

[0039] FIG. 18 is a schematic view of a flow diverter region of the cartridge of FIG. 16.

[0040] FIG. 19 is a schematic, side view of an ultrasonic horn coupled to a cartridge for lysing of sample components according to another embodiment of the invention.

[0041] FIG. 20 is a schematic side view of an ultrasonic transducer coupled to a cartridge containing beads for lysing of sample components according to a further embodiment of the invention.

#### DETAILED DESCRIPTION

[0042] The present invention provides a cartridge for performing various operations on a fluid sample as the sample flows through a series of interconnected, interactive regions within the cartridge. The regions are located sequentially along a fluid flow path through the cartridge, so that a segment of the fluid stream is exposed to a specific operation at one region, then another operation at the next region, etc. The sample flows through the interactive regions so that it is simultaneously in contact with more than one region at a given time. The sample flow is preferably continuous, so that the operations at each region occur simultaneously and sequentially on the fluid stream.

[0043] The cartridges of the present invention allow for significantly improved processing of a fluid sample for the detection and/or analysis of chemical components in the sample, such as biological molecules. A pioneering improvement over the prior art is the ability to rapidly process a fluid sample that is larger in volume than any interactive region within the cartridge, thereby permitting increased sensitivity in the detection of low copy concentrations of analytes, such as nucleic acid. The cartridges may also be designed to automatically conduct processes, such as mixing reagents with the fluid sample, lysing, filtering, and introducing the mixture into a reaction chamber or separate reaction vessel appropriate for further processing, e.g., detection or amplification of the analyte.

[0044] Since the operations on the fluid sample are performed on the sample stream as it flows through the various regions of the cartridge, any incorporated microfluidic processing chip or other component can be very small, as much as one hundred times smaller than with the bolus-oriented approach. This allows the entire processing facility to be small, yet capable of processing relatively large fluid samples (e.g., 0.1 to 10 mL), and thus to take advantage of the unique properties of very small microfluidic chips or other fluid processing components.

[0045] In a preferred embodiment, the invention provides a device for separating a desired analyte from a fluid sample and for concentrating the analyte into a volume of elution fluid smaller than the original sample volume. The desired analyte may comprise, e.g., organisms, cells, proteins, nucleic acid, carbohydrates, virus particles, bacterias, chemicals, or biochemicals. In a preferred use, the desired analyte comprises nucleic acid.

[0046] As used herein, the term "nucleic acid" refers to any synthetic or naturally occurring nucleic acid, such as DNA or RNA, in any possible configuration, i.e., in the form of double-stranded nucleic acid, single-stranded nucleic acid, or any combination thereof. As used herein, the term "fluid sample" includes both gases and liquids, preferably the latter. The fluid sample may be an aqueous solution containing particles, cells, microorganisms, ions, or small and large molecules, such as proteins and nucleic acids, etc. In a particular

use, the fluid sample may be a bodily fluid, e.g., blood or urine, or a suspension, such as pulverized food. The fluid sample may be pretreated, for example, mixed with chemicals, centrifuged, pelleted, etc., or the fluid sample may be in a raw form.

[0047] FIG. 2 shows an example of a cartridge 101 according to a preferred embodiment of the invention. The cartridge is designed to process a fluid sample and amplify nucleic acids, such as by polymerase chain reaction (PCR). The cartridge 101 includes a sample port 103 for introducing a fluid sample into the cartridge and a sample flow path extending from the port 103 into the body of the cartridge.

[0048] The sample flow path includes a channel 105 leading from the sample port 103 to a mixing chamber 107 for mixing of the sample with lysing reagents. The sample flow path also includes a lysing chamber 119 where the sample contacts a filter to capture components, e.g., cells, spores, or microorganisms in the sample. The captured components are lysed in chamber 119. The sample flow path further includes a flow-through component 122 for capturing a desired analyte, e.g. nucleic, acid, from the sample as the sample flows through the component 122.

[0049] The flow-through component 122 is preferably a microfabricated chip having a chamber with internal microstructures formed therein. The microstructures have sufficiently high surface area and binding affinity with the desired analyte to capture the analyte as the sample flows through the chip. The microstructures preferably comprise an array of columns integrally formed with at least one wall of the chamber and extending into the chamber. Various embodiments of the microfabricated chip are described in detail below with reference to FIGS. 6-14.

[0050] In an alternative embodiment, the flow-through component 122 comprises a channel or chamber formed in the cartridge. The channel or chamber contains at least one solid support for capturing the desired analyte from the fluid sample as the sample flows through the solid support. Suitable solid supports include filters, beads, fibers, membranes, glass wool, filter paper, polymers and gels.

[0051] The sample flow path also includes a channel 135 leading to flow controllers 41A and 41B, and a channel 136 leading to a vented waste chamber 139. The flow controllers 41A and 41B are arranged to direct the sample into the waste chamber 139 after the sample flows through the capture component 122. The flow controllers 41A and 41B may be, e.g., valves, flow diverters, or fluid diodes.

[0052] A flow path for carrying elution fluid is also formed in the cartridge 101. In the preferred embodiment, the cartridge includes a storage chamber 127 for storing elution fluid. The elution flow path extends from the chamber 127 through a channel 131 and passes through the flow-through component 122, thereby releasing captured analyte from the component into the elution fluid. In an alternative embodiment, the cartridge includes a separate inlet port, in place of or in addition to the storage chamber 127, for introducing elution fluid into the cartridge from an external source.

[0053] The elution flow path diverges from the sample flow path after passing through the component 122. In this example, the elution flow path follows the channel 135 to the flow controllers 41A and 41B. The flow controllers 41A and 41B are arranged to direct the elution fluid and eluted analyte into a reagent chamber 141 containing PCR reagents. The reagent chamber 141 is in fluid communication with a reaction chamber 143 for PCR amplification.