

[0069] FIG. 40 illustrates a micro-channel structure.

[0070] FIG. 41 illustrates surface treatment schemes for the micro-channel structure.

[0071] FIGS. 42a-42d illustrates micro-channel layout designs. FIG. 42a illustrates a single channel with a zip-zag route. FIG. 42b illustrates multiple parallel channels. FIG. 42c illustrates a interconnected two-dimensional channel matrix. FIG. 42d illustrates a surface pattern to generate random flow.

[0072] FIG. 43 illustrates a fluid reservoir where a capillary is used for metering of target fluid volume.

[0073] FIGS. 44a and 44b illustrate images of probe spots and the effect of the micro-channel structure on the areas available for hybridization.

[0074] FIG. 45 illustrates use of multiple pins on top of an elastic cover slip to generate effective movement of target molecules.

[0075] FIG. 46 illustrates a group of vibrating pins inserted into the target fluid to generate movement of target molecules.

[0076] FIGS. 47A and 47B illustrate a hybridization chamber for turbulent flow and volume exclusion hybridization. FIG. 47B illustrates the inner view of the chamber in FIG. 47A.

#### DETAILED DESCRIPTION OF THE INVENTION

[0077] In accordance with embodiments of the present invention, systems and methods are provided which can facilitate interaction between probes immobilized on a substrate with target molecules in a fluid.

##### [0078] I. Probe Deposition

[0079] Probes can be immobilized on the surface of the microarray substrate by any method known in the art. For example, probes can be printed onto the surface using the capillary bundle system described herein below or the printing systems described in the following co-pending patent applications: U.S. application Ser. No. 10/080,274 entitled "Method and Apparatus Based on Bundled Capillaries for High Throughput Screening" by Shiping Chen et al., filed Feb. 19, 2002, which is a continuation-in-part of U.S. application Ser. No. 09/791,410 entitled "Method and Apparatus Based on Bundled Capillaries For High Throughput Screening" by Jianming Xiao et al., filed Feb. 22, 2001; U.S. application Ser. No. 09/791,994 entitled "Microarray Fabrication Techniques and Apparatus" by Shiping Chen et al., filed Feb. 22, 2001; U.S. application Ser. No. 09/791,998, entitled "Microarray Fabrication Techniques and Apparatus" by Shiping Chen et al., filed Feb. 22, 2001; U.S. Patent Application Publication 2002/0051979 A1 entitled "Microarray Fabrication Techniques and Apparatus" by Shiping Chen et al., filed Feb. 22, 2001; and PCT applications WO 01/62377 and WO 01/62378, which are incorporated by reference herein in their entirety as if fully set forth herein.

[0080] Printing systems described in these applications have a print head composed of one or more bundles of randomly bundled or discretely bundled capillaries. Each of the capillaries has a channel extending from the proximal

end to the distal end of the capillary and has a channel-facing wall. This bundle of capillaries has a portion where at least the proximal ends of the capillaries are immobilized in a planar matrix and a facet is formed for printing. The immobilized portion can be sufficiently rigid that it may be used to print a probe or a group of probes upon a surface with minimal or no deformation (deformation may result in portions of the probes not being printed to the surface). The immobilized portion is therefore sufficiently rigid to ensure good contact with the surface across the portion of the facet in contact with the surface. The distal ends of the capillaries may be free or may be attached to reservoirs containing probes. The capillaries include, but are not limited to, fiber optic or other light-conducting capillaries, through which light as well as liquid can be conveyed, and other flexible or rigid capillaries. Probes can also be attached to the surface using, for example, covalent bonds in accordance with various methods known in the art.

[0081] A capillary bundle 110 as depicted in FIG. 3 can be fabricated by using capillary tubes, such as those used for capillary electrophoresis. The tubes are bound at one end 102 to form a delivery head 110. The tubes may be gathered in either a random or an ordered fashion and bound, as discussed in the patent applications discussed above. The minimum number of tubes may depend upon the number of probes to be deposited. The number can be more than 100, preferably more than  $10^3$ , more preferably more than  $10^4$ , more preferably more than  $10^5$  or more than  $10^6$  or more than  $10^7$ .

[0082] The outer diameter of the capillary tubes can range from, for example, 5 to 500 micrometers, or preferably 30 to 300 micrometers, or more preferably 40 to 200 micrometers. The inner diameter of the tubes can range from, for example, 1 to 400 micrometers, or preferably 5 to 200 micrometers, or more preferably 10 to 100 micrometers. A capillary bundle as described herein may be attached or secured to a frame that is adapted to hold the capillary bundle in a print system. A delivery head may alternatively have a frame that holds a plurality of capillary bundles.

[0083] The capillary bundle has an input end 104 and an output end 102. Capillaries on the input end 104 may be left unbound and placed in contact with reservoirs, such as the wells in a microtiter plate, that hold the probes to be assayed such that the capillary can draw fluid from the well. Capillaries on the output end 102 can be tightly bound and processed to form a two dimensional array. The minimum number of tubes may depend upon the number of probes to be deposited (e.g.,  $10^3$  to  $10^7$ ).

[0084] The probes can be delivered by applying pressure to the reservoirs (as illustrated in FIG. 4) or by gravity (as illustrated in FIG. 5) or by any of the other methods discussed in the pending U.S. and foreign patent applications noted above.

[0085] Numerous methods can be used to drive fluid from its reservoir into the capillary and towards the reaction chamber. These methods can be used alone or in combination of one or more other methods.

[0086] In one embodiment, a differential air pressure can be established and maintained between the proximal and distal ends of the capillary bundles, which will translate into hydraulic pressure to drive the probe fluids. FIG. 4 illus-