Review of analytical figures of merit of sensors and biosensors in clinical applications

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Although the development of clinical sensors and biosensors has increased in recent years, improvements in sensitivity, selectivity, limits of detection, fast response and miniaturization are yet to be attained. Health care appears to provide the best opportunity for sensor development. Among the wide range of different sensors and biosensors, electrochemical biosensors are the most common in the clinical field, due to their high sensitivity and selectivity, portability, rapid response time and low cost. This article provides an up-to-date overview of the analytical performance of sensors and biosensors in clinical applications by discussing recent improvements, particularly due to the impact of nanotechnology.
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1. Introduction

Thévenot et al. [1] defined "chemical sensor" as a device that transforms chemical information, ranging from the concentration of specific components to the global properties of samples, into an analytically useful signal. Chemical sensors usually contain two basic components connected in series: a molecular recognition system (receptor) and a physico-chemical transducer. When the receptor is a biological element, this device is called a biosensor, and combines biorecognition components with physical transducers for detection of target compounds. However the terms sensor and biosensor are often used with interchangeable meaning or, instead, the term "(bio)sensors" is used to refer to both sensors and biosensors. The interaction of the analyte with the biorecognition element is converted to a measurable signal by the transduction system. The signal, which may be electrical or optical, is then converted into a readout or display by appropriate hardware and software.

(Bio)sensors can be classified from the point of view of their applications, (i.e. in food safety, environmental monitoring, clinical analysis, and medical diagnosis) or on the basis of their chemical and biolog-ical-recognition element used for sensing (i.e. enzymes, antibody/antigen, nucleic acids and whole cells). DNA fragments, membrane components, organelles or intact cells have recently complemented the set of components available for bio-recognition [2]. Other types of classification, based on the transducer principle, have also been followed for reviewing (bio)sensors: electrochemical [1,3,4], optical [5,6] or piezoelectric [7] detection.

According to Luong et al. [8], the most common types of biosensor are electrochemical (including amperometric, conductimetric, impedance and potentiometric biosensors) and optical (including fiber optic and surface-plasmon resonance). Besides, the most successful application of biosensors in clinical analysis is the electrochemical determination of glucose in blood by encapsulating GOx within polyethylene on the metal electrodes [9] and measuring the amount of oxygen consumed by the enzyme. Such biosensors are now commercialized in different configurations available mostly in single-use formats for self monitoring of blood glucose [10]. Although there has been an ever-increasing interest in developing new sensors, not many have reached the degree of recognition of the glucose sensor.

Luong et al. [8] reviewed the commercialization of biosensors with emphasis on their applications in the clinical field, and they remarked that the slow, limited technology transfer could be attributed to cost considerations and some key technical barriers (e.g., sensor stability and reliability). The poor biocompatibility between the available materials and the complex nature of the clinical samples could lead to undesirable phenomena {e.g., cross reactivity, inhibition of the detection method, and non-specific adsorption of unwanted species in the samples [8]}, which could affect the accuracy, the sensitivity and the life-span of the sensor.

Significant upfront investment in research and development is a prerequisite for successful commercialization of biosensors. According to Baldini [11], a biochemical sensor is a highly interdisciplinary "object", and the development of a new sensor requires a team of scientists from different backgrounds (e.g., chemistry, physics, optoelectronics, engineering, biochemistry, and medicine).

This review paper brings together the following aspects of research on (bio)sensors, carried out during the past few years with a view on clinical applications:
(1) definition of some of the relevant analytical figures of merit;
(2) advantages and disadvantages of (bio)sensors according to their transduction principle;
(3) comparison of the analytical performance of clinical (bio)sensors, based on a database containing their analytical figures of merit organized by target analyte; and, finally,
(4) remarks on recent and promising approaches in sensing and on opportunities in research and development of clinical sensors.

It is not possible to review the entire body of information in this area, given the numerous target analytes studied by the large variety of (bio)sensors, and also the excellent reviews already published in some of the topics. However, the main aim of this review is to discuss the analytical performance of some clinical (bio)sensors in order to improve their assessment.

2. Fundamental figures of merit

In analytical chemistry, the validation of a method is an essential step for demonstrating that the results of following an analytical procedure will be close enough to the unknown true value for the content of the analyte under study. A method can be validated by assessing its figures of merit, which are those quantifiable terms that may indicate the extent of the quality of the process, and their assessment is required for ensuring the quality of results [12]. Figures of merit include concepts related to the methods and to the analyte [i.e. sensitivity, selectivity, limit of detection

(LOD) and signal-to-noise ratio] and concepts concerning the final results (i.e. traceability, uncertainty, representativity). In univariate calibrations, where the concentration of a single analyte is predicted from a single instrumental signal, the quantification of figures of merit is simple, well known and well defined [12], while, in multivariate calibrations, the increasing complexity of data makes the evaluation of figures of merit much more difficult.

In the following sections, some figures of merit for the chemical-measurement process are reviewed following the IUPAC recommendations [12], in order to contextualize their use to characterize sensor performance.

2.1. Sensitivity and selectivity for assessing analytical reliability
The sensitivity for a given analyte is defined as the slope of the analytical calibration curve, and an analytical method is sensitive when a small change in analyte concentration causes a large change in the response. Within the linear range of response for the method, the sensitivity is a well-defined value.

Selectivity is defined as the ratio of the slopes of the calibration lines of the analyte of interest and a particular interference. A method is selective when the response of the analyte can be differentiated from every other response. In this case, the method is completely able to quantify accurately an analyte in the presence of interferences, and only the analyte of interest will contribute to the measured signal.

Improvements in sensitivity and selectivity of the sensors have always been of paramount interest [13], and chemical modifications of the electrode surface (e.g., deposition of nanoparticles (NPs) and/or nanotubes (NTs) and the incorporation of enzymes in transduction system) have been identified as excellent opportunities for improvements [14].

2.2. Limit of detection for assessing analytical capacity
Usually, the LOD is the concentration or the quantity derived from the smallest signal that can be detected with acceptable degree of certainty for a given analytical procedure. This lowest amount is the signal corresponding to k times the standard deviation, s, of the blank above the mean blank value. The k value is a numerical factor chosen according to the level of confidence required, and, when a value of 3 is taken for k, that means that the probability of a signal higher than $3s$ above the blank originating from the blank is less than 5%.

Tan et al. [15] used the LOD as a figure of merit that describes the ability of a biosensor to discriminate the signal from the noise level, thus defining the signal-to-noise ratio that is the distance between the analytical signal of the analyte and the instrumental noise. Besides