

Detection of Biological Molecules: From Self-Assembled Films to Self-Integrated Devices

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Detection of molecules involved with the functioning of living things impacts a broad spectrum of applications from pathogen detection to drug development and biochemically-guided medical care^[1-4]. Faced with the complexity of molecular level interactions that typically characterize biological molecules, sensing technologies win and lose: on one hand they can exploit this richness to realize the specificity required for detecting a unique analyte (e.g. small molecules, nucleic acids, polypeptides) against a complex sample background, on the other hand the complexity makes it difficult to fully control how a device will interact with minimally processed samples such as environmental specimens or blood. For example, uncontrolled physical adsorption of molecules to the surfaces of a device can lead to fouling and compromise its accuracy and performance.

Biological molecules are often detected from an analyte mixture by selective binding to a solid support. The function of the sensor is then to detect such surface binding events, to convert them (typically) to an electrical signal, and to extract information from the signal such as identity and concentration of the analyte. These functions, simple in principle, pose a number of challenges in practice. Under optimal conditions only the analyte of interest should interact with the sensor. This challenge is often addressed by rendering the sensor surface highly specific for the analyte "target" by pre-attachment of sensing "probe" molecules (Fig. 1). For example, a probe antibody or a probe oligonucleotide could be chemically immobilized on the sensor. This approach is often sufficiently effective even though perfect selectivity for a unique analyte target may remain difficult on account of complicating factors such as probe/surface interactions and nonspecific (i.e. independent of probe) adsorption of target or other molecules to the solid support. Emergence of a universal understanding of these issues is unlikely partly because they are application specific. Nevertheless, research progress has made it possible to formulate approximate guidelines for the chemical modification of sensor surfaces so as to optimize device performance. This paper will provide an overview of methods used to derivatize surfaces with biomolecular probes on silica-like and metal supports.

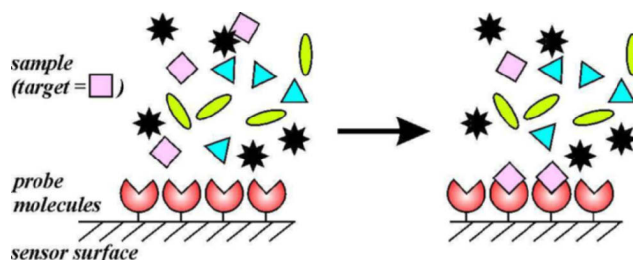


Figure 1. "Probe" sensing molecules, immobilized on a solid support (left), are used to uniquely bind "target" analytes (right).

A number of approaches have been developed for detecting probe-target interactions with the most familiar based on optical (e.g. fluorescence, luminescence, surface plasmon resonance), radiolabeling, electrochemical (e.g. amperometry, capacitance), and microgravimetric mass-based means^[5-11]. A brief survey of the advantages and drawbacks of various detection methods will be presented. One crucial consideration from the viewpoint of method selection is adaptability to parallel formats in which detection of several to thousands of analytes can be accomplished simultaneously^[12, 13]. Another is amenability to measurement replication, wherein a specimen can be analyzed multiple times to provide statistical information from which data integrity can be judged.

A complete diagnostic device could be as simple as a solid support (e.g. a polymer membrane or a glass slide) derivatized with an appropriate set of probe molecules and coupled to an external fluidic delivery and measurement system. The supports in such devices are most commonly "passive" in that the role of the solid support does not extend beyond its service as a surface to which probes are attached. Detection and data processing are accomplished by external, typically macroscopic hardware. Existing device platforms based on passive supports have met with remarkable success, for instance in highly-parallelized diagnostics such as DNA microarrays now widely employed at academic and industrial research centers. In light of this success it is intriguing to consider what technological advancements may be forthcoming in the near term, and whether they can speed assimilation of biomolecular detection into critical applications such as clinical diagnostics. One technological direction with

excellent prospects is continued integration of microelectronics and biosensing, with advantages including "active" supports with circuitry that (i) provides functionality (detection, data processing) for simplifying use and increasing device portability, (ii) allows tuning of binding event thermodynamics and kinetics, including possibility of real-time feedback to improve measurement accuracy, (iii) combines multiple, orthogonal detection modes, and (iv) takes advantage of the extensive manufacturing base of the semiconductor industry to provide affordable technology.

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