

interfaced with the system using hermetic seals, such as silicone gaskets, although any mechanism of interfacing the pumps with the system can be used as needed depending on specific configurations.

[0184] In another aspect of the system, flow rates within the channels can be regulated and controlled. This can include control of flow rate, impeding of flow, switching of flows between various input channels and output channels, and volumetric dosing. In an embodiment having a plurality of channels, the flow rate of samples can be controlled in unison or separately. In an embodiment in which the flow rate is controlled in unison, pressure supplied by the pumping mechanism can be adjusted as needed depending on the number of parallelizations of channels. Alternatively, variable and differential control of the flow rates in each channel can be achieved using various techniques known in the art including, for example, a multi-channel individually controllable syringe manifold. More particularly, the input channel distribution can be modified to decouple all parallel networks of channels. An output can collect the output from all channels via a single manifold connected to a suction. Alternatively or in addition, the output from each network can be collected separately for downstream processing. Flow rate can be controlled by the pumping mechanism, a valve system, and/or by a controller.

[0185] Any number and variety of microfluidic valves can also be included in the system to block or unblock the pressurized flow of particles through the channels. Valves can be positioned in or near any number of inlets and outlets, as well as in or near channels, channel branches, pumping mechanisms, and controllers. In one embodiment, a thin cantilever can be included within a branch point of the channels such that it may be displaced towards one or the other wall of a main channel, typically by electrostatic attraction, thus closing off or changing a pressure resistance within a selected branch channel. Alternatively or in addition, valves can be microfabricated in the form of electrostatically operated diaphragms, as are well known in the art. Mobile diaphragms and flexible membranes within a multi-layer structure can be used such that under pressure, flexing occurs to block or change resistance in or near inlets, outlets, channels, and/or channel branches, and can redirect flows into specific channel branches and/or outlets. Typical processes for including such microfabricated valves can include the use of, for example, selectively etched sacrificial layers in a multi-layer structure. In another embodiment, the microvalve can include one or more mobile diaphragms or flexible membranes formed in a layer above a channel branch, inlet, or outlet such that upon actuation, the membrane is expanded up to decrease resistance within a channel branch, inlet, or outlet, or expanded down into the channel to increase resistance within the same. In this way, flow of particles within the channels can be directed and controlled depending on predetermined parameters. Further details and discussion of such microfluidic diaphragms are disclosed in PCT Publication No. PCT/US2006/039441 entitled, "Devices and Methods for Cell Manipulation" filed Oct. 5, 2007 and incorporated herein by reference in its entirety. A person skilled in the art will appreciate that any microvalves and/or microfabricated valves known in the art can be used within and throughout the system as required.

[0186] In another aspect of the system, one or more microfluidic, size-based separation modules or filters can optionally be included to prevent clogging within the channels by pre-

venting certain particle sizes or particle types from entering the channels and/or to facilitate collection of particles for downstream processing. Typically, particles larger than the largest channel dimension can be removed prior to injection into the channel to prevent clogging within the system. In one embodiment, a filtering process can be performed apart from the system to remove particles, including dust and debris, which are too large and/or too small from the sample that will ultimately be introduced into the channels. In another embodiment, one or more filters can be included somewhere within the system. For example, one or more filters can be positioned just after the inlet such that the sample is required to pass through the filters to enter the channels. One filter can be included to remove particles larger than a required size and another filter can be included to remove particles smaller than a required size. Filters can also optionally be included within a positive pumping mechanism so that the sample is filtered before entering the inlet. Alternatively or in addition, filters can be disposed within valve systems, within the channels, and/or near the output of the channels as needed in specific configurations of the system. In other embodiments, channel sizes can be sequentially reduced over a portion of the system to facilitate separation of larger particles from the substance.

[0187] Various types of microfluidic filters known in the art can be used to remove specific particle sizes or types from the sample. Structural filters can be used for filtration, including mesh filters, microfabricated frits, pillar structures, microposts, affinity columns, or flow restrictions within channels. In one embodiment, one or more mesh-style filters can be used to separate specific particles from the sample. A mesh-style filter can mechanically prevent particles of a certain size from traveling through specifically sized holes or gaps within the mesh. Additionally, the mesh can selectively allow passage of particles based on their size, shape, or deformability. Two or more mesh-style filters can be arranged in series or in parallel, for example, to remove particles of increasing or decreasing size successively. In another embodiment, microposts, such as those described in U.S. Publication No. 2007/0264675 entitled, "Microfluidic Device for Cell Separation and Uses Thereof" filed May 8, 2007 and incorporated herein by reference in its entirety, can be included in the output region of the chip. Microposts can be included in various positions on the chip as needed for filtration. In one embodiment, if tagged particles being analyzed and directed into a specified channel or reservoir are missed by another filter or analysis device, one or more microposts positioned downstream can act as a filter to direct these particles into an additional channel or collection reservoir to ensure a larger portion are collected. In other embodiments, diffusional filtration can be used in addition to or as an alternative to structurally based filters.

[0188] A variety of techniques can be employed to fabricate the chip having channels formed therein for the separation, ordering, and focusing of particles. The technique used can be selected based, in part, on the material chosen for forming the chip. Exemplary materials for fabricating a microfluidic chip can include glass, silicon, steel, nickel, poly(methylmethacrylate) (PMMA), polycarbonate, polystyrene, polyethylene, polyolefins, silicones (for example, poly(dimethylsiloxane)), and any and all combinations thereof. Methods for forming channels within these materials are also well known in the art, and can include soft lithography, photolithography (for example, stereolithography or x-ray photolithography), molding, embossing, silicon micromachining, wet or dry