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 cylindrical shape with 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 at 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, 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 the optical axis of the first camera and the optical axis of a third camera of the at least three cameras are at different radial positions, relative to the longitudinal axis, around the vessel; 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 cylindrical shape with 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 at 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, 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 the optical axis of the first camera and the optical axis of a third camera of the at least three cameras are at different radial positions, relative to the longitudinal axis, around the vessel; 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.

[0005b] 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 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 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

What is claimed is:

1. A method for three-dimensional (3D) imaging of a sample in a vessel having a cylindrical shape with 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 at 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,

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

the optical axis of the first camera and the optical axis of a third camera of the at least three cameras are at different radial positions, relative to the longitudinal axis, around the vessel; 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.

2. The method of claim 1, wherein the expected paths of light account for at least a shape of the vessel and a refractive index of the sample.

3. The method of claim 1 or 2, wherein:

generating the 3D image of the sample includes generating a voxel grid; and

generating the 3D image of the sample includes, for each voxel within the voxel grid:

using the one or more look-up tables to determine which pixels of the pixels in the at least three 2D images correspond to the voxel; and

determining whether to attribute an object or object portion to the voxel based on the pixel values associated with the determined pixels.

4. The method of claim 3, wherein:

the pixel values are pixel intensity values; and.

determining whether to attribute an object or object portion to the voxel includes:

comparing (i) the pixel intensity values associated with the determined pixels to (ii) an intensity threshold; and

attributing the object or object portion to the voxel only if the pixel intensity values for all of the determined pixels are above the intensity threshold.

5. The method of claim 3 or 4, further comprising:

using, by the one or more processors, a clustering algorithm to group voxels within the voxel grid into discrete objects;generating, by the one or more processors, one or more additional 3D images of the sample; and

tracking, by the one or more processors, one or more of the discrete objects across two or more 3D images of the sample.

6. The method of claim 5, wherein tracking the one or more discrete objects includes:

tracking, by the one or more processors, an apparent discrete object across the two or more 3D images of the sample; and

determining, by the one or more processors, that the apparent discrete object is not an actual object based on instability in a tracked path of the apparent discrete object.

7. The method of claim 6, wherein determining that the apparent discrete object is not an actual object based on instability in a tracked path of the apparent discrete object includes:

determining that the apparent discrete object is not an actual object based on (i) a change in direction of the tracked path, or (ii) a disappearance of the apparent discrete object, between two successive 3D images.

8. The method of any one of claims 1 through 7, wherein capturing the at least three respective 2D images of the sample in the vessel includes:

capturing the at least three respective 2D images while the optical axes of the first camera and the third camera are within the horizontal plane.

9. The method of any one of claims 1 through 8, wherein capturing the at least three respective 2D images of the sample in the vessel includes:

generating a synchronization signal that causes the at least three cameras to capture the at least three respective 2D images simultaneously.

10. The method of any one of claims 1 through 9, wherein the second camera is inclined or declined between 10 degrees and 80 degrees relative to the horizontal plane.

11. The method of claim 10, wherein the second camera is inclined or declined between 15 degrees and 25 degrees relative to the horizontal plane.

12. A system for three-dimensional (3D) imaging of a sample in a vessel having a cylindrical shape with 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 at 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,

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

the optical axis of the first camera and the optical axis of a third camera of the at least three cameras are at different radial positions, relative to the longitudinal axis, around the vessel; 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.

13. The system of claim 12, wherein the expected paths of light account for at least a shape of the vessel and a refractive index of the sample.

14. The system of claim 12 or 13, wherein:

the 3D image of the sample includes a voxel grid; and

the instructions cause the computing system to generate the 3D image of the sample at least by, for each voxel within the voxel grid:

using the one or more look-up tables to determine which pixels of the pixels in the at least three 2D images correspond to the voxel; and

determining whether to attribute an object or object portion to the voxel based on the pixel values associated with the determined pixels.

15. The system of claim 14, wherein:

the pixel values are pixel intensity values; and

the instructions cause the computing system to determine whether to attribute an object or object portion to the voxel at least by:

comparing (i) the pixel intensity values associated with the determined pixels to (ii) an intensity threshold; and

attributing the object or object portion to the voxel only if the pixel intensity values for all of the determined pixels are above the intensity threshold.

16. The system of any one of claims 12 through 15, wherein the instructions further cause the computing system to:

use a clustering algorithm to group voxels within the voxel grid into discrete objects;

generate one or more additional 3D images of the sample; and

track one or more of the discrete objects across two or more 3D images of the sample.

17. The system of claim 16, wherein the instructions cause the computing system to track the one or more discrete objects at least by:

tracking an apparent discrete object across the two or more 3D images of the sample; and

determining that the apparent discrete object is not an actual object based on instability in a tracked path of the apparent discrete object.

18. The system of claim 17, wherein the instructions cause the computing system to determine that the apparent discrete object is not an actual object based on (i) a change in direction of the tracked path, or (ii) a disappearance of the apparent discrete object, between two successive 3D images.

19. The system of any one of claims 12 through 18, wherein the optical axis of the first camera is within the horizontal plane.

20. The system of any one of claims 12 through 19, wherein at least the second camera includes a telecentric lens.