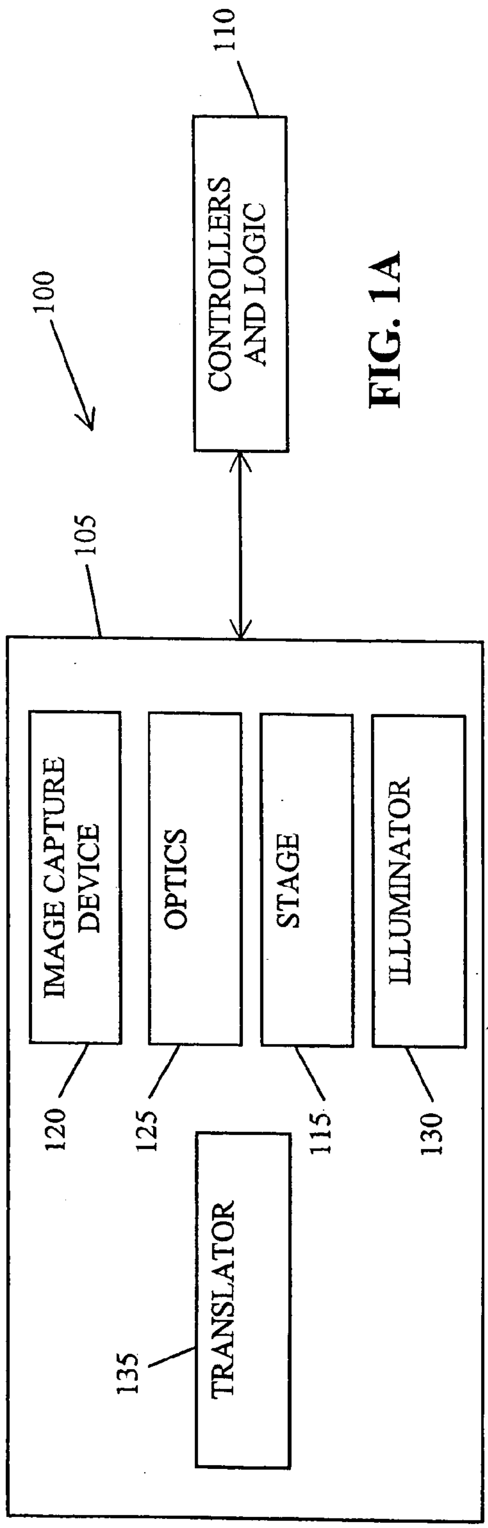

100
105
110
CONTROLLERS AND LOGIC
IMAGE CAPTURE DEVICE
OPTICS
STAGE
ILLUMINATOR
TRANSLATOR
120
125
115
130
135

FIG. 1A

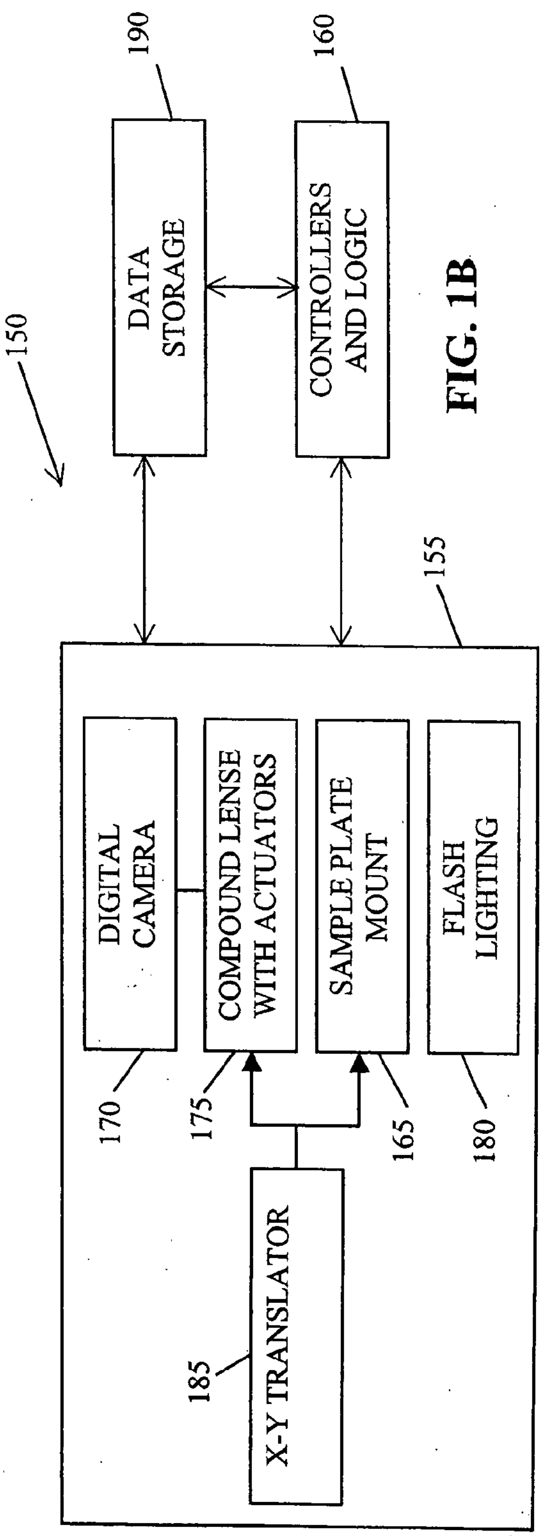

150
155
190
160
DATA STORAGE
CONTROLLERS AND LOGIC
DIGITAL CAMERA
COMPOUND LENSE WITH ACTUATORS
SAMPLE PLATE MOUNT
FLASH LIGHTING
X-Y TRANSLATOR
170
175
165
180
185

FIG. 1B

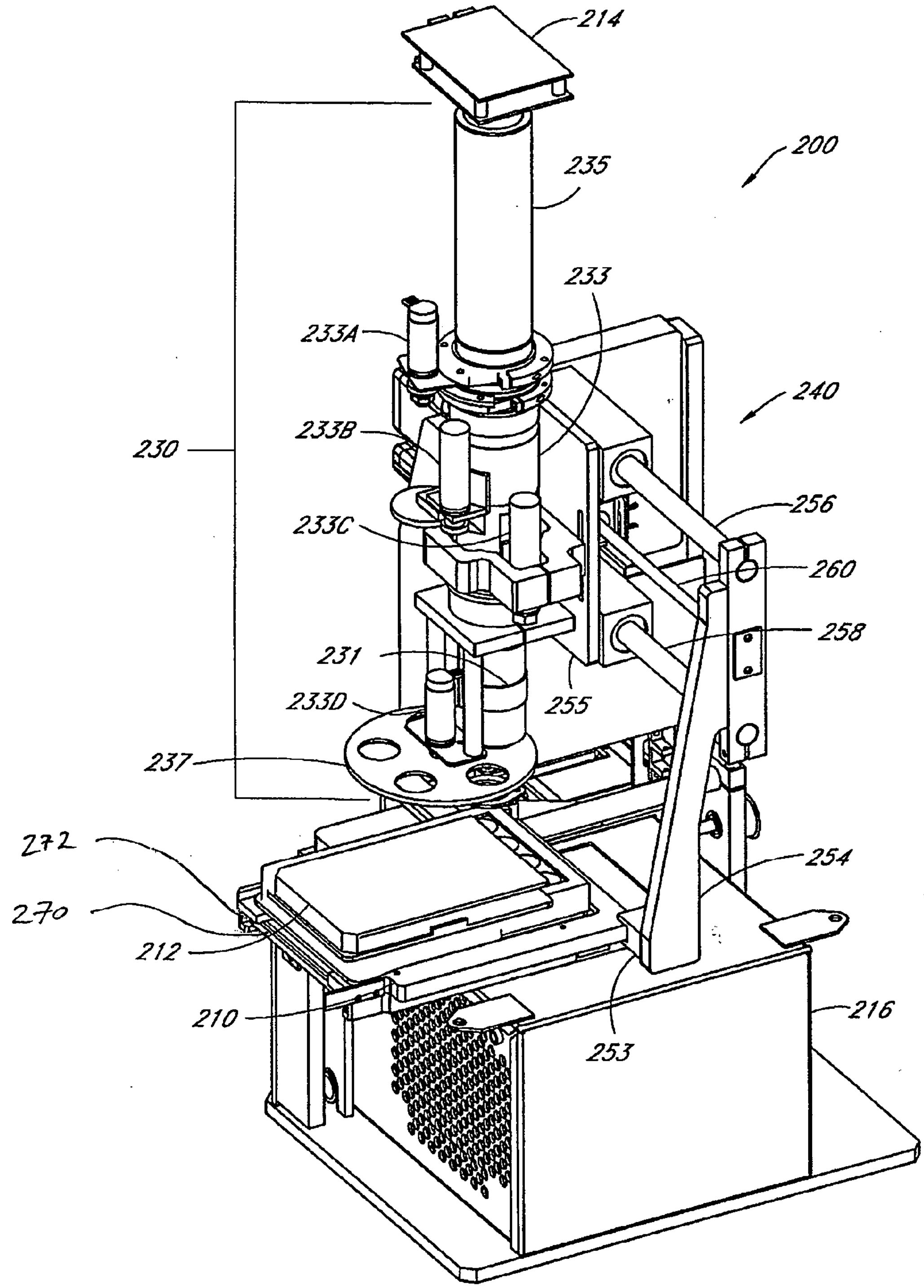

214
200
235
233
233A
240
233B
230
256
233C
260
258
231
255
233D
237
272
254
270
212
216
210
253

FIG. 2

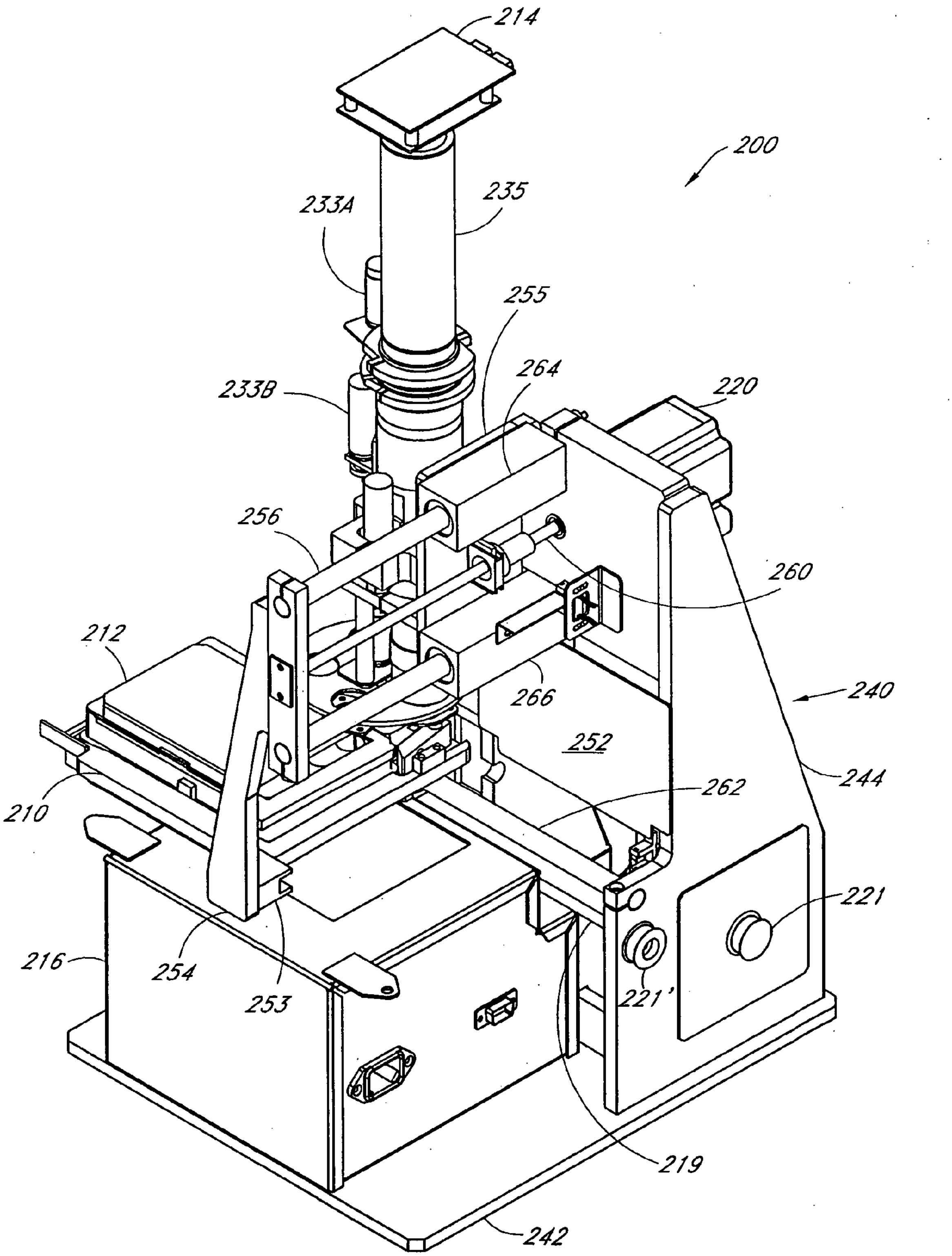

214
200
235
233A
255
264
220
233B
256
260
212
266
240
252
244
210
262
221
216
254
253
221'
219
242

FIG. 3

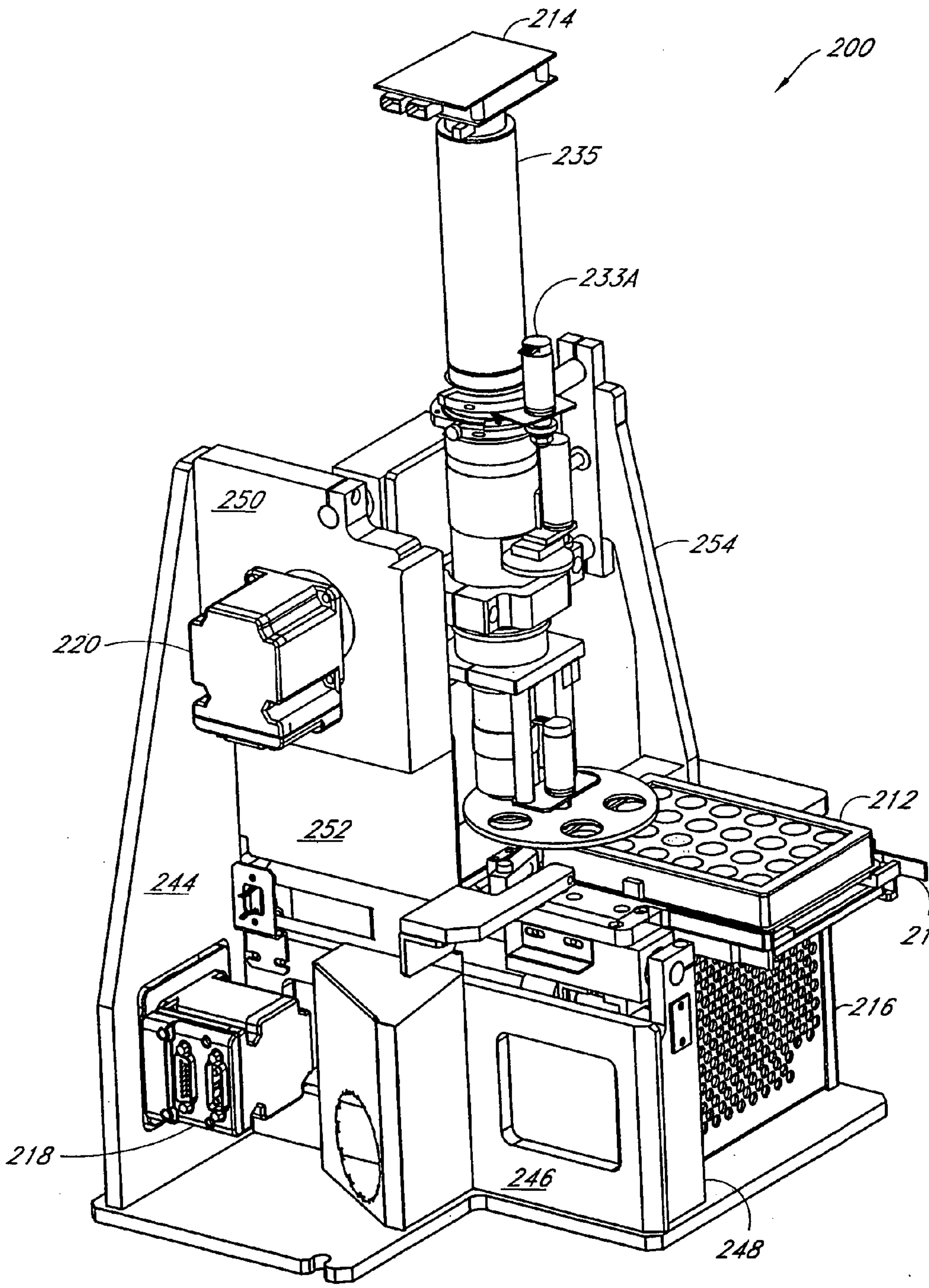


FIG. 4

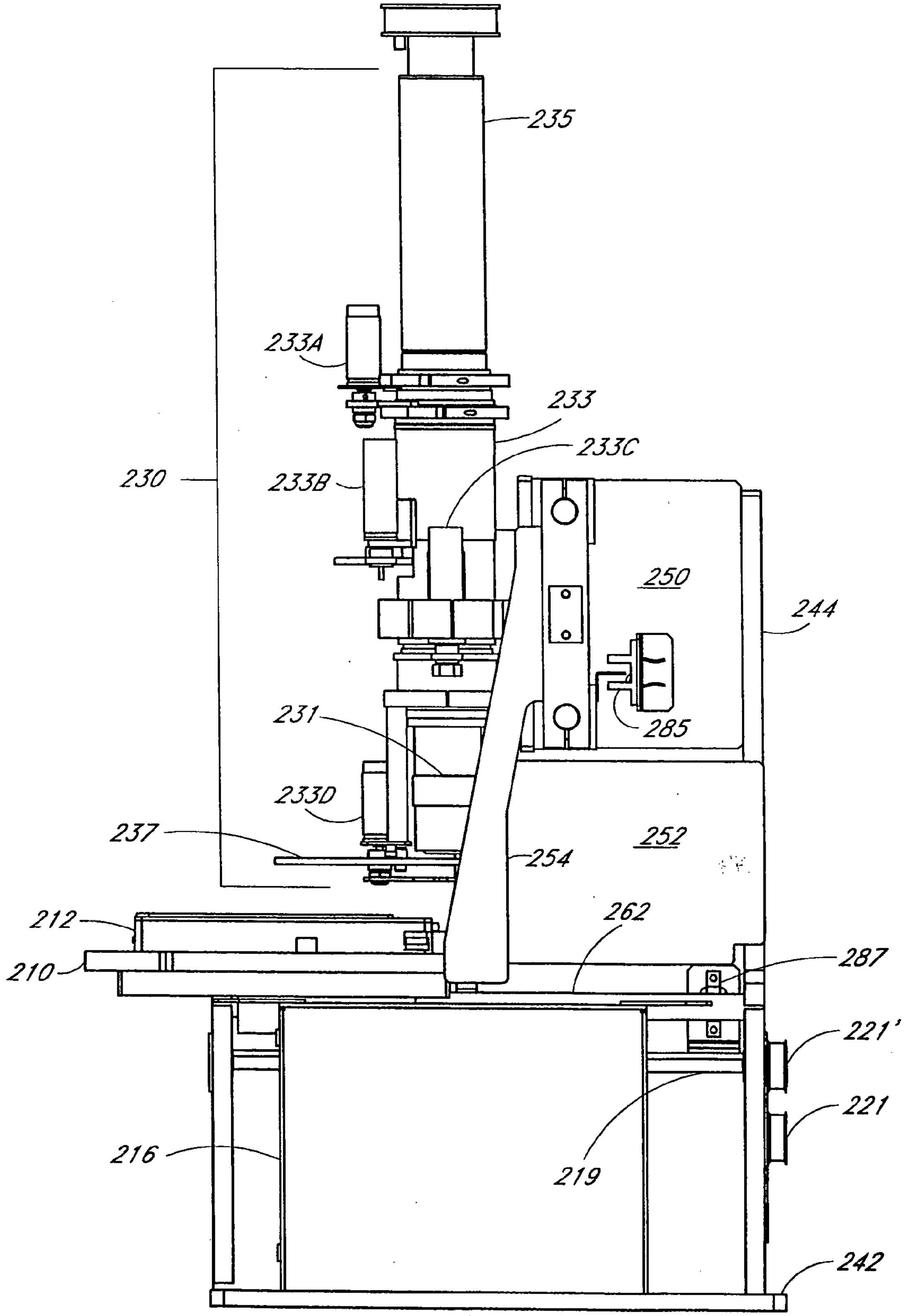

235
233A
233
233C
230
233B
250
244
285
231
233D
252
237
254
212
262
287
210
221'
221
216
219
242

FIG. 5

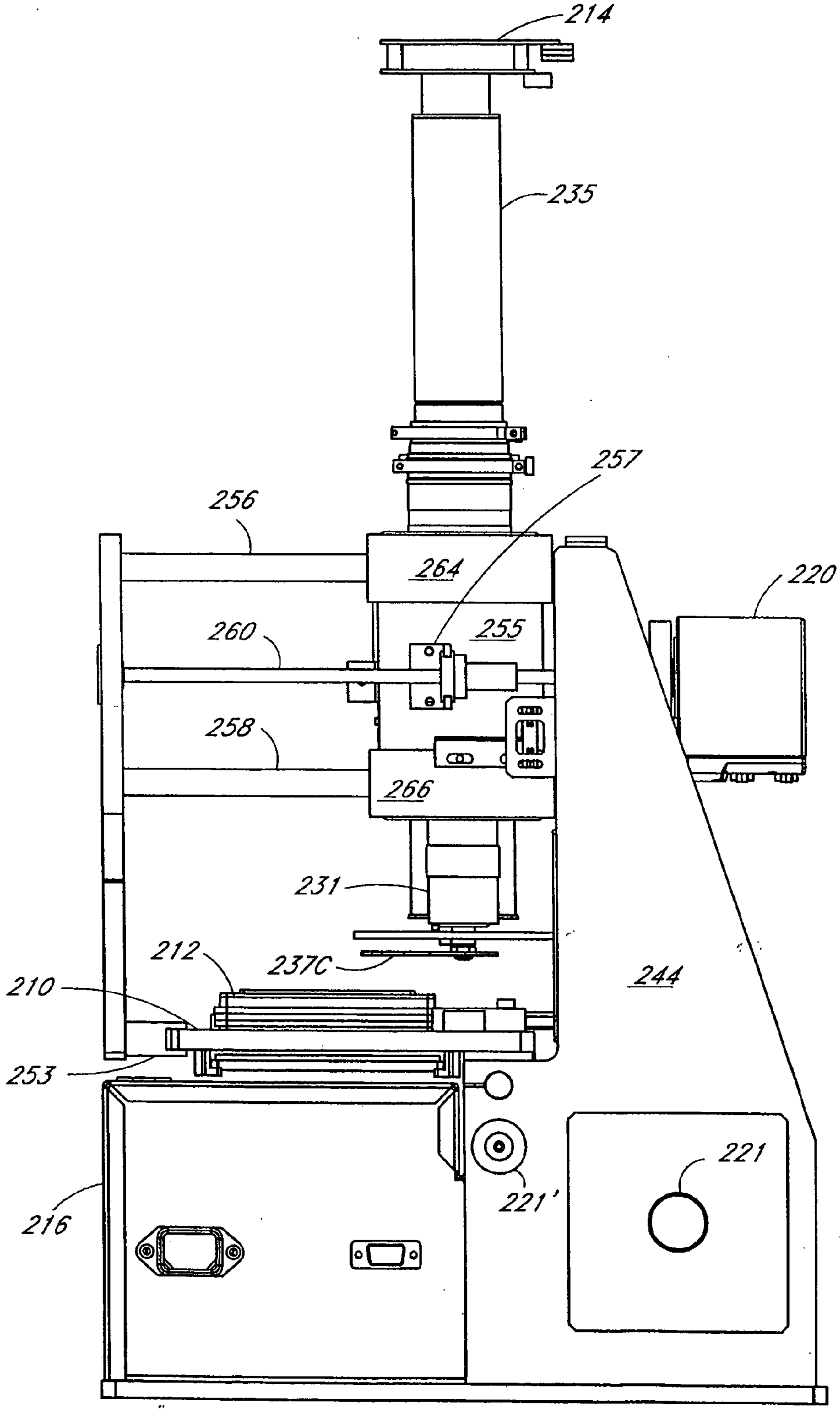

214
235
257
256
264
220
255
260
258
266
231
212
237C
210
244
253
221
221'
216

FIG. 6

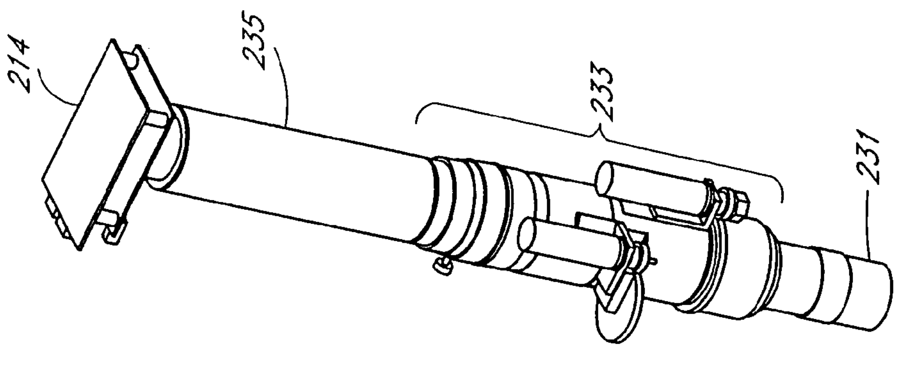


FIG. 7B

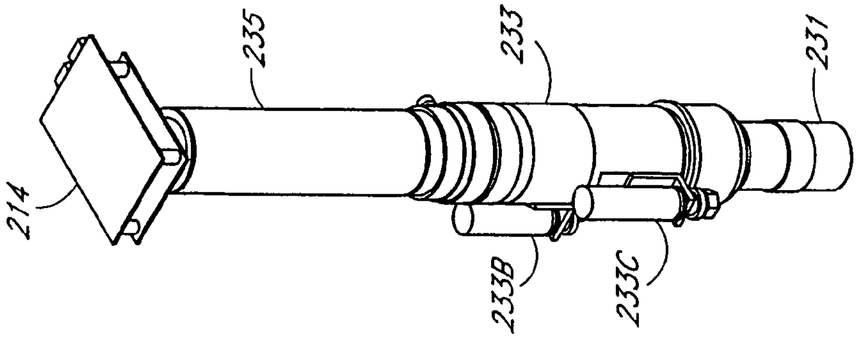


FIG. 7A

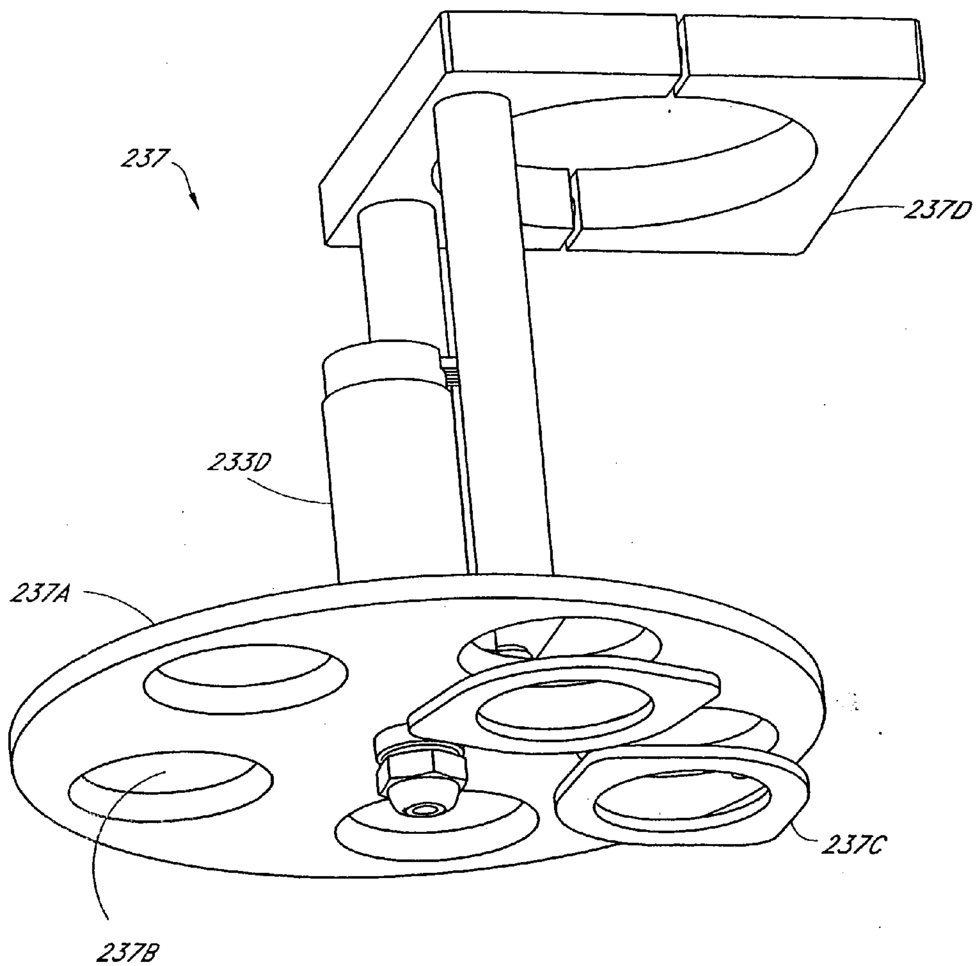


FIG. 8

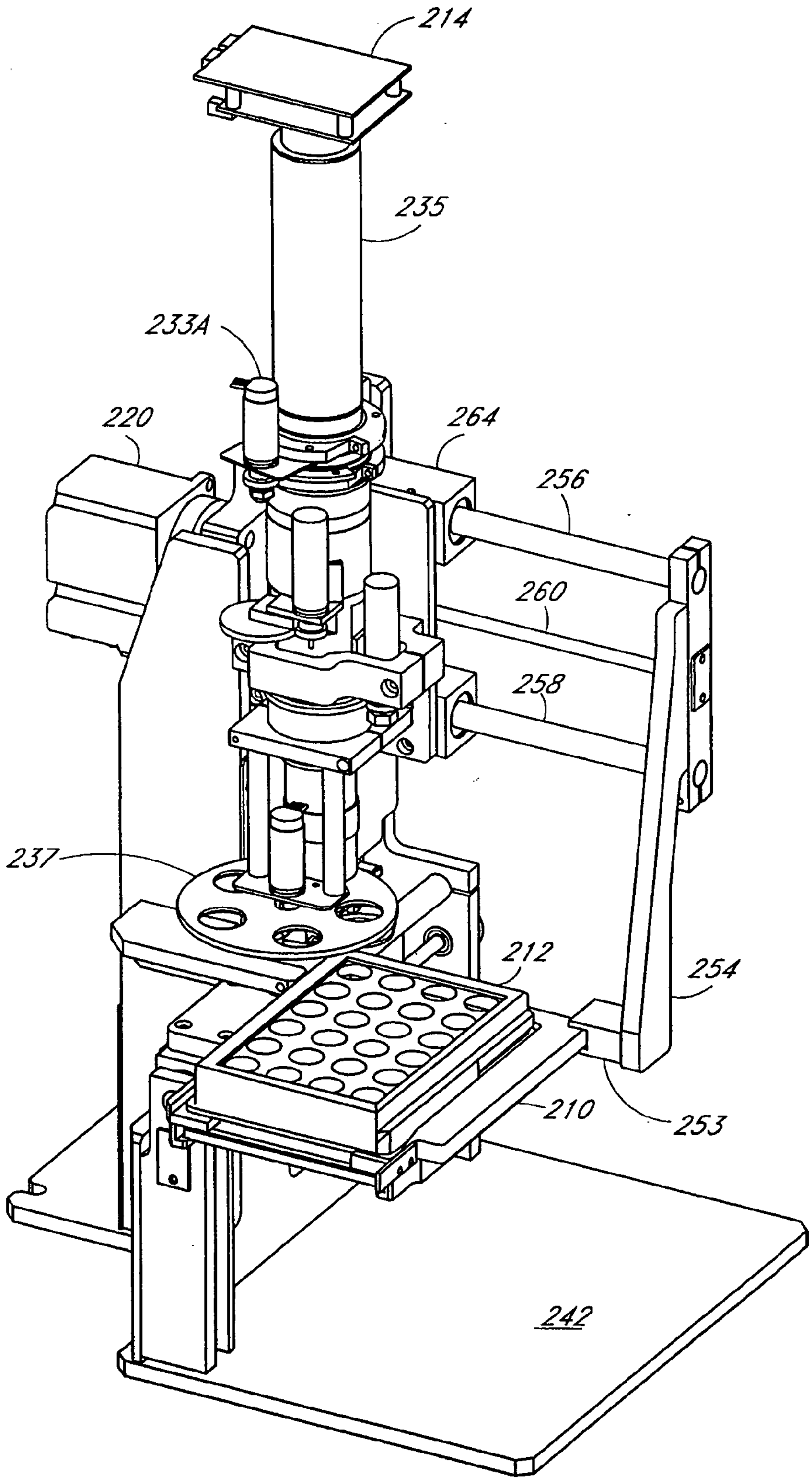
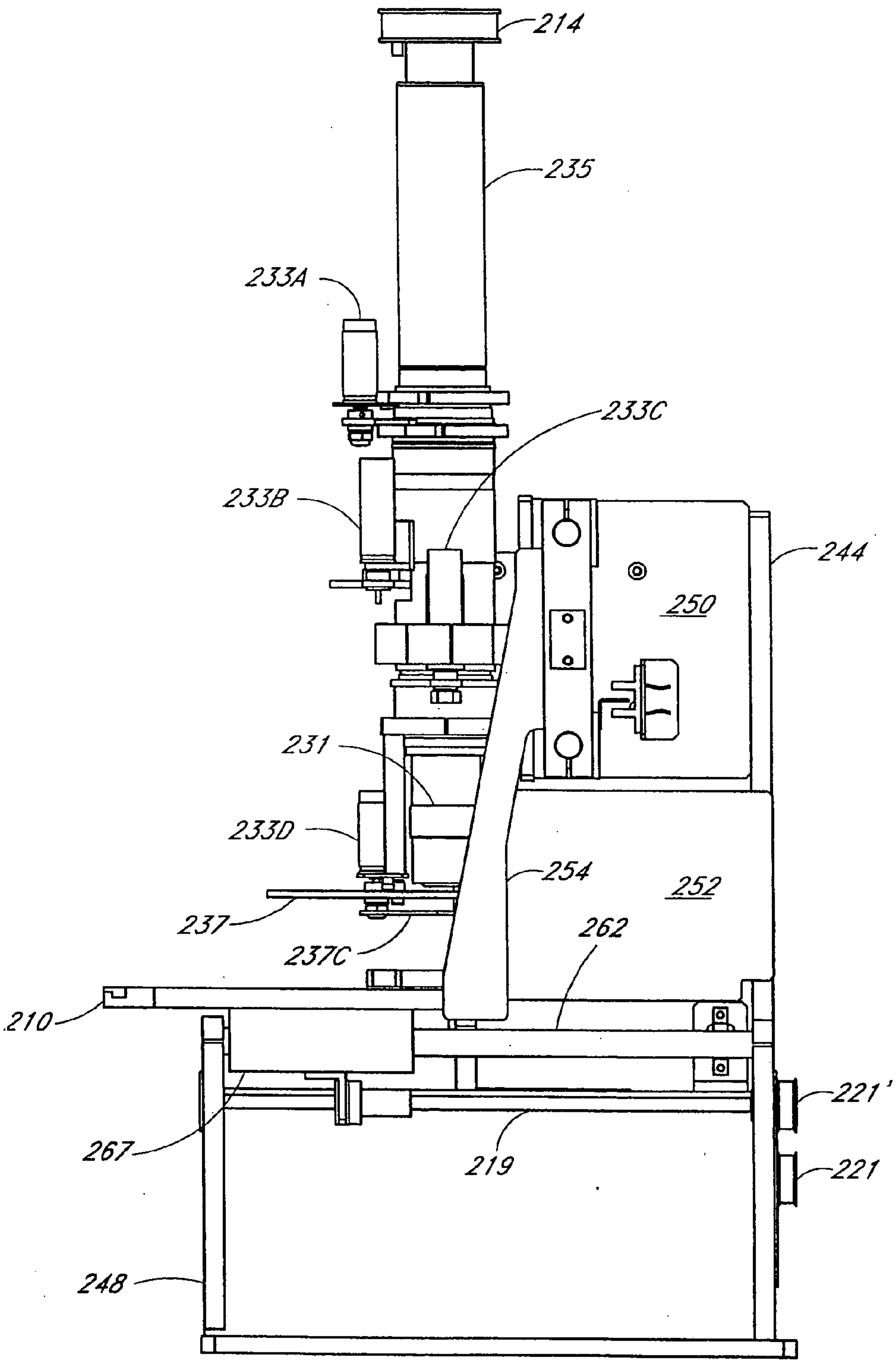


FIG. 9



214
235
233A
233C
233B
244
250
231
233D
254
252
237
237C
262
210
221'
267
219
221
248

FIG. 10

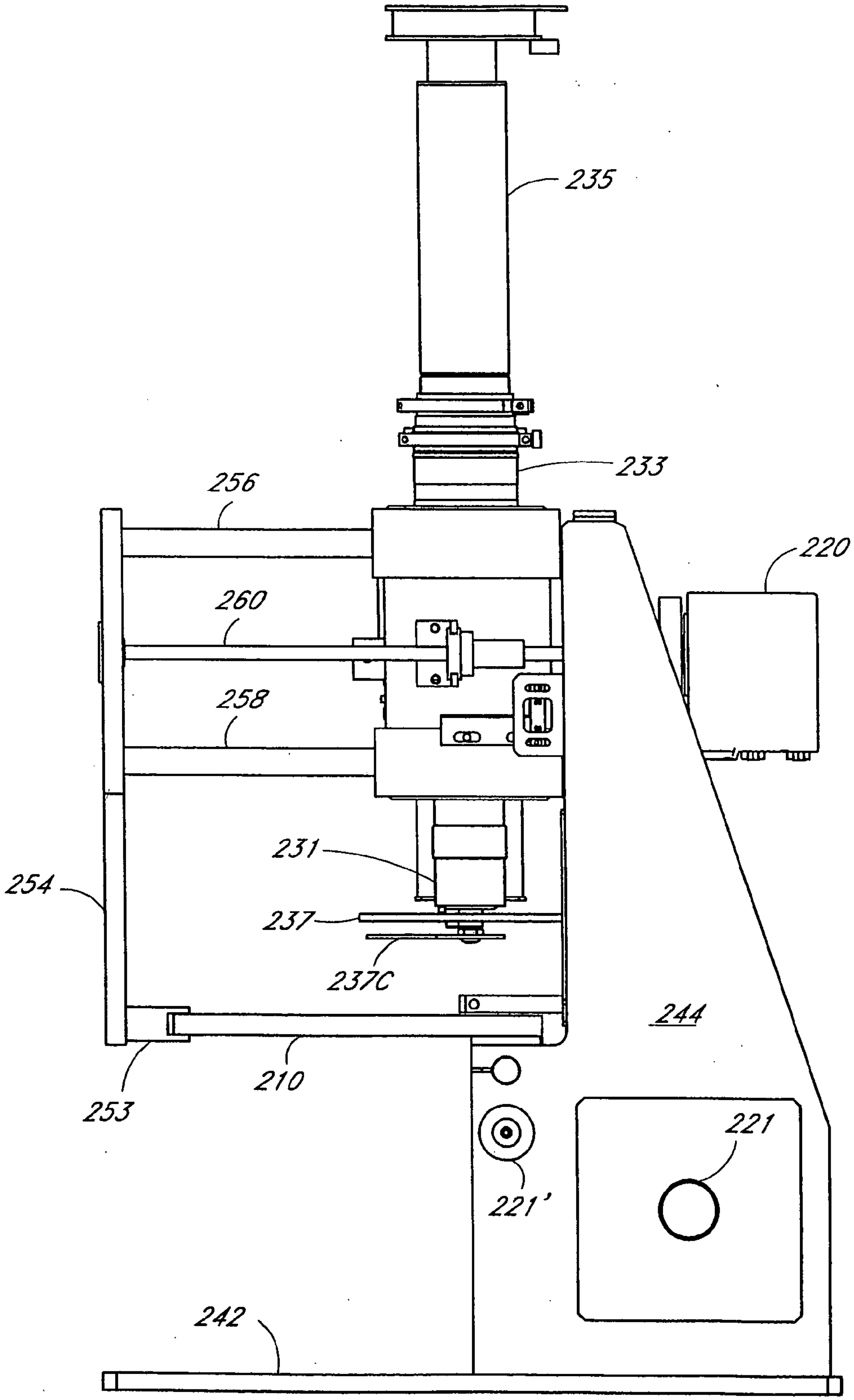


FIG. 11

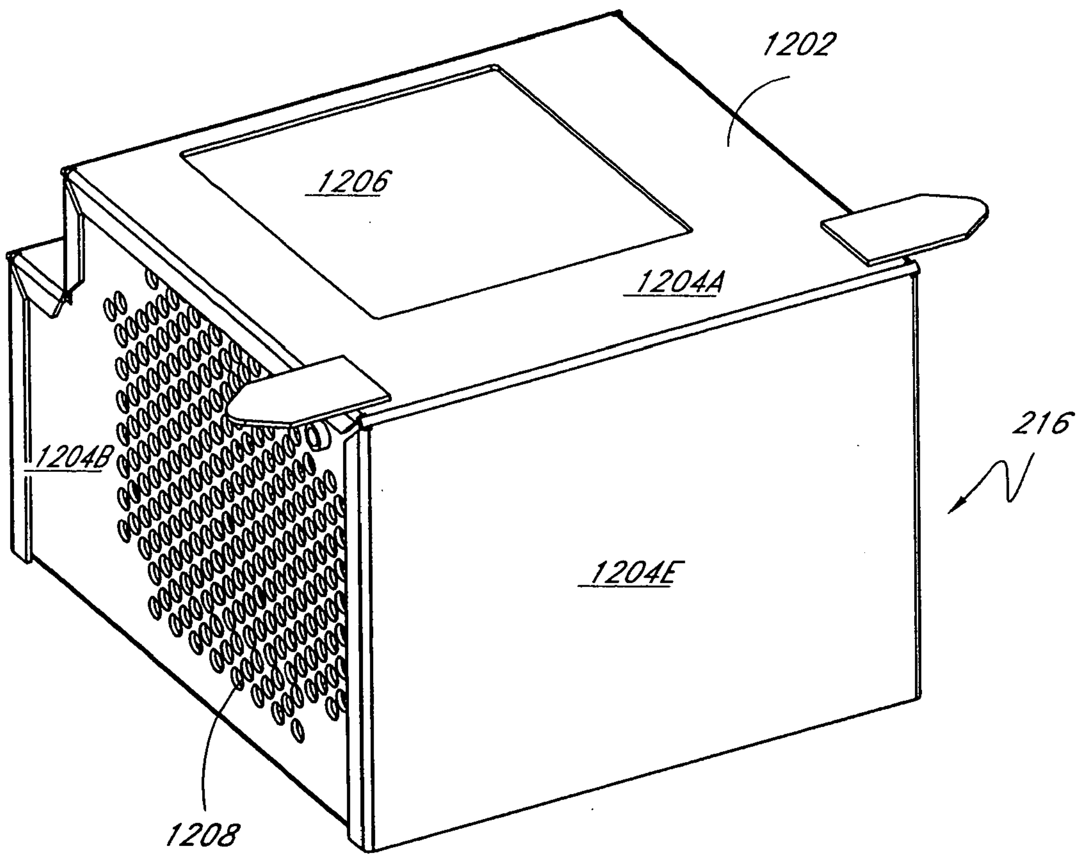


FIG. 12

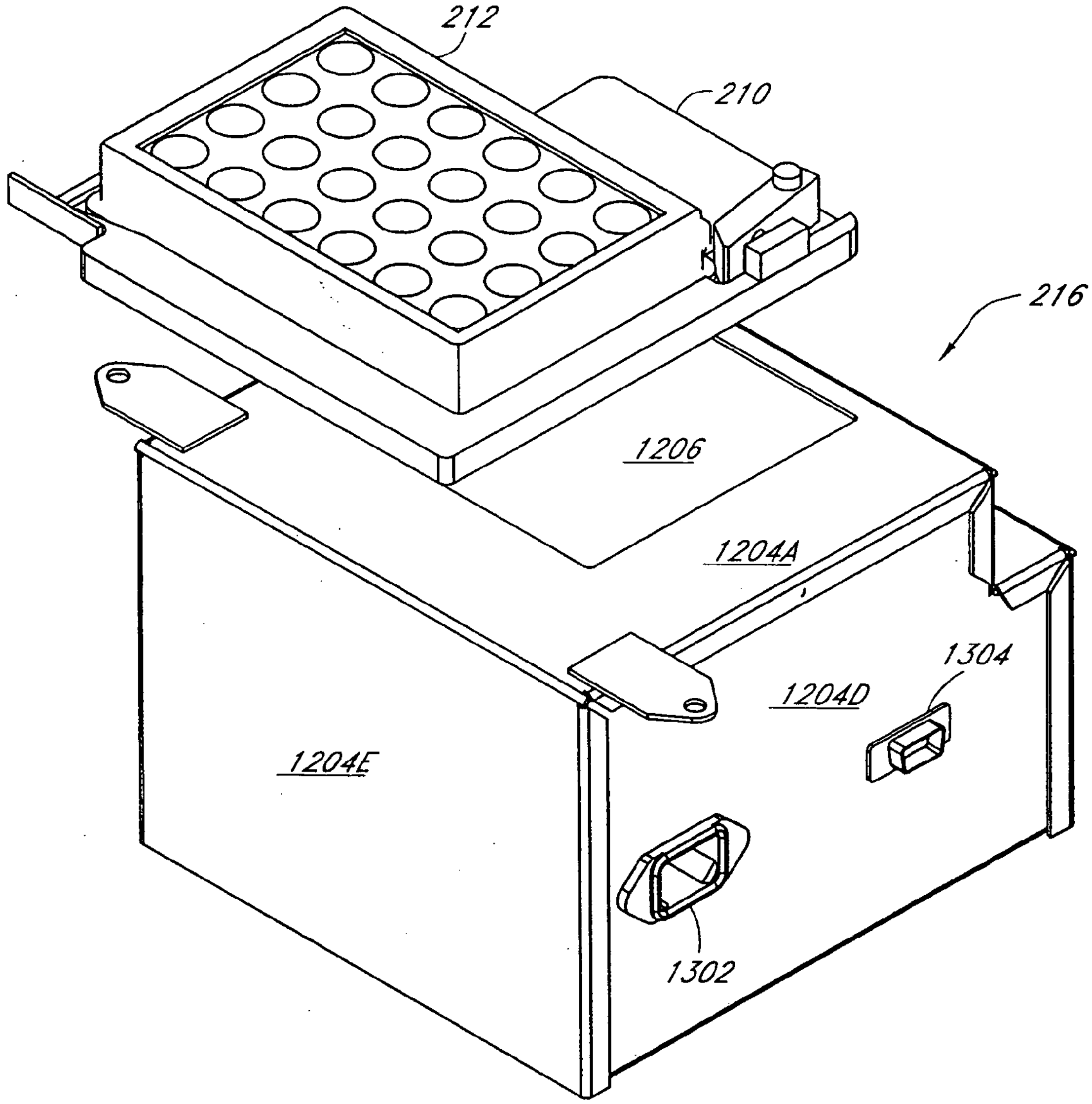


FIG. 13

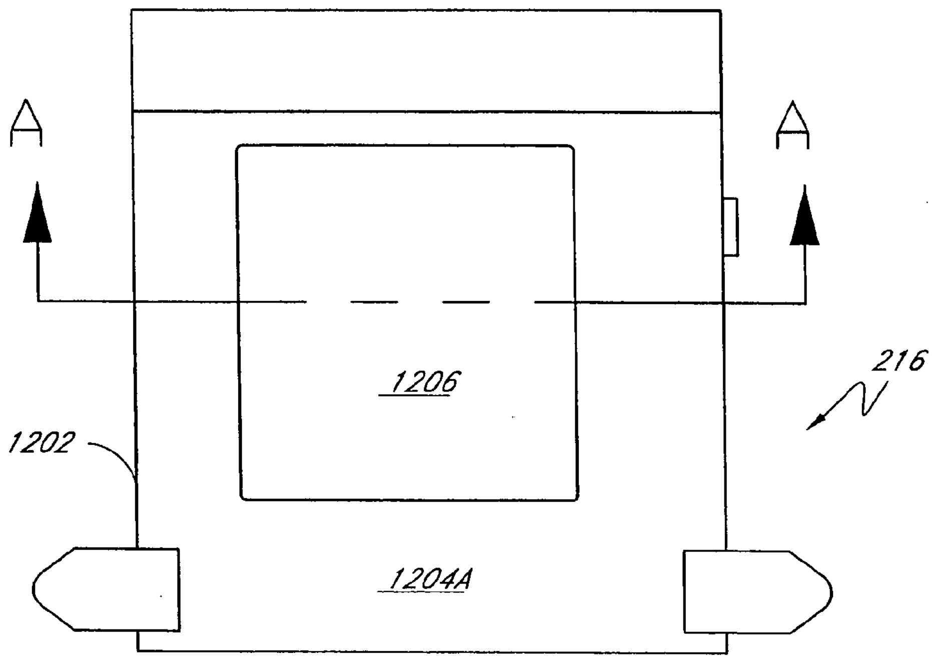


FIG. 14A

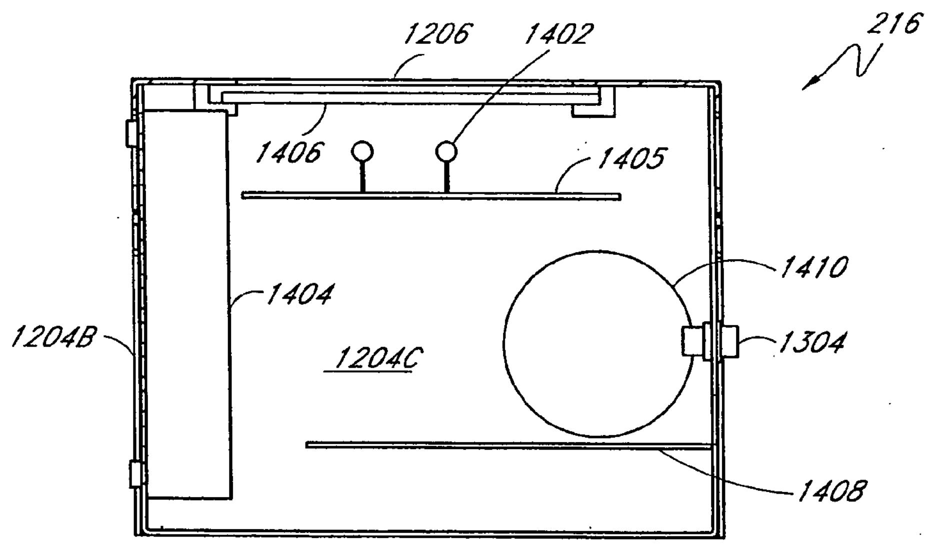


FIG. 14B

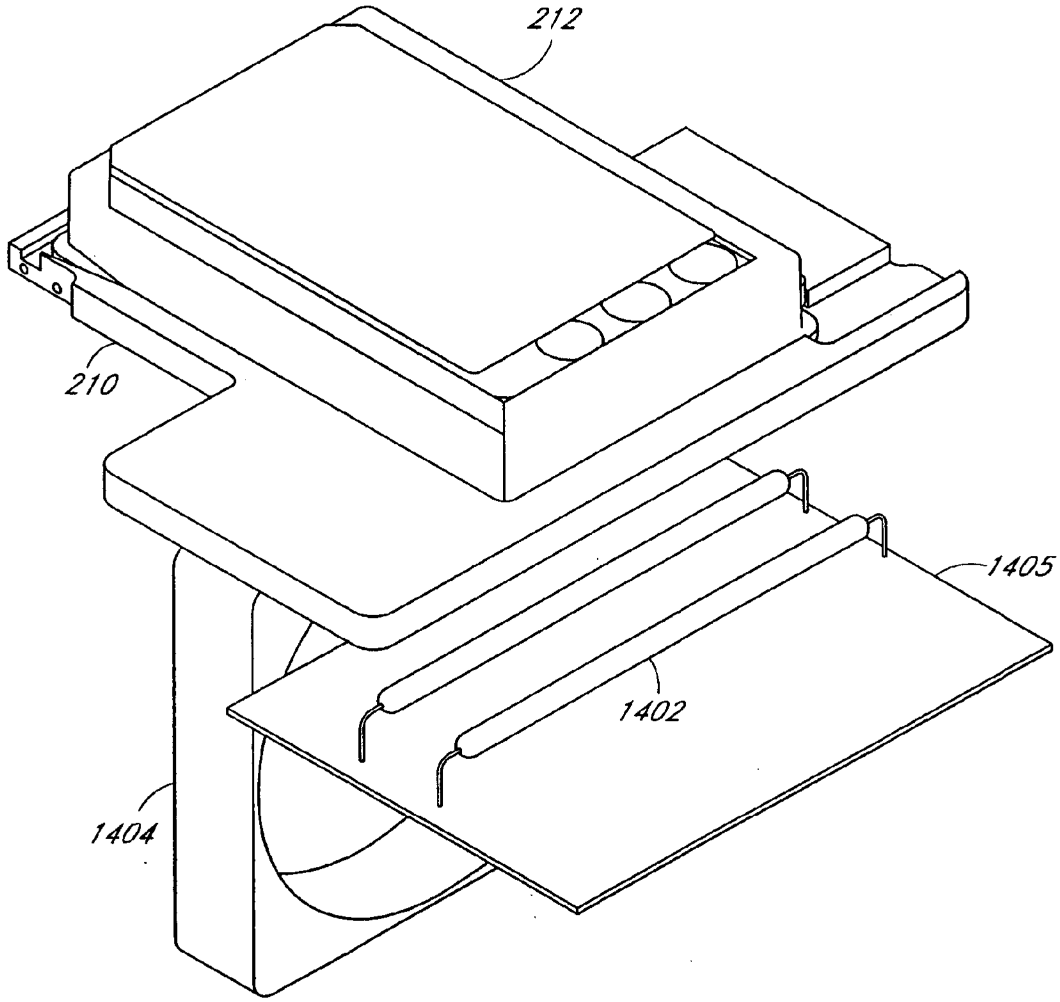


FIG. 15

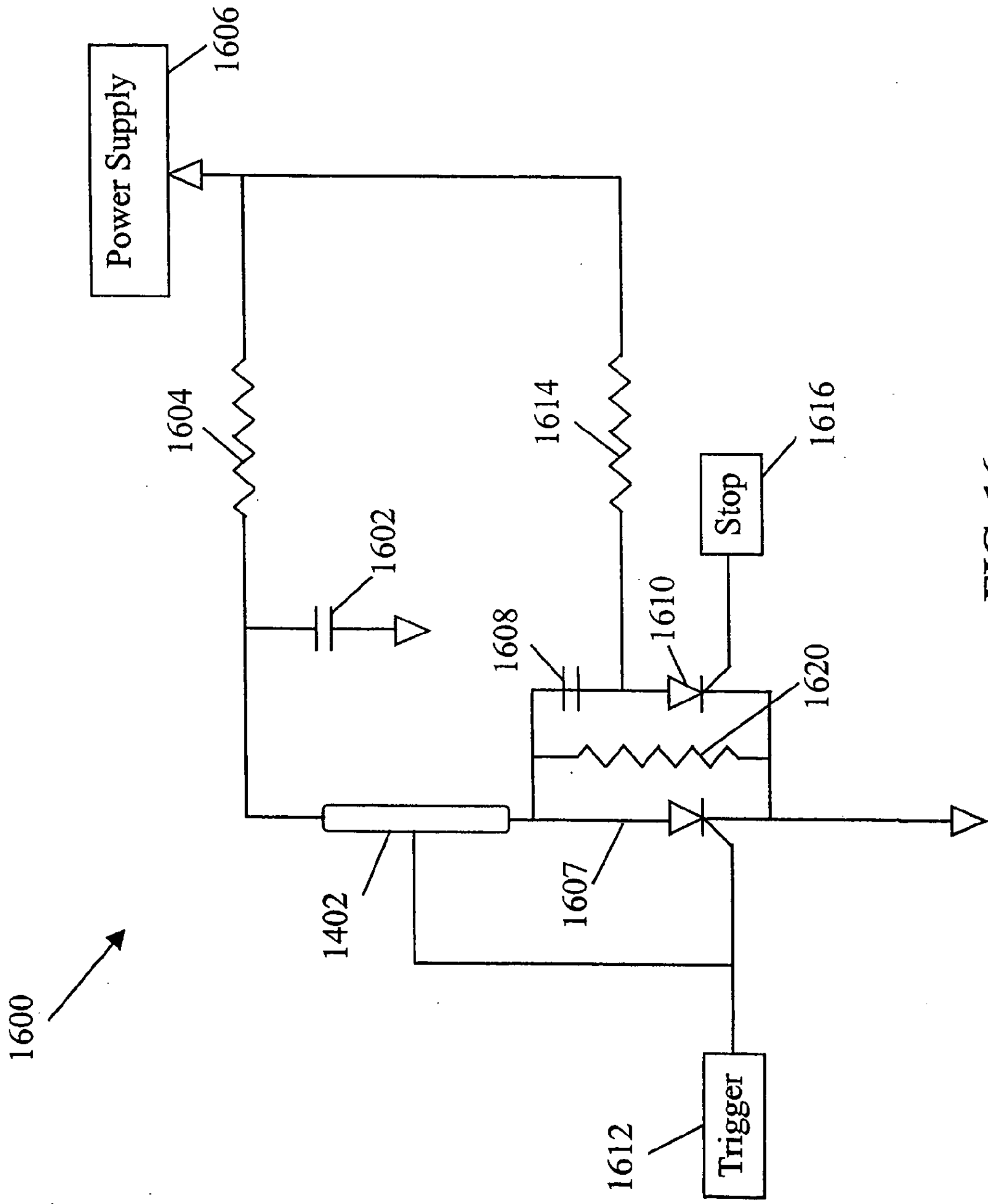

Power Supply
1606
1604
1614
Stop
1616
1602
1608
1610
1620
1402
1607
1600
Trigger
1612

FIG. 16

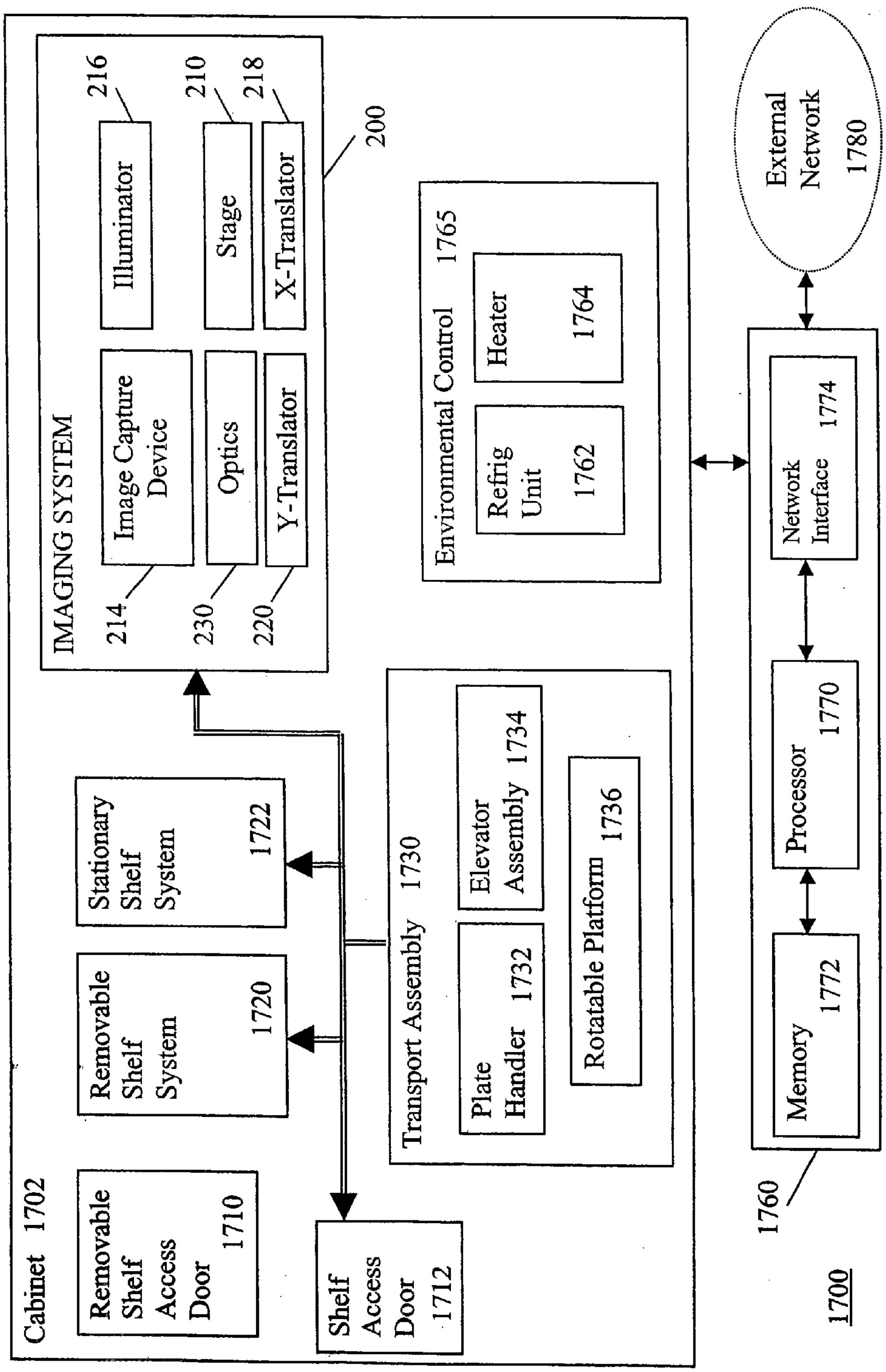

Cabinet 1702
Removable Shelf Access Door 1710
Shelf Access Door 1712
Removable Shelf System 1720
Stationary Shelf System 1722
IMAGING SYSTEM
Image Capture Device
214
Optics
230
Y-Translator
220
Illuminator
216
Stage
210
X-Translator
218
200
Transport Assembly 1730
Plate Handler 1732
Elevator Assembly 1734
Rotatable Platform 1736
Environmental Control 1765
Refrig Unit 1762
Heater 1764
Memory 1772
Processor 1770
Network Interface 1774
1760
External Network 1780
1700

FIG. 17

AUTOMATED IMAGING SYSTEM AND METHOD

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 60/444519, titled "AUTOMATED SAMPLE ANALYSIS SYSTEM AND METHOD," filed on Jan. 31, 2003, having attorney Docket Number DPINTL.012PR, Provisional Patent Application No. 60/444585, titled "REMOTE CONTROL OF AUTOMATED LABS," filed on Jan. 31, 2003, having attorney Docket Number DPINTL.014PR, U.S. Provisional Patent Application No. 60/444586, titled "AUTOMATED IMAGING SYSTEM AND METHOD," filed on Jan. 31, 2003, having attorney Docket Number DPINTL.013PR and Provisional Patent Application No. 60/474989, titled "IMAGE ANALYSIS SYSTEM AND METHOD," filed on May 30, 2003, having attorney Docket Number DPINTL.015PR, each of which is hereby incorporated by reference for all purposes.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The invention is generally related to devices and methods for capturing and analyzing images of objects in a field of view. More particularly, the invention is directed to an imaging system and related methods for automating the detection and analysis of substances in samples using imaging techniques.

[0004] 2. Description of the Related Technology

[0005] X-ray crystallography is used to determine the three-dimensional structure of macromolecules, e.g., proteins, nucleic acids, etc. This technique requires the growth of crystals of the target macromolecule. Typically, crystal growth of macromolecules is dependent on several environmental conditions, e.g., temperature, pH, salt, and ionic strength. Hence, growing crystals of macromolecules requires identifying the specific environmental conditions that will promote crystallization for any given macromolecule. Moreover, it is insufficient to find conditions that result in any type of crystal growth; rather, the objective is to determine those conditions that yield well-diffracting crystals, i.e., crystal configurations that provide the resolution desired to make the data useful. This may require performance of hundreds of screening experiments, varying the different conditions, for each macromolecule. In the screening experiments, samples under investigation are periodically evaluated to determine if suitable crystallization of the sample has taken place.

[0006] Heretofore, the conventional systems and methods for performing these tasks have been mostly manual, or at best involved only limited automation of some subsystems. In some systems, monitoring of samples involves an operator performing visual inspection of the samples under a microscope. In other systems, monitoring of the samples is accomplished by photographing samples stored in microtiter plates. The images of the samples are captured using a camera in cooperation with a microscope and a light source.

[0007] Because crystallization is highly sensitive to temperature conditions, it is very important to provide lighting without adding energy to the sample. Known systems use incandescent or fluorescent light sources that remain on for the entire imaging process. To avoid heating the sample, these systems use heat absorbing filters. However, this approach nonetheless often results in the exposure of the sample to excessive heat, as well as in the reduction of illumination to the sample. Light emitting diodes are sometimes used to limit the amount of heat transferred to the sample, but the diodes provide light only at a single wavelength and in insufficient quantity. In these situations, expensive camera systems are often used to compensate for the diminished spectrum and quantity of light. Since a large depth of field is preferable in photographing the samples, it is sometimes necessary to use a small aperture in the lens. However, this requires compensation by providing additional light, which means further undesired heating of the sample.

[0008] Consequently, there is a need in the industry for devices and methods that enhance the automation of monitoring the crystallization of substances for use in crystallographic analysis.

SUMMARY OF THE INVENTION

[0009] The inventive systems and methods disclosed here have several aspects, no single one of which is solely responsible for the desirable attributes of the systems and methods. Without limiting the scope of the invention as expressed by the claims which follow, its more prominent features will now be discussed briefly.

[0010] In general terms, the invention concerns an imaging system and related methods for automating the task of monitoring crystallization of samples for use in crystallographic analysis. The imaging system receives sample plates at a plate mount. The system moves the plate into position so that a camera can take a picture of the sample through a microscope positioned over the sample. A light source provides illumination of the sample. Control circuitry and logic of the imaging system allows automatic monitoring of each well in a sample plate. The imaging system stores and analyzes the images captured by the camera to produce the best possible image of the sample. An operator, or a software module, may then analyze the images to characterize the crystal growth in the sample in any given well of the sample plate.

[0011] In one embodiment, an automated sample analysis system for incubating and analyzing multiple samples for, e.g., protein crystallization, includes an imaging system. A temperature controlled cabinet houses sample storage, transport, and imaging systems. The system is automated and can be controlled by software, preferably running on a processor external to the cabinet that can be reconfigured remotely. The system can include an array of storage shelves having multiple shelf columns arranged around a core. Each shelf can store a multi-well plate. The core houses a sample transport system that includes a multi-axis robot that rotates about a vertical axis to access the shelves in the shelf array. The transport system retrieves and replaces the multi-well plates in the shelves and can move plates from the shelves to the imaging system where each sample can be automatically imaged.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The above and other aspects, features, and advantages of the invention will be better understood by referring to the following detailed description, which should be read in conjunction with the accompanying drawings, in which:

[0013] **FIG. 1A** is a high-level block diagram of an imaging system according to the invention.

[0014] **FIG. 1B** is high-level block diagram of another imaging system according to the invention.

[0015] **FIG. 2** is a perspective view of an imaging system according to the invention.

[0016] **FIG. 3** is a perspective view of the imaging system shown in **FIG. 2**, viewed from a different angle.

[0017] **FIG. 4** is a perspective view of the imaging system shown in **FIG. 2**, viewed from yet a different angle.

[0018] **FIG. 5** is a plan front view of the imaging system shown in **FIG. 2**.

[0019] **FIG. 6** is a plan, right side view of the imaging system shown in **FIG. 2**.

[0020] **FIGS. 7A and 7B** are perspective views from different angles of a lens system as can be used with the imaging system shown in **FIG. 2**.

[0021] **FIG. 8** is a perspective view from below of a photo-filter carriage that can be used with the imaging system shown in **FIG. 2**.

[0022] **FIG. 9** is a perspective view of certain components as assembled in the imaging system shown in **FIG. 2**.

[0023] **FIG. 10** is a plan front view of certain components as assembled in the imaging system shown in **FIG. 2**.

[0024] **FIG. 11** is a plan, right side view of the components shown in **FIG. 10**.

[0025] **FIG. 12** is a perspective view of a light source as can be used with the imaging system shown in **FIG. 2**.

[0026] **FIG. 13** is a perspective view of a sample mount with the light source shown in **FIG. 12**, viewed from a different angle.

[0027] **FIG. 14A** is a plant top view of the light source shown in **FIG. 12**.

[0028] **FIG. 14B** is a cross-sectional view along the plane A-A of the light source shown in **FIG. 14A**.

[0029] **FIG. 15** is a exploded, perspective view of certain components of the sample mount and the light source shown in **FIG. 13**.

[0030] **FIG. 16** is a functional block diagram of an illumination duration control circuit as can be used with the light source shown in **FIG. 12**.

[0031] **FIG. 17** is a functional block diagram of an automated sample analysis system in which the imaging system according to the invention can be used.

DETAILED DESCRIPTION Of CERTAIN INVENTIVE EMBODIMENTS

[0032] Embodiments of the invention will now be described with reference to the accompanying figures, wherein like numerals refer to like elements throughout. The terminology used in the description presented herein is not intended to be interpreted in any limited or restrictive manner, simply because it is being utilized in conjunction with a detailed description of certain specific embodiments of the invention. Furthermore, embodiments of the invention may include several novel features, no single one of which is solely responsible for its desirable attributes or which is essential to practicing the inventions herein described.

[0033] The imaging system disclosed here is an automated assembly that positions a sample plate and obtains images of samples stored in the wells of the plate. In some embodiments, the imaging system stores the images in a digital storage device for further analysis.

[0034] **FIG. 1A** is a high-level block diagram of an imaging system **100**. In this embodiment, the imaging system **100** has an assembly **105** that is controlled by controllers and logic **110**. The assembly **105** includes a stage **115** that holds and transports target samples to be imaged by an image capture device **120**. The imaging system **100** employs an optics assembly **125** to enhance the view of the target samples before the image capture device **120** obtains the images of the samples. An illuminator **130** is configured as part of the assembly **105** to direct light at the samples held in the stage **115**.

[0035] The assembly **105** also includes a translator **135** that provides the structural support members and actuators to move any one combination of the stage **115**, image capture device **120**, optics **125**, or illuminator **130**. The translator **135** may be configured to move the combination of components in one, two, or three dimensions. As will be discussed in detail below, in some embodiments the stage **115** remains stationary while the translator **135** moves the image capture device **120** and optics **125** to a desired well position in a sample plate held by the stage **115**. In other embodiments of the imaging system **100**, the translator **135** moves the stage **115** in a first axis and the image capture device **120** and optics **125** in a second axis which is substantially perpendicular to the first axis.

[0036] The controllers and logic **110** of the imaging system **100** provide instructions to and coordinate the activities of the components of the assembly **105**. The controllers may include a microprocessor, controller, microcontroller, or any other computing device. The logic includes the instructions to cause the controller to perform the tasks or processing described here.

[0037] **FIG. 1B** is high-level block diagram of an imaging system **150**. The imaging system **150** includes an assembly **155** in communication with controllers and logic **160**. The assembly **155** may also be in communication with a data storage device **190**, which itself may be configured for communication with the controllers and logic **160**. The controllers and logic **160** control and coordinate the activities of the components of the assembly **155**.

[0038] In this embodiment, the assembly **155** includes a sample plate mount **165** suitably configured to receive micro-titer plates of various configurations and sizes. Alternatively, the sample plate mount **165** can be configured to receive any sample matrix that carries samples, regardless of whether the samples are stored in individuals sample wells, rest on the surface of the sample matrix (e.g., as droplets), or are embedded in the sample matrix. A source of flash lighting **180** is arranged to direct light bursts to the samples stored in the micro-titer plate carried by the sample plate mount **165**. An inventive system and method of providing the flash lighting **180** will be discussed with reference to **FIG. 16**.

[0039] The assembly **155** includes a compound lens **175** that cooperates with a digital camera **170** to acquire images of the samples in the sample plate. The compound lens **175** may consist, for example, of an objective lens, a zoom lens, and additional optics chosen to provide the digital camera **170** with the desired image from the light from the samples. In one embodiment, as will be discussed further below, the compound lens **175** may be motorized (i.e., provided with one or more actuators) so that the controllers and logic **160** can automatically focus the scene, zoom on the scene, and set the aperture.

[0040] In this embodiment, the assembly **155** includes an x-y translator that moves either the sample plate mount **165** or the compound lens **175**, or both. Of course, if the digital camera **170** is coupled to the compound lens **175**, the x-y translator moves both the digital camera **170** and the compound lens **175**. In some embodiments, the x-y translator **185** is configured to move the sample plate mount **165** in two axis, e.g., x and y coordinates. Alternatively, the x-y translator **185** moves the compound lens **175** in two axis, while the sample plate mount **165** remains stationary. In yet another embodiment, the x-y translator consists of multiple and separate actuators that move independently from one another the sample mount **165** or the compound lens **175**.

[0041] It should be noted that the assembly **155**, the controllers and logic **160**, and the data storage **190** are depicted as separate components for schematic purposes only. That is, in some embodiments of the imaging system **150** it is advantageous to, for example, integrate the data storage device **190** into the assembly **155** and to include the controllers and logic **160** as part of one or more of the components shown as being part of the assembly **155**. Similarly, the sample mount **165**, digital camera **170**, compound lens **175**, flash lighting **180**, and x-y translator **185** need not all be configured as part of a single assembly **155** as shown.

[0042] Exemplary ways of using and constructing embodiments of the imaging system **100** or **150** will be described in detail below with reference to **FIGS. 2-16**, which depict a specific embodiment of the imaging system. Of course, since there are multiple ways to implement the imaging system, the following description of the specific embodiment should not be taken to limit the full scope of the inventive imaging system.

[0043] Illustrative Embodiment

[0044] With reference to **FIGS. 2-6** and **9-11**, perspective and plan views of an imaging system **200** according to the invention are illustrated. The imaging system **200** includes a sample plate mount **210** that receives a sample plate **212**. An x-translator having an actuator **218** (see **FIG. 4**) is coupled to the sample plate mount **210** to move the sample plate mount **210** into position above a light source **216** and below a lens assembly **230**. A digital camera **214** is coupled to the lens assembly **230** to capture images of the wells in the sample plate **212**. A y-translator having an actuator **220** (see **FIG. 3**) is coupled to the lens assembly **230** to move the lens assembly **230** into position over a desired well of the sample plate **212**.

[0045] Support Platform

[0046] The digital camera **214**, lens assembly **230**, sample plate mount **210**, light source **216**, x-translator **218**, and y-translator **220** are mounted on a platform **240** (see **FIG. 2**). The platform **240** generally consists of several structural members, brackets, or walls, e.g., base **242**, side wall **244**, front wall **250**, bracket **252**, bracket **246**, post **248**, and support member **254**. The light source **216** can be fastened to the base **242**. Rails **256** and **258**, which support the lens assembly **230** are fastened to the wall **250** of the platform **240** and to the support member **254**. The sample plate mount **210** is supported by a rail **262** and an outport guide **253** of the support member **254**. The rail **262** is supported through attachment to the side wall **244** and the post **248**. Of course, there are multiple, equivalent alternatives to providing support for and configuring the lens assembly **230**, sample plate mount **210**, light source **216**, and x-, y-translators **218** and **220** on the platform **240**.

[0047] The platform **240** may be constructed of any of several suitable materials, including but not limited to, aluminum, steel, or plastics. Because in some applications it is critical to keep vibration of the platform **240** to a minimum, materials that provide rigidity to the platform **240** are preferred in such applications. With regard to the rails **256**, **258**, and **262**, these are preferably manufactured with very smooth surfaces to carry the lens assembly **230** or the sample plate mount **210** in a smooth fashion, thereby avoiding vibrations. As illustrated in **FIGS. 3 and 9**, supporting the lens assembly **230** may be done by coupling the linear plain bearings **264** and **266** to the rails **256** and **258**. A similar coupling using a "bushing"**267** (see **FIG. 10**) may be employed to fasten the sample plate mount **210** to the rail **262**. Bearings **264**, **266**, and **267** are chosen to provide smooth bearing surfaces for smooth translation of the load, e.g., the lens assembly **230** or the sample plate mount **210**.

[0048] Sample Plate Mount

[0049] The sample plate mount **210** may be constructed from any rigid material, e.g., steel, aluminum, or plastics. Preferably the sample plate mount **210** is configured to accommodate, either directly or through the use of adapters, various standard sizes of micro-titer plates. Micro-titer plates that maybe used with the sample plate mount **210** include, but are not limited to, crystallography plates manufactured by Linbro, Douglas, Greiner, and Corning. As will be described further below, the sample plate mount **210** is coupled to an actuator **218** for moving the sample plate mount **210** in one axis.

[0050] Translators

[0051] The imaging system **200** includes two independent translators. Typically, the sample plate mount **210** and the lens assembly **230** move on a plane that is substantially parallel to a plane defined by the sample plate **212** carried by the sample plate mount **210**. In one embodiment, the controllers and logic **110** or **160** can control x-, y-translators to position the sample plate mount **210** and the lens assembly **230** at the coordinates of a specific well of the sample plate **212**.

[0052] An x-axis translator for moving the sample plate mount **210** consists of an actuator **218** (see **FIG. 4**) that rotates a threaded rod **219** (or "lead screw") about its axis in clockwise or counter-clockwise directions. In the embodiment shown in **FIGS. 3, 4**, and **10**, the actuator **218** is coupled to the rod **219** via a belt (not shown) and pulleys **221** and **221'**. The sample plate **210** mount is fastened to a "bushing"**267** (see **FIG. 10**) that rides on the rail **262**. The sample plate mount **210** is also supported by the outport guide **253** (see **FIGS. 6 and 11**) of the support member **254**. The "bushing"**267** is additionally coupled in a known manner to the rod **219**. When the actuator **218** turns in one direction, its power is transmitted via the belt and pulleys **221** and **221'** to the rod **219**, which then moves the "bushing"**267** and, thereby, moves the sample plate mount **210** in a linear direction.

[0053] A y-axis translator for moving the lens assembly **230** consists of an actuator **220** (see **FIG. 3**) that rotates a threaded rod **260** about its axis in clockwise or counter-clockwise directions. In the embodiment shown in **FIGS. 3, 6**, and **9**, for example, the actuator **220** is coupled to the rod **260** through a slotted disc coupling (not shown). The lens assembly **230** is coupled to bearings **264** and **266** that respectively ride on rails **256** and **258**. The bearings **264** and **266** are coupled to the rod **260** through plate **255** and the bracket **257** (see **FIG. 6**) in a known manner. When the actuator **220** turns in one direction, its power is transmitted via the slotted disc coupling to the rod **260**, which then moves the bearings **264** and **266** and, thereby, moves the lens assembly in a linear direction.

[0054] The actuators **218** and **220** may be direct current gear motors or 3-phase servo motors, for example. Of course, the type of motors employed as the actuators **218** or **220** will depend on, among other things, the weight of the sample plate mount **210** plus sample plate **212** or the lens assembly **230** and the digital camera **214**. Another factor in determining the type of motor is the desired speed. In one embodiment, actuators **218** and **220** having a positioning precision of **10**-microns are used. Suitable motors may be obtained from PITMANN of Harleysville, Pa.

[0055] In the embodiment of the x-, y-translators described above, each translator mechanism independently translates along an axis of motion each of the sample plate mount **210** and the lens assembly **230**. However, it should be noted that in other embodiments of the imaging system **200**, it may be desirable to maintain the lens assembly stationary and only move the sample plate mount **210**, which would then have one or more translators to position the sample plate mount **210** anywhere in an x-y coordinate area. Similarly, the imaging system **200** may be configured so that an x-y translator (or set of x-, y-translators) moves the lens assembly in the x-y coordinate area, while the sample plate mount **210** remains stationary over the light source **216**. In one embodiment, the x-, y-translators employ optical sensors **285** and **287** (see **FIG. 5**) as to sense the start or end positions ("home positions") of the lens assembly **230** or the sample plate mount **210**.

[0056] In yet another embodiment, the imaging system **200** may also include a z-axis translator (not shown) to lift or lower the sample plate mount **210**, lens assembly **230**, or light source **216**. The z-axis translator may consist of, for example, an actuator, a lead screw, one or more rails, and appropriate bearings and fasteners.

[0057] The actuators **218** and **220** may be governed by a controller (not shown). Suitable controllers may be obtained from J R Kerr Automation Engineering of Flagstaff, Ariz. The controller may be configured to interpret high level commands from a computing device. In one embodiment, when a specific axis is addressed, the controller causes the actuator **220**, for example, to move and keeps count of the travel distance and final location. The controller can be programmed to move the actuator **220** at varying speed, torque, and acceleration.

[0058] Image Capture Device

[0059] In some embodiments of the imaging system **200**, the image capture device can be a film camera, a digital camera, a CMOS camera, a charge coupled device (CCD), and the like, or some other apparatus for capturing an image of an object. The embodiments of the imaging system **200** described here employ a digital camera **214**. A suitable digital camera **214** is, for example, a CMOS digital camera. However, it should be apparent that several digital photography devices could also be employed. The CMOS camera **214** is preferred because it provides random access to the image data and is relatively low cost. In conventional imaging systems for crystallography, a CMOS camera is typically not used because in those systems the level of light is insufficient for this type of camera. In contrast, the imaging system **200** is configured to provide the level of light necessary to allow use of a CMOS camera.

[0060] The digital camera **214** can be a CMOS camera having a pixel resolution of 1280×1024 pixels, Bayer color filter, a pixel size of 7.5×7.5 microns, and a data interface governed by the IEEE 1394 standard (commonly known as "Firewire"). The digital camera **124** may be fully digital and not require a frame grabber. The digital camera **124** may also have a centered pixel area, e.g. a 1024×1024 or 800×600 pixel subset of the array, which enhances the image quality since the edges of the array where optical distortions increase are avoided. In one embodiment, the digital camera **214** is connected separately to a host computer (not shown) via a Firewire data interface. This allows for rapid transfer of large amounts of image data, e.g., five images per second.

[0061] Lens Assembly

[0062] One embodiment of the lens assembly **230** includes an objective lens **231**, a zoom lens **233**, and an adapter **235**. These optical components are chosen to provide suitable field of view, magnification, and image quality. The objective lens **231**, zoom lens **233**, and adapter **235** may be purchased from, for example, Navitar Inc. of Rochester, N.Y.

[0063] In one embodiment, the zoom lens **233** may be the "12X UltraZoom" zoom lens manufactured by Navitar. The zoom lens **233** may provide a 12:1 zoom factor, a focus range of about 12-mm, and an aperture of about 0.14. The zoom lens **233** preferably includes adapters for mounting the objective lens **231**. The zoom lens **233** may have actuators **233A**, **233B**, and **233C** for providing, respectively, automatic aperture adjustment, autozoom, and autofocus functionality. In one embodiment, actuators **233B** and **233C** have gear reductions of 262:1. Of course, the gear reduction ratio is chosen to suit the particular application. For example, a 5752:1 gear ratio for the focus actuator **233C** may be too slow for some applications of the imaging system **200**. The actuators **233A**, **233B**, and **233C** may be obtained from Navitar or from MicroMo Electronics, Inc. of Clearwater, Fla.

[0064] The objective lens **231** may be, for example, a 5X Mitutoyo Infinity Corrected Long Working Distance Microscope Objective (model M Plan Apo 5) microscope accessory. The objective lens **231** is coupled to the zoom lens **233**. Since the light source **216** delivers sufficient light to the sample plate **212**, the lens assembly **230** is configured to allow for setting a small aperture in order to increase the depth of field. The objective lens **231** preferably provides a working distance that allows adequate room beneath the lens assembly **230** to manipulate a sample plate **212** and provide a photo-filter carriage **237** in the image path. In one embodiment, the working distance of the objective lens **231** is about 34-mm.

[0065] The adapter **235** serves to allow use of the digital camera **214**. The adapter **235** may be, for example, a 1X Adapter model number 1-6015 sold by Navitar. Of course, different combinations of objective lenses **231** and adapters **235** may be used, e.g., a 2X Adapter and 2X Objective combination. The combination of 1X Adapter and 5X Objective provides a suitable image for most applications of the imaging system **200**. In some embodiments, it is desirable to use a 0.67X Adapter **235** with a 10X Objective **231**, for example, to provide a higher image resolution.

[0066] The optical components of the lens assembly **230** can be provided with actuators for remote and automatic control. To allow software control of the optical components, controllers and control logic (not shown) can control the actuators **233**A, **233**B, **233**C, and **233**D. The actuators (e.g., dc motors) may be coupled to the aperture of the, magnification and focus of the zoom lens **233**, as well as the photo-filter carriage **237**. In some embodiments, the actuators **233**A, **233**B, **233**C, and **233**D are preferably provided with encoders to provide position information to the controllers. In one embodiment, the actuators on the lens assembly **230** are 17-mm direct current motors with 100:1 gear reducers. These motors may be obtained from PITMANN® of Harleysville, Pa.

[0067] The lens assembly **230** may also include a photo-filter carriage **237** that is configured to hold optical filters (not shown). For example, the photo-filter carriage **237** can hold polarization plates or color light filtering plates. **FIG. 8** illustrates one embodiment of a photo-filter carriage **237** that may be used with the imaging system **200**. The photo-filter carriage **237** includes a filter wheel **237**A for receiving one or more photo-filters (not shown) in openings **237**B. The photo-filters may be held in place in the filter wheel **237**A in a variety of ways. For example, in the embodiment illustrated in **FIG. 8**, caps **237**C in cooperation with suitable fasteners hold the photo-filters in place. The filter wheel **237**A may be coupled to an actuator **233**D for remote and automatic control of the filter wheel **237**A. The actuator **233**D and the filter wheel **237**A may be fastened, in a conventional manner, to a clamp **237**D that is coupled to, for example, the objective lens **231** or the zoom lens **233** (see **FIGS. 1 and 9**). In one embodiment, a polarization filter is coupled to a filter wheel so that the polarization filter covers about **90** degrees of the wheel. In this embodiment, the polarization filter can be rotated so that the applied polarization varies between zero and ninety degrees. Thus, the use of the polarization filter with a polarized light source can provide analysis of the effect of samples on polarized light. For example, when a polarized light source and the polarization filter are cross-polarized then minimal light should get to the objective lens **231**, unless the sample re-orients the polarized light, such as can happen when the light passes through crystals.

[0068] The digital camera **214** in combination with the lens assembly **230** provides a broad depth of field to allow imaging of objects such as protein crystals at varying depths within a sample droplet stored in a sample well of a sample plate **212**. In one embodiment, the lens assembly **230** has a 12:1 zoom lens and, in cooperation with the digital camera **214**, can provide a **1** micron optical resolution. In some embodiments, the lens assembly **230** and the digital camera **214** may be integrated as a single assembly.

[0069] Light Source

[0070] The light source **216** will now be described with reference to **FIGS. 12-15**. **FIG. 12** shows a perspective view of the light source **216**. Since the crystallization of substances is often highly sensitive to temperature changes, the light source **216** is preferably configured to minimize the amount of heat transferred to the sample plate **212**, e.g., by isolating and removing heat generated by the electronics **1408** and illuminators **1402** (see **FIG. 14B**).

[0071] Housing

[0072] With reference to **FIGS. 12, 14B** and **15**, the light source **216** includes a housing **1202** adapted to store one or more illuminators **1402** (see **FIGS. 14B and 15**), cooling elements **1404**, heat reflecting glass **1406**, light diffuser plate **1206**, and corresponding electronics **1405** and **1408**. In one embodiment, the housing **1202** consists of a plurality of walls that serve as structural support for the internal components and that substantially isolate the internal components from the external environment. The housing **1202** can be constructed of a variety of materials including, but not limited to, stainless steel, aluminum, and hard plastics. A material with a low coefficient of heat transfer is preferred so as to substantially keep heat generated within the housing **1202** from reaching the outside through the walls of the housing **1202**. However, depending on the application, use of metals is appropriate when cooling elements **1404** are provided. In some embodiments, one or more of the internal surfaces of the walls of the housing **1202** may be coated with a suitable material that absorbs or reflects various types of radiation and prevents them from reaching the outside of the housing **1202**.

[0073] In the embodiment of the light source **216** shown in **FIGS. 12-14B**, the top wall **1204**A of the housing **1202** has an opening to receive and support a light diffuser plate **1206**. The plate **1206** serves to diffuse light from the illuminators **1402** onto the sample plate **212**. The plate **1206** may be, for example, a sheet of translucent plastic. In one embodiment, inside the housing **1202** and adjacent and below the plate **1206**, a heat reflecting glass ("hot mirror") **1406** (see **FIG. 14B**) is provided. The heat reflecting glass **1406** prevents most infra-red energy from exiting the housing **1202**.

[0074] The wall **1204**B of the housing **1202** may be provided with a plurality of orifices **1208** that allows a cooling element **1404**, such as fan, to draw air into the housing **1202** for cooling the internal components. A wall **1204**C (see **FIG. 14B**) of the housing **1202** can be fitted with an opening **1410** for receiving a duct that guides forced air out of the housing **1202**. A wall **1204**D (see **FIG. 13**) of the housing **1202** can be fitted with a power plug **1208** communications port **1302**. The housing **1202** is preferably adapted to isolate an operator of the imaging system **200** from high voltages that may be used to fire the illuminators **1402**.

[**0075**] Of course, the housing **1202** may be configured in a variety of ways not limited to that detailed above. For example, the ventilation openings **1208** on wall **1204**B may be replaced by one or more fans built into the wall **1204**B or the wall **1204**E. Moreover, depending on the specific location of the light source **216** in any given application of the imaging system **200**, the ventilation openings **1208** may be located on the bottom wall (not shown) of the housing **1202**, for example.

[**0076**] Illuminators

[**0077**] With reference to **FIGS. 14B and 15**, the light source **216** includes one or more illuminators **1402** that generate light rays. The illuminators **1402** may be, for example, incandescent bulbs, light emitting diodes, or fluorescent tubes of various types including, but not limited to, mercury- or neon-based fluorescent tubes. In one embodiment, the illuminators **1402** are two xenon tubes. Xenon tubes are well known in the relevant technology and are readily available. The xenon tubes **1402** can include borosilicate glass that absorbs ultra-violate radiation. Xenon tubes are preferred because they produce sufficient light to allow use of a CMOS camera **214** in the imaging system **200**. Xenon tubes are also preferred since they provide a broad spectrum of light rays, which enables use of color to enhance detection of crystal growth in the wells of the sample plate **212**.

[**0078**] The actual dimensions of the illuminators **1402** are chosen to suit the specific application. For example, in the imaging system **200** the xenon tubes **1402** are long enough to cover one dimension of the sample plate **212** so that it is not necessary to move the light source **216** when the lens assembly **230** or sample plate mount **210** are repositioned. As shown in **FIG. 14B**, the illuminators **1402** may be supported on a board **1405**, which may also support electronics for control of the illuminators **1402**.

[**0079**] Off-axis Lighting

[**0080**] In one embodiment, two illuminators **1402** are positioned to provide both on-axis and off-axis lighting of the wells in the sample plate **212**. As used here, the imaging axis of the lens assembly means the principal axes of the lens assembly. For example, first and second xenon tubes **1402** can be positioned, respectively, a first and second distance from the imaging axis of the lens assembly **230**. Typically, the first and second distances are substantially equal in length, and the first xenon tube is positioned opposite the imaging axis from the second xenon tube.

[**0081**] In one embodiment, the xenon tubes **1402** are mounted about an inch on either side of the area directly under the lens assembly **230**. This configuration allows the use of an indirect lighting effect when only one xenon tube is fired. That is, when two xenon tubes are positioned off the imaging axis, the controllers and logic **110** or **160** can control the tubes to provide on-axis or off-axis illumination of the sample plate **212**. One xenon tube can be fired to provide off-axis illumination of the sample plate **212**. When the two xenon tubes are fired simultaneously a more conventional backlit scene is obtained. In some applications, off-axis illumination is preferred because it produces shadows on small objects in a sample droplet stored in a well of the sample plate **212**. The shadows caused by off-axis lighting enhance the ability of the controllers and logic **110** or **160**, or an operator, to detect objects in the sample.

[**0082**] In one embodiment, for example the imaging system **150** shown in **FIG. 1B**, the controllers and logic **160** control the assembly **155** to capture two images of a droplet in a well plate of the sample plate **212**. The imaging system **150** captures one image with the light source **216** lighting the sample with a first xenon tube. The imaging system **150** captures a second image with the light source **216** lighting the sample with the second xenon tube. The controllers and logic **160** can then combine the data from both images and perform an analysis based on the combined data. This results in enhanced characterization of the sample since the combination of the images typically provides more information about crystallization of the sample than a single image acquired with standard back lighting of the scene.

[**0083**] Filters

[**0084**] In one embodiment, a source filter **270** (**FIG. 2**) may be inserted in a filter slot **272** so that the filter **270** is interposed between the light source **216** and the sample plate **212**. The various filters **270** may be inserted and removed from the filter slot **272** by a plate handler. Thus, the filter **270** may be automatically removed, or exchanged with another filter, by the imaging system **200**. The source filter **270** may be any type of filter, such as a wavelength specific filter (e.g. red, blue, yellow, etc.) or a polarization filter.

[**0085**] Flash Mode

[**0086**] In one embodiment of the imaging system **200**, the light source **216** includes one or more illuminators **1402** (e.g., fluorescent tubes) adapted to provide flash lighting. That is the illuminators **1402** are controlled to illuminate only momentarily the sample plate **212** as the digital camera **214** captures an image of a well in the sample plate **212**. This arrangement provides benefits over known devices in which illuminators remain in the on-position throughout the entire time that the sample plate **212** is handled by an imaging system. In the imaging system **200**, since the illuminators **1402** are turned on for only a fraction of a second per image, very little heat radiation is transferred to the wells of the sample plate **212**. Hence, one benefit of this configuration is that the imaging system **200** can provide high illumination levels for the camera **214** while minimizing energy or radiation transfer to the samples in the sample plate **210**. An exemplary control circuit **1600** that provides controlled flash lighting is described below with reference to **FIG. 16**.

[**0087**] Flash Lighting Circuitry

[**0088**] **FIG. 16** is a functional block diagram of an illumination duration ("flash") control circuit **1600** for an illuminator **1402**. Although only one illuminator **1402** and control circuit **1600** is shown, multiple illuminators **1402** can be used and independently controlled using additional control circuits **1600**. The illuminator **1402** can be, for example, a xenon tube having a length greater than the maximum width of the sample plate **212** to be used in the imaging system **100, 150**, or **200**. By having such a dimension, the illuminator **1402** can be located underneath and along one axis of the sample plate **212** to illuminate all the wells in one row or column of the sample plate **212** without repositioning the illuminator **1402**.

[**0089**] A first end of the illuminator **1402** is connected to a first capacitor **1602** and a first resistor **1604**. The opposite end of the first resistor **1604** is connected to a power supply **1606**. The power supply **1606** may be controlled by a dedicated RS**232** line, for example. The opposite or second end of the first capacitor **1602** that is not connected to the illuminator **1402** is connected to ground or a voltage common.

[**0090**] The second end of the illuminator **1402** is connected to the anode of a first silicon controlled rectifier ("SCR") **1607** and a first terminal of a second capacitor **1608**, respectively. An SCR is a solid state switching device that can provide fast, variable proportional control of electric power. A resistor **1620** is connected between the first terminal of the second capacitor and the cathode of a second SCR **1610**. The second terminal of the second capacitor **1608** is connected to an anode of the second SCR **1610**. The cathode of the first SCR **1607** is connected to the ground or voltage common potential. The cathode of the second SCR **1610** is connected to the cathode of the first SCR **1607** and is similarly connected to ground or the voltage common potential. The anode of the second SCR **1610** is also connected to a second resistor **1614** that connects the anode of the second SCR **1610** to the power supply **1606**.

[**0091**] A trigger **1612** of the illuminator **1402** is connected to the gate of the first SCR **1607** so that both can be triggered simultaneously. This common connection controls the trigger **1612** of the illuminator **1402** and the start of illumination. The gate of the second SCR **1610** controls a stop or end of illumination.

[**0092**] The duration of illumination provided by the illuminator **1402** can be controlled as follows. Initially, the first and second SCRs **1607** and **1610**, respectively, are not conducting. The first capacitor **1602** is charged up to the level of the voltage of the power supply **1606** using the first resistor **1604**. The power supply **1606** can, for example, charge the first capacitor to 300 volts or more.

[**0093**] The size of the first capacitor **1602** relates to the amount of energy that can be transferred to the illuminator **1402**. The illuminator **1402** provides an illumination based in part on the amount of energy provided by the first capacitor **1602**. The first capacitor **1602** can be one capacitor or a bank of capacitors. The first capacitor **1602** can be, for example, a 600 μF capacitor.

[**0094**] The size of the resistors **1620** and **1614** are determined in part by the desired voltage rise time on the second capacitor **1608**. Smaller resistors **1620** and **1614** allow the second capacitor **1608** to charge quickly. However, the second SCR **1610** can inadvertently trigger if the voltage impulse at its anode is too great. Thus, the value of the resistors **1620** and **1614** are typically chosen to allow the second capacitor **1608** to recharge before the next image flash trigger, but not to recharge so quickly as to inadvertently trigger conduction in the second SCR **1610**.

[**0095**] The resistor **1620** provides an electrical path from the anode of the first SCR **1607** to ground or voltage common to allow the second capacitor **1608** to charge.

[**0096**] The illuminator **1402** is ready to trigger once the first capacitor **1602** is charged. The second capacitor **1608** is charged by the power supply **1606** through the second resistor **1614** concurrent with the charging of the first capacitor **1602**. The second capacitor **1608** is chosen to be large enough to generate a current potential that shuts off the first SCR **1607** and, thus, to terminate illumination by the illuminator **1402**. The second capacitor **1608** can be a single capacitor or can be a bank of capacitors. The second capacitor **1608** can be, for example, a 20 μF capacitor.

[**0097**] After the first and second capacitors **1602** and **1608** have been charged, the duration of illumination can be controlled. The illuminator **1402** initially illuminates when the trigger signal is provided to the control of the illuminator **1402** and the gate of the first SCR **1607**. The illuminator **1402** can include a triggering circuit that triggers the illuminator **1402** in response to a logic signal. If the illuminator **1402** does not include this circuit, an external triggering circuit can be included.

[**0098**] The first SCR **1607** conducts in response to the trigger signal. The first SCR **1607** then continues to conduct even in the absence of a gate signal. The first SCR **1607** can be shut off by interrupting the current through the SCR or by reducing the voltage drop across the first SCR **1607** to below the forward voltage of the device.

[**0099**] The second SCR **1610** is controlled by a stop signal generator **1616** to connect the second capacitor **1608** in parallel with the first SCR **1607**. However, the second capacitor **1608** is charged in opposite polarity to the voltage drop across the first SCR **1607**. Thus, when the second SCR **1610** initially conducts, the voltage from the second capacitor **1608** is placed in opposite polarity across the first SCR **1607** thereby shutting off the first SCR **1607**.

[**0100**] After the first SCR **1607** is triggered by a gate signal and begins to conduct, the second end of the illuminator **1402** and the first terminal of the second capacitor **1608** are pulled to ground via the first SCR **1607**. The illuminator **1402** then illuminates in response to the current flowing through the illuminator **1402**. The second SCR **1610** controls turn-off of the illuminator **1402**. The second SCR **1610** begins to conduct when a stop signal is applied to the gate of the second SCR **1610**. This pulls the second terminal of the second capacitor **1608** to ground. Because a capacitor resists instantaneous voltage changes, the voltage across the second capacitor **1608** momentarily causes the voltage at the anode of the first SCR **1607** to be pushed below the ground or voltage common potential. A negative voltage at the anode of the first SCR **1607** results in a loss of current flowing through the first SCR **1607**, which results in shut down of the first SCR **1607**. The second capacitor **1608** discharges almost immediately. The illuminator **1402** shuts off when the first SCR **1607** turns off because there is no longer a current path through the illuminator **1402**.

[**0101**] Thus, a microprocessor, controller, or microcontroller can be programmed to control the trigger **1612** and stop signal generator **1616**. The processor controls the trigger signal to initiate illumination with the illuminator **1402**. The processor then controls the stop signal to control termination of the illuminator **1402**. The processor can thus control the trigger and stop signals to control the duration of the illumination. The processor can control the duration of the illumination (a "flash") in predetermined intervals or can control the duration of the illumination over a range of time. For example, the processor can control the duration of the flash in microsecond steps across an interval of approximately 20 μS - 600 μS. Alternatively, the processor can control the lower range of the duration of the flash to be 0, 20, 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, or 550 μS. In another alternative, the processor can control the upper range of the duration of the flash to be 40, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550 or 600 μS. In one embodiment, the digital camera **214** issues the signal to turn on the illuminator **1402** so that the "flash" will be in synchronization with the electronic shutter of the digital camera **214**.

[**0102**] The power supply **1606** can be a controllable high voltage power supply. The microprocessor, controller, or microcontroller can also control the output voltage of the power supply **1606** to further control the illumination provided by the illuminator **1402**. For example, the microprocessor can control the output voltage of the power supply **1606** to vary the illumination provided by the illuminator **1402** for the same illumination duration. Thus, for a given illumination duration, the microprocessor can control the power supply **1606** to a lower output voltage to minimize the illumination. Similarly, for the same illumination duration, the microprocessor can control the power supply **1606** to a higher output voltage, thereby increasing the illumination.

[**0103**] The microprocessor can control the output voltage of the power supply **1606** over a range of, for example, 180-300 volts. The illuminator **1402** may not consistently illuminate for voltages below 180 volts when the illuminator **1402** is a xenon flash tube. The microprocessor can control the output voltage of the power supply **1606** using a digital control word. Thus, the microcontroller can control the output voltage of the power supply **1606** in steps determined in part by the number of bits in the control word and the tunable range of the power supply **1606**. The microcontroller can, for example provide a 10-bit control word, an 8-bit control word, a 6-bit control word, a 4-bit control word, or a 2-bit control word. Alternatively, the power supply **1606** output voltage can be continuously variable over a predetermined range.

[**0104**] Thus, the microcontroller can control a level of illumination by controlling the illumination duration, the power supply **1606** output voltage, or a combination of the two. The microprocessor's ability to control the combination of the two permits a wider range of brightness outputs than if only one parameter were controllable. The microprocessors ability to control both illumination duration and power supply **1606** output voltage is advantageous for different lens zoom conditions. When magnification is low, such as when the lens is zoomed out, a relatively small amount of light is required. When magnification is high, a relatively large amount of light is required to capture an image. Use of filters and varying apertures may also be used to adjust the amount of light from the light source.

[**0105**] Operation

[**0106**] The imaging system **200** includes software modules that control and direct the lens assembly **230** to perform the following functions. In one embodiment, the imaging system **200** is configured to automatically control the brightness of the image. For example, after the camera **214** captures an image of a well of the sample plate **212**, the software determines whether the brightness is within predetermined thresholds. If the brightness does not fall within the thresholds, the controllers and logic of the imaging system **200** iteratively adjust the illumination intensity of the illuminators **1402** to adjust the brightness of the images until the brightness falls within the thresholds. In some embodiments, the brightness of the image may be evaluated based on a predetermined region (or set of pixels) of the image captured.

[**0107**] The imaging system **200** can also be configured with software to automatically focus the image. An exemplary autofocus routine is as follows. Once the lens assembly **230** is positioned over a sample of the sample plate **210**, the objective lens **231** is moved along its imaging axis to a predetermined starting position. The camera **214** then acquires an image of the sample and/or well at that focus position. In one embodiment, the software obtains a "focus score." This may be done, for example, by examining the brightness values of a set of pixels (e.g., a 500×3 pixel area) in the captured image, applying a low pass filter, and computing the sum of the squares of the differences in brightness of adjacent pixels for the set of pixels. The position and focus score data points are stored in an array. The objective lens **231** is moved to the next predetermined incremental position on its imaging axis, and the process of acquiring an image, computing the focus score, and storing the position and focus score values is repeated. This process continues until the objective lens **231** has been moved to all the predetermined or desired positions, e.g., until it reaches a predetermined end position by incrementally moving in a predetermined step size from the starting position. In one embodiment, the step size depends at least in part upon a predetermined maximum number of images to be acquired during the autofocus routine.

[**0108**] Next, the software searches the lens position/focus score array to identify the lens position with the best focus score. In one embodiment, the software then proceeds to compute the lens positions that are midway from the best focus score position to positions adjacent to it in the array. That is, the software examines the array of positions already imaged, finds the nearest position greater than the lens position associated with the best focus score, and calculates a "midpoint" position between them. A similar process is performed with regard to the nearest lens position that is less than the best focus score position. The software then acquires images at the midpoint positions and obtains corresponding focus scores. The software once again evaluates the array to identify the image with the best focus score, using a step size that is, say, one-half of the initial step size. These tasks are repeated until, for example, a maximum number of images acquired during autofocus, or a minimum step size, has been reached.

[**0109**] In some embodiments, the imaging system **200** performs the processes of autofocusing and automatically adjusting the brightness, as described above, for each sample of a sample plate **212** received by the imaging system **200**. After the desired brightness and focus are set, the imaging system **200** then captures an image and stores it in, for example, the data storage **190**. In one embodiment, the automatically determined brightness and focus are also stored for each sample. In another embodiment, the software of the imaging system **200** calculates and stores a value associated with the mean of the brightness and focus positions for the aggregate of samples of the first plate. This value is then associated with each of the position/focus score data points in the array. Subsequent plates are examined using the mean brightness and focus as initial imaging values.

[**0110**] The imaging system **200** may also include additional functionality related to automatically finding the edges of a droplet in a well of a sample plate **212**. In one embodiment, after the edges of the drop have been found, the imaging system **200** finds the centroid of the droplet and moves the lens assembly **230** to the centroid. The imaging system **200** then determines the magnification required to image substantially only that area corresponding to the droplet, adjusts the zoom, and acquires the image.

[**0111**] In another embodiment, the imaging system **200** may be configured to perform automatic adjustment of aperture. In this embodiment, the imaging system **200** receives settings for either maximum image resolution or maximum depth of field. The imaging system **200** then determines the corresponding aperture by, for example, looking at one or more tables having values correlating aperture with maximum resolution and/or maximum depth of field. Of course, magnification data may be part of these tables.

[**0112**] In yet another embodiment, the imaging system **200** may be configured to perform automatic zoom of a substance in a sample stored in a well of the sample plate **212**. In one embodiment, for example, the imaging system identifies a "crystal-like object" in the sample, calculates its centroid, moves the lens assembly **230** and digital camera **214** to the centroid, adjusts the zoom level, and captures an image of the "crystal-like object." In another embodiment, the imaging system **200** can be configured to capture an image of a sample or a crystal-like object, perform image analysis of the image, adjust imaging parameters (e.g., focus, aperture, zoom, illumination filtering, image filtering, brightness, etc.) and retake an image of the sample or crystal-like object. The imaging system **200** can perform this process iteratively until predetermined thresholds (e.g., contrast, edge detection, etc.) are met.

[**0113**] Thus, in one embodiment of the imaging system **200**, the imaging system receives a sample plate **212** and for each sample performs the following functions including, automatic adjustment of brightness and aperture, autofocus, automatic detection of the sample droplet, and acquisition and storage of images. The imaging system **200** stores the aperture, brightness, focus position, drop position and/or size. The imaging system **200** may then use mean values of these factors as initial imaging settings for subsequent plates.

[**0114**] To increase the amount of data available for analysis of the sample, or crystal detection, in some embodiments an illumination source filter **270** (**FIG. 2**) may be inserted in the filter slot **272** so that the filter **270** is interposed between the light source **216** and the sample plate **212**. In one embodiment the various filters **270** may be inserted and removed from the filter slot **272** by a plate handler. Thus, the filter **270** may be automatically removed or exchanged by the imaging system **200**. Alternatively, or additionally, an image filter (such as those that may be placed in the photo-filter carriage **237**) may be interposed between the sample droplet in the sample plate **212** and the objective lens **231**. In one embodiment, the image filter includes a polarization filter that provides a variable amount of polarization on the light incident on the objective lens **231**. The use of these filters can be automatically controlled by imaging software routines and/or determined by operator defined variables.

[**0115**] The motorized control of aperture, focus, and zoom of the lens assembly **230** in conjunction with remote control of the light source **216** (e.g., brightness and direction of illumination) allows dynamic optimization of contrast, field of view, depth of field, and resolution.

[**0116**] Imaging System Integrated With Automated Sample Analysis System

[**0117**] **FIG. 17** depicts a functional block diagram of an automated sample analysis system **1700** having an imaging system **100**, **150**, or **200**. The system **1700** includes controllers and logic **1760** for controlling various subsystems housed in a cabinet **1702**. The system **1700** can further include a shelf access door **1712** for allowing access to a removable shelf system **1720** and/or a stationary shelf system **1722**. In one embodiment, a removable shelf access door **1710** can be provided. The system **1700** can include a transport assembly **1730** that can consist of a plate handler **1732**, an elevator assembly **1734**, and a rotatable platform **1736**. The system **1700** can further include an environmental control subsystem **1765** that employs a refrigeration unit **1762** and/or a heater **1764**.

[**0118**] In one embodiment, the system **1700** also includes an imaging system **200** as has been described in above. The imaging system **200**, having subcomponents **210**, **214**, **216**, **218**, **220**, and **230**, which are fully detailed above with reference to **FIGS. 2-16**, can be housed in the cabinet **1702**. This arrangement ensures that the samples in the sample plates remain at all times within the confines of a controlled environment. That is, once a sample plate is stored in the cabinet **1702**, it is unnecessary to expose the sample plate to the environment external to the cabinet since the system **1700** is capable of automatically (i.e., without operator intervention) carry out the imaging of the sample within the cabinet **1702**.

[**0119**] Embodiments of an automated sample analysis system **1700** having an imaging system in accordance with the invention are described in the related United States Provisional Patent Application entitled "AUTOMATED SAMPLE ANALYSIS SYSTEM AND METHOD," having attorney Docket Number DPINTL.012PR, which is referenced above.

[**0120**] While the above detailed description has shown, described, and pointed out novel features of the invention as applied to various embodiments, it will be understood that various omissions, substitutions, and changes in the form and details of the device or process illustrated may be made by those skilled in the art without departing from the spirit of the invention. The scope of the invention is indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

What is claimed is:

1. An automated imaging system comprising:

an imaging device configured to automatically capture an image of a sample;

a lens coupled to the imaging device; and

an automated lens translator configured to move the lens along a first axis substantially parallel to the sample.

2. The imaging system of claim 1, further comprising an automated well plate translator configured to selectively position a well plate along a second axis substantially perpendicular to the first axis.

3. The imaging system of claim 1, wherein the lens comprises a motorized aperture.

4. The imaging system of claim 1, wherein the imaging device comprises at least one of an automated focus, zoom, and filter wheel.

5. The imaging system of claim 1, further comprising a polarization filter disposed between the imaging device and the sample.

6. The imaging system of claim 1, wherein the filter wheel rotates so that the polarization filter rotates between the imaging device and the sample to provide varying polarization angles.

7. The imaging system of claim 1, the filter wheel rotates so as to provide at least 90 degrees variance of rotational angles of the filter.

8. An imaging system for obtaining images of a sample, the imaging system comprising a first illuminator placed off an imaging axis of the imaging system, whereby the illuminator illuminates the sample from below and at an angle relative to the imaging axis.

9. The imaging system of claim 8, comprising a second illuminator positioned away from the imaging axis, wherein the second illuminator is positioned substantially opposite the imaging axis from the first illuminator.

10. A method of automatically imaging at least one sample in a well plate, the method comprising:

moving the well plate along a first axis to a position x;

moving an imaging device along a second axis substantially perpendicular to the first axis to a position y; and

capturing an image of at least one sample of the well plate, wherein the sample is substantially positioned at coordinates (x,y).

11. An automated sample analysis system comprising:

a temperature controlled cabinet;

a plurality of shelves within the cabinet, each shelf configured to store a sample carrier;

a transport assembly, within the cabinet, configured to retrieve the sample carrier from one of the shelves and to transport the sample carrier to a destination; and

an imaging system configured to receive the sample carrier from the transport assembly and to image at least one sample of the sample carrier.

12. The automated sample analysis system of claim 11, wherein the transport assembly is configured to transport a source filter from a storage location to a position between a light source and the imaging system.

13. The automated sample analysis system of claim 11, wherein the source filter comprises a polarizing filter.

14. A method of imaging at least one well in a well plate, the method comprising;

storing the well plate on a shelf at a selected environment;

retrieving the well plate from the shelf using an automated well plate transport assembly;

transporting, at the selected environment, the well plate to an imaging system using the automated well plate transport assembly;

autonomously imaging, at the selected environment, at least one well in the well plate using the imaging system;

transporting the well plate from the imaging system to the shelf using the automated well plate transport assembly; and

repositioning the well plate in the shelf.

15. A method of adjusting a light intensity in an automated crystallization imaging system, the method comprising:

charging a first capacitor;

connecting the first capacitor to an illuminator to generate flash illumination; and

controlling a period of time the first capacitor is connected to the illuminator to adjust the illumination from the illuminator.

16. The method of claim 15, wherein connecting the first capacitor to the illuminator comprises activating an SCR connecting the first capacitor to the illuminator.

17. The method of claim 15, wherein controlling the period of time the first capacitor is connected to the illuminator comprises momentarily interrupting a current flow through the SCR using a second capacitor.

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