Editorial

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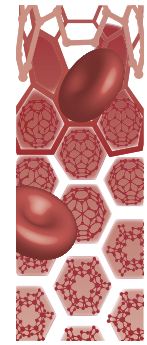

Can nanostructures improve hydrogel-based biosensors performance?

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Introduction: hydrogels & sensors

In everyday life, we use devices, modules or systems that are able to detect and monitor events or changes in the external environment. These machines are commonly named 'sensors', they find applications in a multitude of instruments and they have revolutionized our life in the last decades [1]. There are different classifications for sensors, regarding the nature of their signal transduction (e.g., optical sensors, electrochemical sensors, magnetic sensors) or the typology of their sensing mechanism (e.g., physical sensors or chemical sensors) [2]. Moreover, great interest is given to the applications of sensors and how they can be employed. In the context of interest of this work we are going to focus on biomedical applications of sensors, especially on innovative smart and soft sensors based on conductive polymer hydrogel (CPH) formulations [3].

Hydrogels are three dimensional cross-linked networks of polymer chains able to absorb and retain large amounts of water thanks to their so-called 'swelling behavior' [4]. As a result of their high-water content, porosity and consistency they present great flexibility and biocompatibility. Hydrogels represent one of the first family of biomaterials designed to be used in the human body and today they find widespread application in the biomedical field because of their potential as drug delivery vectors, scaffolds for tissue engineering and, obviously, as biosensors [5].

How hydrogels can be used as biosensors?

One of the greatest peculiarities of hydrogels is their ability to respond to external stimuli thanks to their swelling behavior and their great permeability [6]. This characteristic of the hydrogel formulation can be fine-tuned, by using specific polymeric chains, cross-linker molecules or formulation procedures in order to introduce functional groups into the framework, or by accurately modifying the mesh size, the cross-linking degree or the ionic charge of the system [7]. Typically, the output signals that can be generated by hydrogel-based sensors are various: volume-phase transition of the network, change in size or shape or variations in the optical or mechanical properties of the system are clear examples of this. On the other hand, temperature variations, pH solution changes, presence of specific molecules or free antigens are the main externals stimuli that can be sensed using these devices [6]. The methods, through which hydrogels are applied as sensors, are not unique, they can also be used as host-networks thanks to their semiwet and inert structure, they can be applied as amplification devices and finally they can be employed to control the diffusion behavior of molecules inside the matrix.

In this context, in the last decade, great consideration has been given to CPH-based biosensors formulated through the encapsulation of specific molecules (e.g., enzymes or antibody) or even living systems (e.g., cells or bacteria) in the polymeric framework [3,8]. These devices are able to exploit the interaction between the encapsulated system and a target compound to perform the sensing mechanism. Moreover, it has been demonstrated that functionalization of

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these kind of devices with nanostructures, such as nanoparticles (NPs) or nanotubes, can guarantee an improvement in their performance. In the following section we are going to analyze the potentialities of this solution, investigating their features and applications [9].

Nanostructured hydrogels-based sensors

There are various fields of application and various strategies through which hydrogel functionalization with nanostructures can improve sensor performances. Commonly, the encapsulation of nanosystems inside the hydrogel framework is able to improve the responsive ability of the device acting directly on its sensing mechanism [10]. A clear example of that is represented by CPH structures, employed in glucose sensing, functionalized with Pt NPs. These kinds of hydrogel-based glucose sensors exploit the encapsulation of glucose oxidase inside the gel framework in order to catalyze the oxidation of glucose and monitor electrochemistry properties changes in the system [11,12]. The addition of platinum (Pt) NPs magnifies this catalytic process and the presence of these nanostructures in the system reduces the diffusion length of the molecules, improving the charge transfer. As reported by Zhai *et al.* this kind of strategy strongly enhanced the performance of a polyaniline hydrogel with ultrahigh sensitivity, fast response and very low detection limit [13]. A similar working strategy exploiting Pt NPs has been employed by Li and coworkers to improve the performance of a hydrogel-based biosensor used for the detection of various human metabolites such as uric acid, cholesterol and triglycerides through different enzymes that are selectively catalytic to a specific metabolite [14]. The presence of Pt NPs is pivotal in order to improve the sensing performance of the system guarantying rapid response time, low sensing limit and better electrical properties. Studies on this kind of nanostructured hydrogel have resulted in the development of an inkjet-printed amperometric multiplexed biosensor based on a nanostructured conductive hydrogel in which the electrode material and different enzymes were printed on the electrode arrays [15]. Another very important area of use for nanostructured conductive polymer-based hydrogels is represented by their employment as immunosensing platforms for immunoassays. Rong *et al.* reported the development of polypyrrole based hydrogels/Au NPs electrodes for the detection of carcinoembryonic antigens [16]. The system was prepared by electrochemical deposition of an Au NP layer onto the surface of a polypyrrole modified glassy carbon electrode. For the intended application it is mandatory to obtain high selectivity, good responsivity and low detection limit and the Au NPs represent an important tool for achieving this. Their presence in fact improves the conductivity of the whole framework and therefore its sensing ability. Moreover, the NPs can further increase the specific area of the system, encouraging the capture of a larger number of biomolecules and in this specific case antibodies.

On the other hand, in recent years, carbon nanotube (CNT)-based hydrogels have emerged as innovative devices for many applications including bio-sensing [17]. In fact, CNT's addition into a polymeric matrix can result in an increase in the peak currents during oxidation and reduction reactions with an increase in electro-oxidation current during glucose sensing applications [16,18]. Further, the important absorption properties of nanotubes allow an ultrafast near infra-red optical response and photoluminescence of the composite hydrogels. A valuable example of this is provided by the work of Zhang *et al.* [19], in which they fabricated a thermally and optically responsive actuator based on composites of poly(N-isopropylacrylamide) loaded with single-walled CNTs. The nanotube loading (concentration 0.75 mg/ml) was demonstrated to determine a five-times enhancement in the thermal response time of the system and at the same time even the near-infrared optical response was clearly improved. Another advantage linked with the employment of CNTs is related to their high electro-catalytic activity for oxygen reduction reaction: this represents a pivotal tool in order to trigger the response of biosensors which exploit this feature (i.e., redox reaction for sensing hydrogen peroxide or its production) [17]. Finally, it has also been demonstrated that the presence of CNTs strongly improves the mechanical and modulus strength of the whole hydrogel network, guarantying a wider range of possible applications for these devices [20].

Conclusion & future perspective

In spite of significant advancements obtained in CPH-based sensor technology, lack of electrical conductivity, low mechanical strength and sensitivity issues have limited the next level applications of these devices, especially in biomedical fields. In this context, the encapsulation of nanostructures inside hydrogel frameworks represents a valuable tool to overcome many of these limitations and improve the efficacy of these systems. In fact, in the majority of the CPH, the addition of nanosystems has been demonstrated to determine an increase in the electrical conductivity of the whole framework, with beneficial effects on the responsivity of the system. Moreover, considering the formulations exploiting enzymes and catalytic reactions, the presence of a transition metal such a platinum can

magnify the enzymatic response and therefore the sensor performance. The proper addition of nanostructures can also improve the mechanical strength of the system which is often needed for various applications. It is therefore, clear how the proper functionalization of CPH frameworks with NPs or CNT can represent in many cases a turning point to obtain effective devices that can be successfully employed as biosensors.

Author contributions

F Pinelli and F Rossi wrote the first draft of the manuscript. L Magagnin contributed to the final version of the manuscript. All authors provided critical feedback.

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