3D PARTICLE IMAGING IN PHARMACEUTICAL CONTAINERS

FIELD OF DISCLOSURE

[0001] The present application relates generally to particle imaging, and more specifically to techniques for three-dimensional (3D) imaging of particles in containers/vessels in pharmaceutical or other applications.

BACKGROUND

[0002] In certain contexts, such as quality control procedures for manufactured drug products, it is necessary to examine samples (e.g., fluid samples) for the presence of various particles (e.g., protein aggregates or debris). The acceptability of a given sample, under the applicable quality standards, may depend on metrics such as the number and/or size of undesired particles contained within the sample. If a sample has unacceptable metrics, it may be rejected and discarded.

[0003] To handle the quantities typically associated with commercial production of pharmaceuticals, the particle inspection task has increasingly become automated. However, automated inspection systems have struggled to overcome various barriers to achieving good particle measurement fidelity. In particular, accurate sizing and counting of particles in drug products remains a challenge to the industry. The primary technical barrier is the distortion of the image caused when imaging through the sidewall of a curved container (e.g., vial or syringe), which leads to blind spots as well as artificial magnification and/or shape distortion of particles or other objects (e.g., bubbles) in the fluid volume. Moreover, projecting a 3D volume onto a 2D image poses significant challenges for certain particle analysis techniques, such as particle tracking.

[0004] Even if multiple cameras are employed (e.g., as described in U.S. Patent No. 9,418,416 to Milne et al.), technical hurdles remain. For example, the cameras may fail to properly detect particles having certain shapes when those particles are oriented in a particular manner relative to the cameras, and may result in the detection of "ghost particles" where no actual particles exist, as discussed in further detail below. Moreover, to provide useful image information, multi-camera systems may require very precise temporal synchronization and spatial alignment, which can be challenging to achieve. With respect to spatial alignment, for instance, many factors may cause image misalignment, such as interactions between vessels (e.g., vessel flanges) and gripping mechanisms (e.g., grasping components of robotic arms), manufacturing tolerances of vessels, tolerances in camera placement, and so on.

SUMMARY

[0005] In one aspect, the present disclosure provides a method for three-dimensional (3D) imaging of a sample in a vessel having a longitudinal axis orthogonal to a horizontal plane, the method comprising: capturing, by at least three cameras located at different positions around the vessel, at least three respective two-dimensional (2D) images of the sample in the vessel, wherein each of the at least three 2D images comprises pixels having associated pixel values, each of the least three cameras has a respective optical axis, the optical axis of a first camera of the at least three cameras is inclined or declined at a first angle relative to the horizontal plane, the first angle being greater than or equal to zero degrees, and the optical axis of a second camera of the at least three cameras is inclined or declined at a second angle relative to the horizontal plane, the second angle being at least five degrees greater than the first angle; and generating, by one or more processors, a 3D image of the sample based on (i) the pixel values associated with the pixels of the at least three 2D images, and (ii) one or more look-up tables collectively indicating, for pixels in each of the at least three 2D images, expected paths for light traversing the vessel and the sample.

[0005a] In another aspect, the present disclosure provides a system for three-dimensional (3D) imaging of a sample in a vessel having a longitudinal axis orthogonal to a horizontal plane, the system comprising: at least three cameras located at different positions around the vessel, wherein each of the least three cameras has a respective optical axis, the optical axis of a first camera of the at least three cameras is inclined or declined at a first angle relative to the horizontal plane, the first angle being greater than or equal to zero degrees, and the optical axis of a second camera of the at least three cameras is inclined or

declined at a second angle relative to the horizontal plane, the second angle being at least five degrees greater than the first angle; and a computing system comprising one or more processors and a memory, the memory storing instructions that, when executed by the one or more processors, cause the computing system to trigger the at least three cameras to capture at least three respective two-dimensional (2D) images of the sample in the vessel, wherein each of the at least three 2D images comprises pixels having associated pixel values, and generate a 3D image of the sample based on (i) the pixel values associated with the pixels of the at least three 2D images, and (ii) one or more look-up tables collectively indicating, for pixels in each of the at least three 2D images, expected paths for light traversing the vessel and the sample, wherein the expected paths of light account for at least a shape of the vessel and a refractive index of the sample.

[0005b] In another aspect, the present disclosure provides a method of aligning images for three-dimensional (3D) imaging of a sample in a vessel, the method comprising: for each camera of a plurality of cameras located at different positions around the vessel, activating a respective light source that provides backlighting for the vessel relative to the camera, and while the respective light source is activated, capturing, by the camera, a respective two-dimensional (2D) calibration image of the vessel; for each 2D calibration image of the respective 2D calibration images, measuring, by one or more processors, a respective vertical position, horizontal position, and rotation of the 2D calibration image, in part by detecting two or more edges of the vessel as depicted in the 2D calibration image; generating, by the one or more processors, calibration data based on the measured vertical positions, horizontal positions, and rotations for the respective 2D calibration images; capturing, by each camera of the plurality of cameras, a respective set of 2D images of the sample in the vessel; and digitally resampling, by the one or more processors and using the calibration data, at least one set of the respective sets of 2D images to correct for vertical offset, horizontal offset, and rotational offset of the at least one set of 2D images.

[0005c] In another aspect, the present disclosure provides a system for three-dimensional (3D) imaging of a sample in a vessel, the system comprising: a plurality of cameras located at different positions around the vessel; a plurality of light sources, each of the plurality of light sources being positioned relative to the vessel and a different one of the cameras so as to provide backlighting of the vessel when the light source is activated; and a computing system comprising one or more processors and a memory, the memory storing instructions that, when executed by the one or more processors, cause the computing system to for each camera of the plurality of cameras, activate a respective one of the light sources, and while the respective light source is activated, trigger the camera to capture a respective two-dimensional (2D) calibration image of the vessel, for each 2D calibration image of the respective 2D calibration images, measure a respective vertical position, horizontal position, and rotation of the 2D calibration image, in part by detecting two or more edges of the vessel as depicted in the 2D calibration image, generate calibration data based on the measured vertical positions, horizontal positions, and rotations for the respective 2D calibration images, for each camera of the plurality of cameras, trigger the camera to capture a respective set of 2D images of the sample in the vessel, and digitally resample, using the calibration data, at least one set of the respective sets of 2D images to correct for vertical offset, horizontal offset, and rotational offset of the at least one set of 2D images.

[0005d] In yet another aspect, the present disclosure provides a non-transitory, computer-readable medium storing instructions that, when executed by one or more processors of a computing system, cause the computing system to: for each camera of a plurality of cameras, activate a respective one of a plurality of light sources to provide backlighting for a vessel relative to the camera, and while the respective light source is activated, trigger the camera to capture a respective two-dimensional (2D) calibration image of the vessel; for each 2D calibration image of the respective 2D calibration images, measure a respective vertical position, horizontal position, and rotation of the 2D calibration image, in part by detecting two or more edges of the vessel as depicted in the 2D calibration image; generate calibration data based on the measured vertical positions, horizontal positions, and rotations for the respective 2D calibration images; for each camera of the plurality of cameras, trigger the camera to capture a respective set of 2D images of a sample in the vessel; and digitally resample, using the calibration data, at least one set of the

respective sets of 2D images to correct for vertical offset, horizontal offset, and rotational offset of the at least one set of 2D images.

[0005e] ~~Embodiment~~Examples described herein relate to systems and methods that improve upon conventional visual inspection techniques for containers (e.g., pharmaceutical vessels). In particular, a system implementing the instant ~~invention~~disclosure provides for three-dimensional (3D) imaging of a sample within a vessel, by processing two-dimensional (2D) images captured by multiple cameras positioned around the perimeter of the vessel. By processing 2D images corresponding to different perspectives, and accessing one or more look-up tables representing ray optics through the vessel and sample (or representing phenomena that are approximated by other optical modeling techniques), the system generates a 3D image or model of the sample (including any particles and/or bubbles, etc., therein). The system may use the look-up table(s) to determine which pixels of which 2D images correspond to common locations within the sample volume (e.g., the points within the sample at which different ray optic paths, associated with different pixel sensors of the multiple cameras, intersect). In this manner, for example, a 3D voxel grid representing the sample volume may be constructed, e.g., with each voxel being assigned a value to indicate whether an object or object portion is present (or, in some ~~embodiment~~examples, is likely present) in that voxel.

[0006] 3D imaging has important advantages over 2D imaging. For example, the multiple cameras used for 3D imaging greatly reduce the impact of blind spots that each individual camera may have due to curvature of the vessel and refraction. Moreover, the look-up tables can map the optical distortion caused by the curved vessel surfaces, via calculation and/or empirical measurements, in order to correct for such distortion when constructing 3D image. In addition to determining accurate particle position, 3D imaging may allow for accurate determination of particle size and shape, as well as more accurate particle classification.

[0007] Accurate positioning of particles, as well as accurate size and shape determination, greatly assists (and potentially simplifies) particle tracking algorithms. Moreover, 3D imaging can ameliorate issues associated with occlusion by cosmetic defects (e.g., dirt on the vessel surface). For 2D imaging, on the other hand, particles can "hide" behind "dead" regions in the image associated with these defects. This complicates tracking as particles can disappear and reappear on opposite sides of the defects areas. Conversely, with 3D imaging, the position of a given particle is known at all (or most) times, making tracking of the particle comparatively easy. For instance, it is easier to build trajectories from one frame to another (e.g., by simply matching a particle in one 3D frame to the nearest candidate particle in another 3D frame, if the camera frame rate is fast enough).

[0008] Similarly, in the 2D imaging case, particles can occlude one another. In densely populated samples this can become a major challenge. While complex 2D tracking algorithms have been proposed to attempt to overcome these challenges, with varying degrees of success, 3D imaging may remove (or greatly lessen) the problem of particle occlusion in the first instance, and make complex tracking algorithms unnecessary. This is because, even if particles overlap from the perspective of one camera, the positions of those particles can, in all or most instances, be easily differentiated using the two or more other camera images. Moreover, 2D images or frames of particles generally fail to capture the "smoothness" of particle trajectories, which commonly follow circular or helical paths (e.g., after agitation of the vessel). In two dimensions, such paths may map to sharp sinusoidal paths, or even zig-zag paths, with abrupt changes in apparent particle velocity. As a result, the particle tracking algorithm may easily falter and lose a given particle. In three dimensions, of course, the full 3D path can be observed. Thus, with 3D imaging, even relatively simple tracking algorithms may produce useful results.

[0009] In addition, the cameras of the disclosed system are configured/oriented so as to avoid various artifacts that could arise if the optical axes of all of the cameras were within the same plane (e.g., a "horizontal plane" that is orthogonal to the vertical or longitudinal axis of the vessel, as proposed in U.S. Patent No. 9,418,416). One such artifact is depicted in FIGs. 1A and 1B. As seen in FIG. 1A, a fiber 100 exhibits a C-shape within an x-y plane. If the optical axes of all cameras are within the x-y plane (as may likely occur for at least some particles in a given sample, at certain times), then the resulting 2D images may fail to properly detect the shape of the fiber 100, regardless of where, around the z-axis, the cameras are positioned. In particular, because no

camera is "looking down at" or "looking up at" the particle from a different perspective (i.e., from a higher or lower position on the z-axis), the fiber 100 appears to be a solid disc 102 that lies within the x-y plane, as depicted in FIG. 1B. Similar problems are also likely to occur for particles having other shapes, such as a coiled hair or fiber.

[0010] An example of another potential artifact is depicted in FIG. 2, for the case where three cameras (not shown in FIG. 2) are arranged in a horizontal plane around a vessel 200 (e.g., a syringe, vial, etc.). FIG. 2 depicts a top-down view of a cross-sectional slice of vessel 200 and the sample (e.g., drug product) within vessel 200, with each of three optical paths (202a through 202c) corresponding to a different one of the cameras in the horizontal plane. Each of paths 202a through 202c may correspond to a single pixel in a single pixel row for the corresponding camera, for example. For ease of illustration, FIG. 2 does not depict the refraction that occurs as the paths 202a through 202c travel into or though the wall of vessel 200.

[0011] As seen in FIG. 2, in the scenario depicted, objects (e.g., particles) 204a, 204b and 204c are within the paths 202a, 202b and 202c, respectively. Thus, a system processing the images of the three cameras may view the pixels corresponding to paths 202a, 202b and 202c as each being an "object present" pixel. However, if 2D look-up tables are used to determine which positions within the depicted cross-sectional slice correspond to which optical paths, the processing system will translate or map the three detected objects to the intersection location 210. In other words, the system will determine that a particle exists at location 210, even if no particle in fact exists at location 210 when the images are captured. This is referred to herein as the "ghost particle" phenomenon.

[0012] To ameliorate these problems, while still supporting 3D particle detection and tracking, at least one of the three or more cameras may be tilted up (inclined) or down (declined) relative to the optical axes of one or more other cameras. By providing different camera perspectives (in terms of angle/tilt relative to the horizontal plane of a vessel), the likelihood of misidentifying the shape of a particle (e.g., as in FIGs. 1A and 1B), and/or of detecting a "ghost particle" (e.g., as in FIG. 2), may be substantially reduced. However, the optical path(s) of any camera(s) that is/are inclined or declined relative to the horizontal plane will naturally travel through different cross-sectional slices of the vessel/sample. Accordingly, the present ~~invention~~disclosure utilizes a 3D look-up table, rather than a 2D look-up table, for at least one camera. For example, a system implementing the ~~invention~~disclosure may utilize a 3D look-up table at least for any camera that is inclined or declined relative to the horizontal plane (i.e., having an optical axis that is not substantially orthogonal to the longitudinal/vertical axis of the vessel), and possibly for all cameras. The 3D look-up table may account for each pixel in each row of the images captured by a given camera, and map each such pixel to a respective set of voxels in a 3D representation/image/model of the sample. Moreover, in some ~~embodiment~~examples, the 3D look-up table accounts not only for the change in vertical position as a given path (e.g., corresponding to a single pixel) travels through the sample/vessel, but also for the refraction that occurs, in all three dimensions, at the air/vessel interface and the vessel/sample interface.

[0013] The system also determines which pixels in each camera image depict an object or object portion, or a candidate object or object portion. For example, the system may flag any pixel having an intensity over a threshold value as being a pixel in which an object is (or may be) depicted. Based on the flagged pixels for the 2D images of all cameras, and using the 3D look-up table(s) to identify intersections between the optical paths of the various image pixels, the system can assign objects or object portions (or candidate objects/portions) to the appropriate voxels in the 3D image.

[0014] Any suitable number of cameras may be positioned at any suitable number of different angles relative to each other and the vessel, with the problems of shape misidentification and ghost particles generally tending to become less frequent as the number of cameras, and especially the number of cameras having different inclination/declination angles, increases. For example, a large number of cameras may be situated at different positions along the periphery of an imaginary sphere that surrounds the vessel (although the cameras need not all be at the same distance from the vessel). In some ~~embodiment~~examples, at least the inclined or declined cameras may utilize telecentric lenses, in order to capture the entire sample (or most of the sample) within the depth of field of the lens at moderate inclination/declination angles.

[0015] Other inventive techniques, related or potentially related to 3D imaging, are also described herein. For example, to generate an accurate 3D image of a sample, it may be necessary to have pixel-level alignment of the 2D images from the different cameras. If one pixel corresponds to 20 microns in the object plane, for instance, and if a camera lens aperture is placed 180 millimeters (mm) from the object, then even a very slight angular displacement of the lens and camera arm (e.g., due to tolerances in manufacturing of the camera arms) can result in a substantial horizontal or vertical displacement of the imaged object. While the system may be forgiving to variations in the distance between the lens and the imaged object along the optical axis of the camera (e.g., if a telecentric lens is used), and while the effects of perspective as a vessel/sample is tilted towards or away from the camera may in some ~~embodiment~~examples be negligible, it remains important to calibrate for vertical and horizontal/lateral displacements in each image, as well as relative rotation around the optical axis.

[0016] In addition to imprecision in placement of the cameras, other factors may necessitate calibration of the images. For syringes and cartridges, for instance, parts may be gripped using a spring-loaded chuck, which might allow the vessel to be stably oriented even at a slight offset angle relative to the vertical axis. Moreover, in the case of glass syringes, the forming process of the flange can potentially lead to an uneven flange, which may force the syringe to tilt relative to the vertical axis. For pick-and-place robotic systems, vessels may be gripped around a thin section of their cylindrical body, e.g., by three fingers on the outside of the vessel or two fingers on the inside of the vessel. In either case, the limited number of contact points between the vessel and the gripper may allow the syringe to be held squint and/or precess as the syringe rotates. For vials gripped around the neck, a similar problem may arise. Further, a pharmaceutical vessel (particularly if made from glass) can exhibit deviations in form that may affect the apparent vertical alignment of the cylindrical body of the vessel.

[0017] Due to the need for precise (e.g., pixel-level) alignment, digital/software-based calibration may be required regardless of which mechanical techniques are used to handle and present the vessels. It should be appreciated that the above-noted offsets/errors may be small and that, at least in some ~~embodiment~~examples, large misalignments may invalidate basic assumptions about the relationship between optical components (e.g., assumptions that certain cameras are orthogonal to the vertical/longitudinal axis of the vessel such that the horizontal plane of the vessel represents a circular cross-section, etc.). Thus, in some ~~embodiment~~examples, the digital calibration techniques assume or rely on some prerequisite level of hardware alignment.

[0018] Other hardware and/or software techniques may also be used to facilitate 3D imaging of samples in vessels. If particles are tracked in three dimensions based on the constructed 3D images, for example, the system may monitor time-dependent variations in object (e.g., particle) shape, size, and/or position to filter out ghost particles, and/or to identify certain transient shapes (e.g., the disc 102 of FIG. 2) as being incorrect.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] The skilled artisan will understand that the figures described herein are included for purposes of illustration and do not limit the present disclosure. The drawings are not necessarily to scale, and emphasis is instead placed upon illustrating the principles of the present disclosure. It is to be understood that, in some instances, various aspects of the described implementations may be shown exaggerated or enlarged to facilitate an understanding of the described implementations. In the drawings, like reference characters throughout the various drawings generally refer to functionally similar and/or structurally similar components.

[0020] FIGs. 1A and 1B depict an example of actual and apparent particle shapes, respectively, for a particle imaging system in which all cameras have optical axes in the same plane.

[0021] FIG. 2 depicts a top-down, cross-sectional view of a vessel in an example scenario where a “ghost particle” is detected.

[0022] FIG. 3 depicts an example visual inspection system that may be used for the 3D imaging techniques described herein.

[0023] FIGs. 4A through 4D depict example optical paths, for each pixel of a single row of pixel sensors of a camera, as light traverses a vessel containing a sample.

[0024] FIG. 5 depicts an example field depth for a telecentric lens of a camera, relative to a vessel, as the camera is angled relative to a horizontal plane of the vessel.

[0025] FIG. 6 is a simplified block diagram of an example system that may implement the techniques described herein.

[0026] FIGs. 7A and 7B depict an example calibration technique using edge detection.

[0027] FIG. 8 depicts an example arrangement for synchronizing the capture of 2D images for purposes of generating a 3D image.

[0028] FIG. 9 is a flow diagram of an example method for 3D imaging of a sample in a vessel.

[0029] FIG. 10 is a flow diagram of an example method of aligning images for 3D imaging of a sample in a vessel.

DETAILED DESCRIPTION

[0030] The various concepts introduced above and discussed in greater detail below may be implemented in any of numerous ways, and the described concepts are not limited to any particular manner of implementation. Examples of implementations are provided for illustrative purposes.

[0031] FIG. 3 depicts an example visual inspection system 300 that may be used for the 3D imaging techniques described herein. In the depicted embodiment, visual inspection system 300 includes four cameras 302a through 302d mounted on a platform 304, in a generally radial configuration around (and directed in towards) a sample fixture 306. While not shown in FIG. 3, sample fixture 306 may hold or support a vessel containing a sample. The vessel may be a syringe, a vial, a cartridge, or any other suitable type of container formed from any suitable type or types of material (e.g., glass), with at least a portion of the