

[0167] To generate effective motion in the hybridization chamber, a certain amount of "volume exclusion" (VE) liquid may be added to the hybridization chamber together with the target liquid. The VE liquid may be selected to have one or more of the following characteristics: inert, i.e., no adverse effects on dyes and probes; immiscible with the target liquid; lighter or heavier than the target liquid; and having a contact angle similar to that of the target liquid on the substrate slide. For example, one VE liquid which may be used is mineral oil.

[0168] Unlike an entrapped air bubble, the VE liquid can be selected to have similar surface tension characteristics as the target liquid. This can make it easier to move the interface between these two liquids in the chamber and to create relative movement between the two liquids. FIG. 21 illustrates the circulation of both VE and sample liquid in the chamber when the assembly is rotated in the presence of a gravitational field. In the embodiment shown, the VE liquid is less dense than the target liquid. As the assembly is rotated, gravity will draw the more dense target liquid to the bottom of the chamber, thereby displacing the VE. This movement of the target liquid can improve the circulation and mixing of the target liquid.

[0169] When the contact angles of the chosen VE liquid and target liquid are substantially different, the interface of the two liquids may increase the difficulty of causing relative movement of the two liquids using the force of gravity alone. In other cases, it may be desirable to increase the circulation of target liquid beyond the circulation provided simply through the use of gravity and rotation. In these situations, a number of methods can be used to force the VE liquid to move relative to the target liquid. A first method is to put the assembly in a centrifuge. The centrifugal force provides many times the force of gravity to move the VE and the target liquid. A second method is to use a magnetized liquid as described below.

[0170] FIG. 22 illustrates the use of magnetic forces to generate effective movement of target molecules in the hybridization chamber. In one embodiment, magnetic or magnetically reactive particles of various shapes can be added to the target liquid. A varying magnetic field can be generated in the solution to drive the particles moving in either a random or a pre-defined pattern. This moving magnetic field will cause the sample solution to flow in the same pattern. The surface of the magnetic particles can be coated so that the target molecules in the sample solution will not attach to the particles.

[0171] The varying magnetic field can be generated, for example, by using multiple magnetic pins positioned in a designated spatial pattern, such as the pattern shown in FIG. 22. A large magnet positioned under the microarray substrate can be switched on periodically to induce flow in the vertical direction. In FIG. 22, the pins are placed above the sample solution on top of the cover slip. The pin array can also be positioned below the microarray substrate, formed as part of the cover slip or the substrate, or even dipped into the sample solution when there is no cover slip present. Electric coils wrapped around the pins are energized to selectively magnetize certain pins in either a random or a designated timing and sequence. As shown in FIG. 22, the use of a designated magnetization timing and sequence can induce a flow pattern in the target fluid. In a simpler configuration, rotational

magnetic fields can be generated in the sample solution by placing a coil set commonly used in electric motors under the microarray substrate. In yet other embodiments, varying magnetic fields can be generated to induce turbulent flow of the sample solution.

[0172] To avoid the magnetic particles from scratching the probes on the substrate slide when the particles are attracted to the microarray surface due to magnetic forces, the microarray-cover slip assembly can be flipped and the cover slip positioned closer to the magnetic source. Alternatively, two separate magnetic sources above and below the microarray-cover slip assembly can be used, as illustrated in FIG. 23. Each magnetic source generates a magnetic field that moves in the same direction. They are switched on and off in turn. In this way, the particles will follow a zig-zag path bouncing between the substrate and the cover, which induces the liquid sample to flow in the same fashion.

[0173] Magnetic volume exclusion (VE) liquid may also be used to generate effective movement of target molecules during hybridization. Suitable magnetic liquids include ferrofluids and magnetorheological (MR) liquids. Ferrofluids are stable colloidal suspensions of single domain particles of ferromagnetic or ferrimagnetic materials. They have existed for more than sixty years but the concentrated liquids that are used today first appeared in 1965. Ferrofluids are formed of very small magnetic particles held in suspension in a carrier liquid by a surface active layer. The carrier liquid is selected to meet the particular application and can be, for example, a hydrocarbon, ester, perfluoropolyether, water, or other liquid compatible with the target and probe molecules.

[0174] In this embodiment, the carrier liquid of the magnetic particles should be immiscible in the target liquids. By applying a magnetic field near certain parts of the hybridization chamber, the MR VE liquid will be attracted to the magnet, as shown in FIG. 24. Moving the magnetic field in a circular fashion will drive the VE liquid to move along the same route and generate circulative flow in the sample liquid.

[0175] FIG. 25 illustrates a system in which acoustic or ultrasonic waves are applied to the surface of the cover and/or the substrate to generate surface waves to move the target liquid around the reaction chamber. The power and the frequency of the waveform synthesizer are selected so that the target molecules such as DNA/RNA molecules or the hybridized complex between the target molecules and the probes are not destroyed by the sound waves, yet the target liquid is still moved effectively. The transducer can be, for example, one of the following: PZT, loudspeaker, or any electrical energy to acoustic energy converter.

[0176] Because many biochemical molecules bear an electric charge, electric voltages can be used to drive a target molecule in the liquid sample to move toward and hybridize with its complementary probe in the microarray. FIG. 26 illustrates a specific configuration of such a hybridization apparatus. In this system, an electrode is positioned adjacent to the microarray substrate. Multiple electrode pads are provided on the cover slip. The cover slip can be made of, for example, silicon, glass, ceramic or any other suitable material. The electrode pads can be fabricated using, for example, the microfabrication technologies widely used in the semiconductor industry. These electrode pads can be provided on an outside surface of the cover slide or can be