Handbook of Biosensors and Biosensor Kinetics

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Preface

This is the sixth book in the series of books written by one of the co-authors (A.S.), and the second by the other co-author (N.S.). In contrast to the previous five books that dealt with just the kinetics of binding and dissociation (if applicable) of analyte-receptors on biosensor surfaces, the present book analyzes a range of biosensor features, and is aptly titled a handbook. Some of the features analyzed besides kinetics include, in chronological order: fabrication of biosensors (Chapter 3), nanobiosensors (Chapter 5), binding of the same analyte on different biosensor surfaces (Chapter 6), binding of the same analyte (glucose) to different biosensor surfaces (Chapter 7), detection of gases on biosensor surfaces (Chapter 10), and detection of analytes on arrays/microarrays/DNA chips (Chapter 11).

It is hoped that the additional areas, besides the kinetics, covered in the present handbook will help provide a better perspective of the potential of biosensors and where they may be used more effectively. Biosensors are excellent medical devices, and it is anticipated that they will be used in more and more areas to advantage, especially for the detection of biomarkers for different diseases and their diagnosis. If this handbook along with others provides (or aids in the development of) ideas for the future development of biosensors in newer areas, then its purpose is well served, and the time and effort spent in writing it is well worth it.

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CHAPTER 1

Introduction

Chapter Outline

1.1 Introduction

Biosensor applications have expanded considerably over the last few years after a modest beginning with the control application for the detection of glucose in the management of diabetes mellitus (DM). This is due to the ease of application of these biosensors to different areas of application. Some of the more recent areas of application include:

(a) Quantum dot biosensors for ultrasensitive multiplexed diagnostics (Berger, 2010).
(b) GE Healthcare have purchased Biacore™ and Microtal™ and combined the use of the SPR (surface plasmon resonance) biosensor with ITC (isothermal titration calorimetry) to provide orthogonal label-free determinations of affinity, binding kinetics, residence time, and enthalpic efficiency. They have also developed Bia2iTC software that compares outputs for both instruments (GE Healthcare, personal communication, 2010).
(c) Other interesting biosensor applications include (SPIE, Optics/Photonics in Security and Defence, 2006):
    (1) Unmanned/unattended sensors and sensor networks
    (2) Technologies for optical countermeasures
    (3) Optically based biological and chemical detection for defence
    (4) Femtosecond phenomena and nonlinear optics
    (5) Optics and photons for counter-terrorism and crime-fighting
(d) Different sensing platforms have been integrated to achieve results unattainable by a single sensor. For example, electrochemical, mechanical, electrical, and optical signal transduction have been integrated (Center for Biosensors and Bioelectronics, 2010).
(e) Recently, Silicon Kinetics, Inc. (2010) announced the development of new biosensor chips with different surface chemistries. These surface chemistries could accommodate

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carboxyl, streptavidin, benzaldehyde, and Ni-NTA for Histidine-tagged Protein A and Protein G for coupling antibodies. This was the first company that introduced the 3D biosensor surface for label-free biomolecular interaction analysis. The company indicates that their biosensor permits high throughput ranking in multiwall plates, and data-rich kinetic measurements in flow cells, using a single reader instrument and the same chemistry. The company emphasizes that its sensor permits the measurements of slow off-rates which are not measurable by traditional SPR biosensors.

(f) Uludag et al. (2010) have recently indicated that nucleic acid based recognition of viral sequences may be used for the rapid and accurate confirmation of viral infection. This is done using label-free biosensing. The authors indicate that gold nanoparticles may be used to enhance detection sensitivity. Quartz crystal microbalance biosensors may be used upon surfaces where nanoparticle oligonucleotides conjugates are complementary to surface-immobilized ss DNA probes. The authors indicate that their signal amplification assays may be used for the detection of specific DNA sequences of Herpes Simplex Virus (HSV) type 1.

More importantly, the authors developed the biosensor to understand the influence of mass transport in the flow cell (which incidentally is one of the major themes of this book), and the binding kinetics of targets to nanoparticles in solution. Other parameters analyzed include the binding geometries of the targets in the nanoparticle, and the packing of nanoparticles on the surface. All of this points to the influence of the biosensor surface characteristics, and how it may influence the binding kinetics. This is in fact one of the major themes of the book wherein the degree of heterogeneity on the biosensor surface is characterized by a fractal dimension, and how this fractal dimension influences the binding and dissociation kinetics.

The authors conclude by indicating that their analytical model permitted the determination of optimal nanoparticle diameter, concentration, and probe density. Their results were based on both numerical analysis as well as on subsequent associated experimental data. They further emphasize that their analysis suggests that the proximal contact area between the particle and the sensor surfaces, and the available capture area of the particle and the binding dynamics to this capture area very significantly influence the detection limit.

(g) Some of the more recent biosensor applications were presented at Biosensors 2010 held in Glasgow, Scotland from May 25-28, 2010 (http://www.biosensors=congress.elsevier.com). Some of the more interesting ones include:

1. Direct detection of drugs in serum with an electrochemical aptamer-based biosensor (Rowe and Plaxco, 2010)
2. The development of a novel theranostic platform for cytotoxicity evaluation of amyloid-forming neurodegenerative causative proteins (Kim et al., 2010)
3. Theranostic biochips—from biosensors to personalized medicine (Bachmann, 2010)

4. Microfabricated electrochemical probe for the detection of signaling proteins released by single cells (Corgler et al., 2010)
5. Enhancing sensitivity of molecular biosensors through self-assembly (Wei et al., 2010)
6. Detection of amyloid precursor protein (APPTTO) using spectroscopic ellipsometry and QCM techniques (Mustafa et al., 2010)
7. Biomolecule/metal nanoparticle composites on electrodes for sensing biofuel cells and photoelectrochemical applications (Tel-Vered et al., 2010)
8. Single molecule applications for high-resolution AFM topography and recognition imaging (Ebner et al., 2010)
9. Biomarker pattern analysis as an analytical system in the evaluation of an atherosclerotic rich profile (Siegel et al., 2010)
10. Biosensors: a mixed market (Neuman and Turner, 2010)

A conference held in Baltimore, Maryland from May 5-7, 2010 on, "Sample preparation for virus toxin, and pathogen detection and identification" (Mello, 2010) discussed different sample preparation procedures to assist in the detection of harmful pathogens. McLaughlin (2010) of the U.S. Army indicates that the detection and identification of biological warfare agents rely heavily on the ability to purify, enrich, and concentrate molecular targets prior to analysis. Note that the use of analytical technologies in the field is complicated or limited by available methods for processing a wide variety of sample types into a form compatible with multiple analytical technologies, such as biosensors.

Some of the presentations scheduled are on:

(a) Sample preparation and microfluidic technologies (Maricella, 2010)
(b) Point-of-test sample prep and molecular analysis (Gau, 2010)
(c) Sample preparation as a part of an integrated fluidic process for rapid diagnostics (Clarkson, 2010)
(d) A fully integrated system for nucleic acid-based detection of bacteria and viruses in biological samples at POC (point-of-care) (Bau, 2010)
(e) A novel preanalysis system for rapid, quantitative diagnostics (Feaster, 2010)

At the recent 2nd European Congress on Immunology in Berlin, Germany (from September 13-16, 2009) there were quite a few research papers including poster presentations that analyzed different biosensor applications for use in clinical laboratories, not the ones for general home-use such as the glucose biosensor. Both researchers and vendors of different biosensor applications confirmed the above view that the biosensors were being developed for clinical laboratory usage only. Very little, if any, market research or survey has been done to help develop these newer biosensors for home use. Of course, economic feasibility will still have to be discussed with the administration to bring these biosensors into home use.

Nevertheless, some of the newer biosensor applications presented at the above-mentioned Immunology Congress include:

(a) Localization and fine mapping of an antigenic site on the nucleocapsid protein of human parainfluenza virus type 3 (Sezaile et al., 2009). The authors point out that human parainfluenza virus type 3 (hPIVN3) is a respiratory tract pathogen. The current study was performed by the authors to investigate immunodominant regions of hPIV3 nucleocapsid (N) protein by using monoclonal antibodies (mAbs) raised against recombinant N protein and human serum specimens from hPIV3 infected individuals. According to the authors the present study enhances the knowledge of the antigenic structure and should facilitate the development of better diagnostic methods for hPIV3 infection.

(b) Determination of myelin basic protein (MBP)-reactive antibodies in healthy individuals and patients with multiple sclerosis (MS) using a novel highly sensitive assay (Hedegard et al., 2009). The authors point out that autoantibodies to MBP are apparently absent in sera from healthy individuals but their presence has been reported in sera from some patients with MS. The authors have developed a novel assay for anti-MBP antibodies (MBPAbs) to analyze the influence of disease-associated MBPAbs and "natural" MBPAbs in MS patients and healthy individuals, respectively.

(c) Antibodies to Aquaporin-4 in neuromyletic optica (NMO): biological relevance and use as biomarkers (Mader et al., 2009). The authors point out that NMO is a devastating neurological disease, which is clinically characterized by optic neuritis and longitudinally extensive transverse myletis (LETM). Recently autoantibodies in the serum of NMO patients have been detected. These autoantibodies target aquaporin 4 (AQP4). AQP4 is a key constituent of the blood-brain CSF (cerebrospinal fluid). This is a membrane spanning water channel protein localized mainly in the brain and spinal cord. The authors show that various assays with different sensitivity and specificity have been developed. Note that in no other organ is consistency of the internal environment more important than in the brain. In the CNS (central nervous system) a change in the composition of the interstitial fluid could lead to uncontrolled brain activity.

(d) Systematic development of a novel biomarker for diagnostic protein biochips: the rheumatoid arthritis (RA) case study (Leuking et al., 2009). The authors point out that RA is a chronic, systemic, inflammatory disease. They emphasize that diagnosis and treatment of the disease is required (almost mandatory) to prevent extensive joint damage, deformity, and functional impairment. They indicate that the diagnosis of RA patients based on cyclic citrullinated peptides (CCP) is possible with high sensitivity and specificity. However, the authors emphasize that anti-CCP autoantibodies are preferentially detected in patients with severe RA, and less frequently in patients with mild RA. Thus, it may be stated that the present panel of anti-RF and anti-CCP markers may not effectively address the heterogeneity of the disease. The authors are currently developing a novel set of diagnostic markers based on their proprietary materials. In essence,

stratified patient samples are incubated with the large collection of recombinant human proteins currently available for screening purposes to detect autoantibodies against specific targets.

(e) Acoustic biosensor for characterizing immune-cell receptor/ligand interactions (Saitakis and Giseli, 2009).

The authors point out that cells of the immune system come into contact with their environment through molecules on the cell membrane. They show that the interaction of these membrane molecules with their ligands is governed by two-dimensional (2D) kinetics and affinity. The intention of the authors was to develop a technique to analyze the binding of cell membrane molecules in their native state, that is, using whole cells. Acoustic measurements were performed by the authors to monitor in real time the binding of cell suspensions on the surface. The authors claim to have developed a simple approach to detect and to characterize whole-cell receptors interacting with surface immobilized ligands. Their analysis is label-free and noninvasive for investigating membrane interactions in the immune system.

(f) Biochemical characterization of soluble HLA-DR. A potential urinary biomarker for renal transplant rejection (Ding et al., 2009)

The authors have used a sandwich ELISA to determine the efficacy of monitoring soluble Major Histocompatibility Complex Class II (sHLA-DR) in urine for renal posttransplant patients. The authors provided biochemical characterization of the biomarker. The authors noted that a novel monoclonal antibody (mAb) generated in their laboratory was an epitope on the NH_2 domain of HLA-DR alpha chain. Finally, the authors claim that soluble HLA-DR excreted into urine is a useful indicator for kidney inflammation and their test should prove useful for posttransplant monitoring.

(g) Development of an *in vitro* sensitization assay based on monocyte-derived dendritic cells (Reuter et al., 2009)

The authors have developed an assay to assess the allergic potential of active components, and for the detection of surface marker expression changes. Their *in vitro* characterization assay is based on monocyte-derived dendritic cells. The authors state that the dendritic cells, including Langerhans cells, form a sentinel network for pathogen detection, and are the most abundant antigen presenting cells in the skin. The authors conclude by pointing out that their assay provides a basic application in assessing the allergic potential of active components.

(h) Optimization of diagnostic EILSA-based tests for the detection of autoantibodies against tumor antigens in the serum of patients with colorectal cancer (Stefatic et al., 2009).

The authors point out that colorectal cancer is one of the most common cancer types worldwide, and continues to be a serious public health problem. As can be expected, early