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Editorial

A Perspective on the Application of Biosensor and Lab-On-A-Chip Technologies to Biomarker Detection in Biological Fluids

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Recent years have seen a dramatic increase in efforts to enhance the accuracy and speed of existing clinical diagnostic assays, and to devise new techniques for the detection of agents and biomarkers connected to infectious, genetic and other diseases. Generally speaking, such analyses can be arbitrarily divided into tests performed in either the central clinical biochemistry laboratory or *via* point-of-care devices. (With respect to the latter, the blood glucose and pregnancy assays, which involve discardable test strips, will be familiar to many.) Biosensor technology, in principle, could provide rapid, label-free measurements, which can be conducted in highly automatable configurations. Furthermore, the possibility for multiplexing tests using generic sensing physics is certainly an attractive strategy. Microfluidic structures, or so-called "lab-on-a-chip" systems, and nanoscale detection devices could potentially offer inexpensive, speedy and highly convenient small footprint systems with huge savings notably in terms of reagent and operating costs. However, neither biosensor nor lab-on-a-chip technologies have yet to find a prominent place in the biomarker assay field. Aside from simple glucose and ion analyses, and assay of blood gases, there has been virtually no introduction of such devices into the clinical biochemistry operation, despite the considerable promise as outlined above. The dearth of biosensor devices in the clinical biochemistry laboratory also appears to be matched by the lack of employment of the aforementioned lab-on-a-chip structures. This is also the case where they may be expected to be quite prevalent such as the doctor's office, bedside or other "remote" locations. Among a number of reasons for this, it is evident that limit-of-detection and the interfering role played by the macromolecular and cellular components of blood, serum, tissue and urine, for instance, are crucial factors. These moieties tend to adsorb at the sensor-liquid interface or in the channels of microfluidic structures resulting in major problems with respect to sample handling and signal integrity. The overall term often used for this phenomenon is "non-specific adsorption", or NSA for short. For example, even if cleared of cells, a resulting plasma/serum sample will contain proteinaceous species at high concentration in the range of 60-80 g/L, whereas target biomarkers could be at a concentration in the region of ng/L (*i.e.* a difference of nine orders of magnitude). Obviously, the generation of a reliable sensor signal for a target analyte under these conditions will present an enormous detection challenge because of the NSA-induced interference problem. An example would be the unfortunate occurrence of "false positives", that is a response incorrectly interpreted as a genuine binding event. The end result of this issue, with respect to biosensor technology, is that these devices are unlikely to challenge the widespread application of clinical detection methods such as the well-established "enzyme-linked immunosorbent assay" (ELISA), at least in the foreseeable future. With regard to microfluidic devices, the occurrence of protein adsorption in channel structures is expected to cause difficulties in terms of sample processing. Furthermore, lab-on-a-chip systems require a detection component to complete the sample-handling aspect, which is expected to suffer analogous issues to that observed for biosensors.

The adsorption process in these situations will be governed by a complex set of factors including Protein structure, charge and polarity, the physicochemical properties of the biosensor interface (e.g. charge, topography and morphology, surface energy), as well as the pH and ionic strength of the particular sample under analysis. Additional complicating factors will be the occurrence of conformational changes, which can result in irreversible protein attachment to a surface, and the "Vroman effect" that governs the temporal nature of differential protein adsorption. The deleterious effects of protein adsorption to biosensors are by no means restricted to that technology. In fact, the process is also extremely relevant in the field of biocompatibility involving structures such as stents and other implantables, and external components such as those found in dialysis and bypass circuitry equipment. In this case, rather than NSA, the term "fouling" is more often employed as a generic description of unwanted surface adsorption. Unsurprisingly, the biomaterials literature is replete with numerous examples of attempts at producing "antifouling" coatings for a variety of substrates. These strategies almost universally involve research conducted with single protein species in buffered solutions, which is useful, but not necessarily relevant to biological matrices in real-world applications. One outstanding example of surface coating methodology is the use of polyethylene glycol (PEG)-based molecular systems, which are often employed in relatively thick-film configurations. Despite years of research effort, the mechanism that lies behind the antifouling properties of this chemistry remains somewhat obscure. In own research, we have shown that sub-nanometric coatings of a covalently-bound organosilane containing only a single ethylene glycol unit, such as those found repeated in PEG, is capable of very significantly reducing NSA from complex matrices such as full serum.

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On a speculative level, we believe that an intercalated water network stabilized by distal –OH groups is responsible for this effect. This chemistry is being employed with success in the reduction of NSA on acoustic wave sensors, and fouling on biomedical components.

A glance into any clinical biochemistry laboratory reveals groups of large instruments connected together with sizeable trains composed of macroscopic, robotic equipment. The employed technology is very far removed from biochip, biosensor and lab-on-a-chip devices, all of which have been routinely touted for potential application in clinical assays. More promise for these devices appears to be presented by the point-of-care marketplace, where the interest is largely in single-use, disposable systems. The issue of NSA in this application may be less severe but obviously cannot be discounted given the danger of false clinical results. Accordingly, it is clear that much remains to be accomplished before use of biosensor and lab-on-a-chip devices can be contemplated for routine clinical and domestic assays. A major aspect of this is the role played by surface chemistry.

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