ACOUSTIC CONCENTRATION, TRANSFER AND ANALYSIS OF SAMPLES CONTAINING PARTICLES

BACKGROUND

[0001] In life science research and clinical diagnostics, analytical detectors are often used to analyze the size of cells and/or particles disposed within a fluid sample. In view of increasing demand for analysis of the size of cells and/or particles disposed within a fluid, high-throughput approaches and related systems for analyzing the size of cells and/or particles are of interest. Analyzing particles within a fluid sample may require the sample to be loaded into a container and diluted to a particle density suitable for analysis or to have the bulk fluid properties be compatible with the counting and sizing method. Often, in particle sizing within fluid samples, the Coulter Principle is applied as it is effective for biological materials such as cells and viruses as well as non-conductive particles in general. For example, methods of utilizing the Coulter principle for particle counting are disclosed with reference to a Coulter counter (U.S. Patent 2,656,508) to discriminate the presence of non-conducting cells or particles in a conductive fluid.

[0002] Coulter counting employs a conductive solution that forms a conductive path between electrodes where the presence or absence of non-conductive materials (e.g., non-conductive cells and/or particles) varies the resistance of the conductive path between the electrodes. If a particle is moving past the electrodes, the variation in the resistance can be used to determine the particle size. Commercial systems such as those from Beckman Coulter Inc. (Brea, California) can analyze conductive fluid samples by detecting changes in electrical impedance due to the presence of particles in the fluid as they pass through a measurement region positioned between two electrical terminals.

[0003] However, with Coulter counting, as with other methods of particle counting, sample transfer and sample dilution are potential sources of error or contamination. Therefore, improved methods of sample transfer and dilution of particle-containing samples are desired. Sample transfer methods using acoustic radiation (i.e., acoustic pressure waves) have been described in, e.g., US Patent No. 10,156,499. However, reliable transfer of particle-containing fluid for analysis of suspended particles has not previously been achieved.

BRIEF SUMMARY

[0003a] According to a first aspect of the present invention, there is provided a method for acoustic transfer of particle-containing fluid droplets, the method comprising: positioning a fluid sample reservoir containing a fluid sample having suspended cells or particles that is acoustically

coupled with an acoustic radiation generator in alignment with an inlet of an analytical device configured for counting cells or particles; and applying an ejection tone burst of focused acoustic radiation by the acoustic radiation generator to the fluid sample within the fluid sample reservoir to eject a droplet from the fluid sample reservoir such that the droplet contacts the inlet of the analytical device, the droplet containing at least one cell or particle.

[0003b] According to a second aspect of the present invention, there is provided a system for acoustic ejection of particle-containing droplets, comprising: an acoustic radiation generator; a fluid sample reservoir containing a fluid sample, the fluid sample reservoir acoustically coupled with the acoustic radiation generator by an acoustic coupling medium; an analytical device configured for counting cells or particles, the analytical device comprising an inlet positioned in alignment with at least one of the acoustic radiation generator and fluid sample reservoir; and a controller comprising one or more processors and a memory device containing executable instructions that, when executed by the one or more processors, configure the controller to: apply an ejection tone burst of focused acoustic radiation by the acoustic radiation generator to the fluid sample at a target location to eject a droplet containing at least one cell or particle from the fluid sample reservoir such that the droplet contacts the inlet of the analytical device.

[0003c] According to a third aspect of the present invention, there is provided a method for acoustic transfer of particle-containing fluid droplets, the method comprising: applying a first tone burst of focused acoustic radiation by an acoustic radiation generator to a fluid sample within a fluid sample reservoir containing suspended cells or particles such that the first tone burst concentrates the cells or particles at a target location within the fluid sample; and applying a second tone burst of focused acoustic radiation by the acoustic radiation generator to the fluid sample at the target location corresponding to the concentrated cells or particles to eject a droplet from the fluid sample reservoir containing at least one cell or particle.

[0003d] According to a fourth aspect of the present invention, there is provided a system for acoustic ejection of particle-containing droplets, comprising: an acoustic radiation generator; a fluid sample reservoir containing a fluid sample, the fluid sample reservoir acoustically coupled with the acoustic radiation generator by an acoustic coupling medium; and a controller comprising one or more processors and a memory device containing executable instructions that, when executed by the one or more processors, configure the controller to: apply a first tone burst of focused acoustic radiation by the acoustic radiation generator to the fluid sample within the fluid sample reservoir to concentrate cells or particles within the fluid sample; and apply a second tone burst of focused acoustic radiation by the acoustic radiation generator to the fluid

sample at a target location corresponding to the concentrated cells or particles, to eject a droplet containing at least one cell or particle from the fluid sample reservoir.

[0004] Embodiments disclosed herein include a system having an acoustic radiation generator, a fluid sample reservoir containing a fluid sample, and an analytical instrument with an inlet that