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Arnaldo D'Amico · Corrado Di Natale
Lucia Mosiello · Giovanna Zappa
Editors

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Foreword

The Italian Association of Sensors and Microsystems was funded in 1995 with the scope of promoting the research and diffusing the culture of sensors in Italy. The major outcome of the association is the national conference that runs yearly from the first edition in 1996.

The 16th conference was organized by the "Italian National Agency for New Technologies, Energy and Sustainable Economic Development" (ENEA) and was held from 7 to 9 February, 2011 at the ENEA Casaccia Research Centre.

This edition gave special importance to the Metrology and Quality of Measurement. The opening presentation on *Metrology and Measurement Reliability* was held by Prof. R.F. Laitano and the third day of the conference started with a presentation on *Quality of Chemical and Biological Measurement*.

The conference was also the occasion to pay a tribute to the memory of late Prof. Giuliano Martinelli that played a significant role in the community of sensors and microsystems. Memorial lectures were given by the following distinguished colleagues: Joan Morante (University of Barcelona), Udo Weimar and Nicolae Barsan (University of Tübingen) and Giorgio Sberveglieri (University of Brescia). The session was complemented by talks given by the collaborators of Prof. Martinelli at the University of Ferrara: Maria Cristina Carotta, Vincenzo Guidi, and Cesare Malagù. Our heartfelt thanks come to the speakers that honoured, with their presence, the scientific life of Giuliano Martinelli.

The conference numbered about 230 authors from 76 different affiliations with a remarkable participation of the Academic Community, several institutes of the National Research Council (CNR), many research groups of ENEA and a significant presence of sensors companies. In an interdisciplinary approach many aspects of the disciplines have been covered, ranging from materials science, chemistry, applied physics, electronic engineering and biotechnologies.

Special thanks are given to Eng. Giovanni Lelli, Commissioner of ENEA, for his involvement and encouragement and to Eng. Marco Citterio, Director of Casaccia Research Centre, and Secretary Staff for the commitment to the conference

organisation. We would like also to thank all the authors who contributed with their papers to the success of the conference.

This Book gathers a selection of the papers presented at the conference; it contains contributions from both academic and industrial researchers providing a unique perspective on the research and development of sensors, microsystems and related technologies in Italy. The scientific value of the papers also offers an invaluable source to analysts intending to survey the contribution of Italian researchers in the field of sensors and microsystems.

Rome, Italy

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Part I
Biosensors

Chapter 1
Determination of Immunoglobulins G in Human Serum and Cow Milk Using a Direct Immunological Method Based on Surface Plasmon Resonance

Mauro Tomassetti, Elisabetta Martini, Luigi Campanella, Luciano Carlucci, Gabriele Favero, and Franco Mazzei

A new method for IgG analysis in real matrixes, such as serum and several types of fresh or powdered milks was studied using a surface plasmon resonance (SPR) apparatus in the Kretschmann configuration, obtaining satisfactory results.

1 Introduction

Within the framework of research carried out by our team aimed at developing new immunological methods to determine proteins such as Immunoglobulins G in different biological matrixes, such as serum and milk, tests performed in previous researches were based on several different immunosensors and using different transducer types: potentiometric (ISE for NH_3) [1], amperometric (amper. – tyrosinase enzyme sensor) [2], or screen printed electrodes for hydrogen peroxide [3]; our team is currently testing the feasibility of constructing a new immunosensor for IgG determination based on surface plasmon resonance (SPR). Different construction techniques and measurement geometries were used in previous researches, involving also different enzymatic markers. Furthermore, "competitive" immunological procedures were used in most cases. Conversely, the SPR (surface plasmon resonance) transduction technique used in the present research allowed "direct" measurement.

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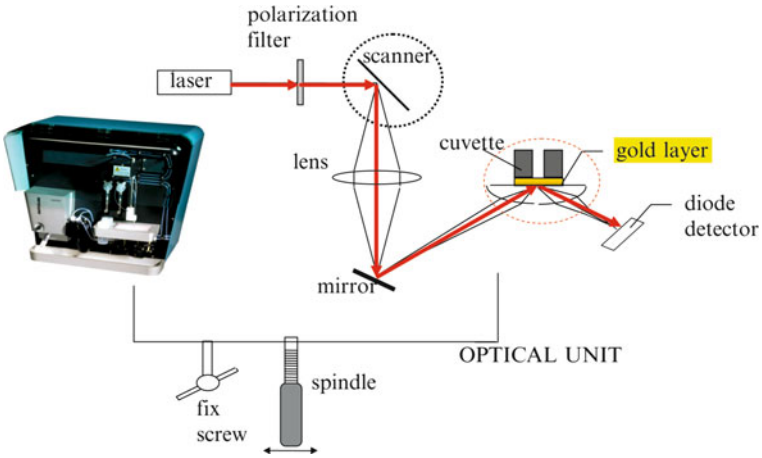

Fig. 1.1 Surface plasmon resonance instrumentation

2 Equipment

The Surface Plasmon Resonance (SPR) experiments for IgG determination were performed using an ESPRIT instrument (Echo Chemie B.V., Utrecht, The Netherlands, shown in Fig. 1.1. In this device, based on the Kretschmann configuration, the intensity of the reflected light is minimum at the angle of resonance. Angles can be measured over a range of 4° using a diode detector. The angle of incidence is varied using an oscillating mirror, which rotates over an angle of 5°, directing a polarized laser (wavelength 670 nm) on a surface (1 ×2 mm) of the disk which is the sensor through a glass semi-cylindrical prism. During each cycle the reflectivity of the mirror is measured for each movement, with a resolution for this configuration of 1 m°.

3 Method

In the experiments a sensor (Xantec Bioanalytical), consisting of a glass disk covered with a 50 nm thick Au layer superimposed on a 1.5 nm Ti layer required for the purpose of adhesion was mounted in a Teflon SPR cell. Before use, the Au surface was cleaned with a solution of concentrated H_2SO_4 and 33% H_2O_2 in a 3:1 ratio and the resulting oxide layer removed by immersion in absolute ethanol for 10 min. The Au surface, which was cleaned in this way before use, was modified by dipping it into a millimolar alcohol solution of mercaptoundecanoic acid, thus obtaining a SAM (self assembled monolayer) that makes it possible to chemically bond the selected antibody (anti-IgG) to the surface by means of a reaction with carbodiimide and succinimide. When the disk thus prepared was placed

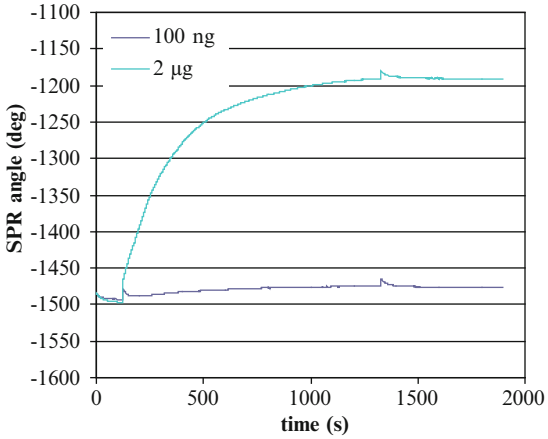

Fig. 1.2 A typical curve obtained with surface plasmon resonance for a fixed concentration of immunoglobulin G of the order of 2 µg L^{-1}

in contact with a solution containing antigen to determine IgG on its surface to form the antibody, thereby changing the resonance angle, which will be a function of the concentration of IgG in the solution. This produced a series of curves for different concentrations of IgG; an example of a typical curve obtained is shown in Fig. 1.2.

4 Results and Discussion

A calibration curve was thus constructed (see Fig. 1.3) in which also the equation of the straight line obtained is reported. The method display a linear range of between 3 and 30 nmol L^{-1} of IgG and an LOD of 1.0 nmol L^{-1}. The method measurement time, which entails the use of surface plasmon resonance, is about half an hour or lower. Also the value of the affinity constant was estimated: the K_{aff} value was found to be of the order of 10^7 L mol^{-1}.

Finally, the method (SPR) was applied to the determination of IgG concentration in human serum and cow's milk, which were respectively found to be 3,820 and 1,070 mg L^{-1}, with an RSD% <10. Lastly, this method was used for the determination of IgG concentration in goat or buffalo milk and in samples of powdered milk for babies. The values obtained are shown in Table 1.1.

It should be noted that the values are very different for the different animal species, regardless of whether fresh whole milk, frozen milk, or powdered milk are analyzed. A significantly low concentration was evidenced, for instance, when stored frozen buffalo milk was analyzed. Of course, the latter showed a much lower concentration than the sample of fresh cow milk.

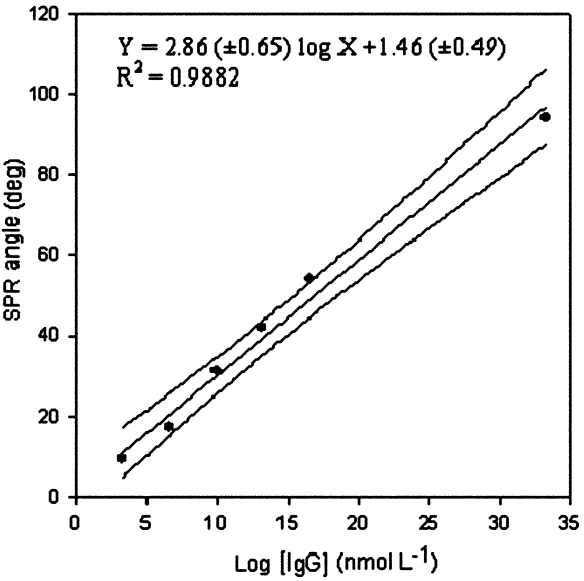

Fig. 1.3 Calibration curve obtained by the direct method based on surface plasmon resonance (SPR) for IgG determination

Table 1.1 Determination of the IgG concentration values in milk and in human serum. Values expressed in mg L^{-1}

Real samples	Surface plasmon resonance IgG concentration found (mg L^{-1}); n = 5; RSD% $\leq$ 10
Cow milk	1,070 (high quality fresh milk)
Goat milk	1,285 (whole)
Buffalo milk	450 (stored in freezer)
Powdered milk samples	650–1,000
Serum	3,820

5 Conclusions

This new "direct" method (SPR) reduces the time needed to perform the analysis, even if the same LOD value is obtained as for the classical immunosensor methods using the competition procedure [4]. It also allows the suitable determination of value of IgG concentration in several real matrices, such as human serum and goat, cow, or powdered milk samples.

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Chapter 2
Erythropoietin Detection: A Biosensor Approach*

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Erythropoietin is a glycoproteic hormone of 165 aminoacids belonging to hemopoietic growth factors. Recombinant EPO has been introduced in early '80 to treat patients with severe anemia and to reduce side effects other EPO produced in eukaryotes have been introduced and different analogs produced over years. Since 2004, when EPO alfa and beta patents were over other molecules have appeared as EPO derivatives. EPO results in the prohibited list of World Anti-doping organization (WADA) and their abuse should be controlled in sport. EPO analysis is quite difficult since the molecule has relatively short half-life, numerous isoforms and many analogs are present on the market. We will report about EPO detection in urine samples. To achieve this, antibodies were used as recognition elements in sensing developments using Surface Plasmon Resonance (SPR) as transduction principle.

1 Introduction

1.1 The Analytical Problem

Erythropoietin (EPO) is a glycoproteic hormone of 165 aminoacids (MW circa 30 KDa), belonging to hemopoietic growth factors. The total molecular mass depends on the glycosylation degree of the protein, which is quite variable, and originates from posttranslational modification, and represents the only difference between the isoforms of human EPO, all biologically active, differing in the

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