

## LINEAR PROBE CARRIER

### RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. application Ser. No. 60/175,225, filed Jan. 10, 2000, 60/190,495, filed Mar. 20, 2000, 60/227,874, filed Aug. 25, 2000 and 60/244,418, filed Oct. 30, 2000. This application is also related to the PCT application entitled "Linear Probe Carrier," Inventors Shiping Chen, Yuling Luo, and Anthony Chen, attorney docket number 473532000140, filed on even date herewith. Each of these applications is incorporated by reference herein in its entirety as if fully set forth below.

### TECHNICAL FIELD

[0002] This invention relates generally to the field of target analysis by binding to probes, as is commonly found in DNA sequence identification. This invention also relates to arrangements of immobilized nucleic acid probes on a solid substrate. More particularly, the invention relates to packaging of probe carrier threads wherein probes are immobilized in an array alone a flexible carrier.

### BACKGROUND OF THE INVENTION

[0003] Identification of molecular structure has become very important in research and in many industries, and the analysis of biological molecules such as nucleic acids and proteins forms the basis of clinical diagnostic assays. The procedures utilized often involve large numbers of repetitive steps which consume large amounts of time. (see, e.g., Sambrook, J., et al., *Molecular Cloning: A Laboratory Manual*. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2nd ed. 1989)). Simpler and quicker analysis of molecules has been provided by the development of arrays of test sites formed on a planar substrate. Each of the test sites includes probes which bind with samples applied to the device. Such probes may be oligonucleotides, proteins, antibodies, or cell-binding molecules and the choice of probes is theoretically limited only by the possibilities of specific binding to or reaction with sample. The binding of a sample to a probe is detected, and the probe identified, thereby identifying the sample. Technology has primarily developed around the use of these two-dimensional, planar arrays, especially in the area of arrays of oligonucleotides, which have become small and dense enough to be termed microarrays.

[0004] The ability to manufacture microarrays in an efficient and cost-effective manner is of considerable interest to researchers worldwide and of significant commercial value. The importance of the microarray technology to the biotechnology industry and to the entire health care sector cannot be overstated. A microarray is capable of dramatically boosting the efficiency of traditional biochemical experiments. Tests that would have taken years can now be completed in hours or even minutes. The applications of this technology affect more than the healthcare sector including gene profiling, disease diagnostics, drug discovery, forensics, agronomics, biowarfare and even biocomputers. Various types of microarray manufacturing devices and technologies have been described.

[0005] The current direction of technical development continues to be toward ever-denser two dimensional arrays of probes on rigid substrates. This approach presents a

number of problems. First, as the number of test sites in an array is increased, the complexity of fabricating the array or pluralities of arrays is greatly increased. Second, the conventional methods of placing bio-molecules as probes on specific test sites—photolithography, mechanical spotting, and ink jetting—are time-consuming, expensive, often lack the desired accuracy and do not meet the desired size constraints. Photolithographic synthesis of probes in situ is a labor intensive technique that may not provide satisfactory accuracy and has a limited range of probe lengths. Mechanical spotting is a slow process in which the smallest test site size is limited by the nature of the process. Chemical ink jetting has an inaccuracy similar to in-situ synthesis and test site size limits similar to mechanical spotting. Third, because of the complexity and extreme precision required in manufacturing individual arrays, and the low throughput, the fabrication cost of each array is very high, often thousands of dollars for arrays containing enough probes to evaluate complex biological samples. Fourth, the expense and complexity of the reading devices for detecting probe-sample hybrids, which is already extremely high, increases with each increase in array density, and because the reader has to carry out a two-dimensional scan with a very high spatial precision (in the order of 10  $\mu\text{m}$ ), processing time for each scan also increases with increasing density of the two-dimensional probe array.

[0006] In addition, the basic operating principle of microarray involves a probe immobilized on a substrate to react with specific molecules in sample fluid. Hybridization requires providing probes with sufficient chances to meet their complementary molecules. In existing systems, this is achieved through diffusion or driving the sample fluid across the microarray. The former is a random process and the later requires complex microfluidic systems.

[0007] Hence, there is a need for an easily- and rapidly-constructed, inexpensive probe carrier which can accommodate thousands or hundreds of thousands of probes, which is capable of compact storage and use, can be manufactured at a high rate of throughput, can facilitate probe/target interaction with a high efficiency and does not require expensive and highly precise reading devices, can carry detailed information about individual probes or groups of probes on the substrate along with the probes themselves, can accommodate probes of varying lengths and degrees of complexity in customized groups, and which is compact, easy to use, and inexpensive enough to allow one-time use with resulting high accuracy.

[0008] There is also a need for improved packaging of such probe carriers whereby the required amount of hybridization fluids is minimized and large numbers of probes can be immobilized on a substrate without the concomitant increase in size as a standard two-dimensional gene chip matrix would necessitate.

### BRIEF SUMMARY OF ASPECTS OF THE INVENTION

[0009] The present invention provides a new direction and approach in making a probe carrier or probe configuration that does not require dense two-dimensional symmetrical arrays built upon a rigid substrate and also does not inherently limit the size of the probes that can be attached to a substrate. In addition, the present invention can be relatively easily fabricated through use of assembly-line-like techniques.