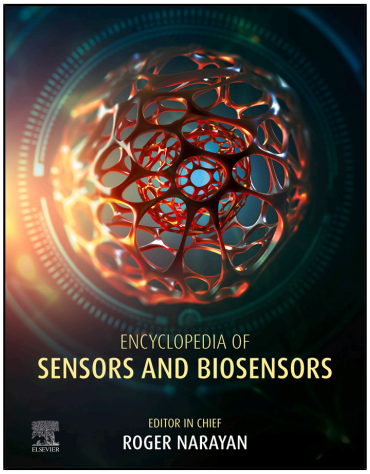

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Sensing Materials: Hydrogels

Filippo Pinelli, Tommaso Nespoli, and Filippo Rossi, Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Milan, Italy

Abstract

The changes of today's world require multiple innovations in various technological fields, including sensors. Because of this, in the last two decades new, soft sensors based on hydrogels formulations emerged, and they have been employed in several applications. Hydrogels are, in fact, incredible biomaterials, extremely hydrophilic, biocompatible, and highly swellable with a polymeric framework able to convert chemical energy to mechanical one with the ability to respond to external stimuli. These features have ensured them great recognition in the fields of sensors and diagnostics, and in this work, we will give an overview of the main developments taking place in this field.

Sensor: Definitions and classifications

In recent years, technological development, due to the need for rapid and continuous measurements, has made sensors of fundamental importance in various areas such as process control, product quality control, medical diagnosis, environmental monitoring, safety alarms, and automotive. These devices can detect the surrounding environment information about a physical parameter such as temperature, mass, pressure, charge, magnetic field, distance, position, or chemical parameter, usually a concentration, and transform it into an analytical signal (Nylander, 1985).

The most obvious division is between physical and chemical sensors: the former provides information about a physical parameter, the latter about a chemical property. However, this division is not so clear. Some sensors, like humidity sensors, combine both a chemical and a physical mechanism (Stetter et al., 2003).

As reported by IUPAC (Hulanicki et al., 1991), chemical sensors have two fundamental units: a receptor and a transducer. The receptor transforms the stimulus into a form of energy which is measured by the transducer. The transducer then converts the energy-carrying information into an analytical signal. IUPAC proposes the following possible classification of the chemical sensors according to the operating principle of the transducer.

1. Optical sensors transform the changes of optical phenomena caused by the interaction between the analyte and the receptor. The optical properties involved are different: absorbance, reflectance, luminescence, fluorescence, refractive index, optothermal effect, and light scattering.
2. Electrochemical sensors, based on electrochemical interaction analyte-electrode, include voltammetric sensors, potentiometric sensors, chemically sensitized field-effect transistors, and potentiometric solid electrolyte gas sensors.

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3. Electrical sensors, based on changes of electrical properties caused by the analyte interaction, include metal oxide semiconductor sensors, organic semiconductor sensors, electrolytic conductivity sensors, and electric permittivity sensors.
4. Mass-sensitive sensors transform a mass change caused by the accumulation of an analyte into a change of the support material's property. They are based on the piezoelectric and surface acoustic wave effect.
5. Magnetic sensors are based on changes in the paramagnetic properties of a gas that is analyzed.
6. Thermometric sensors are based on the heat generated by the chemical reaction or the adsorption reaction in which the analyte is involved.
7. Sensor-based on radiation, for example, X-, β- or Γ-radiation.

In addition to physicochemical sensors, we can also identify biosensors. IUPAC in 1999 (Thvenot et al., 1999) defined biosensors as devices capable of providing quantitative or semi-quantitative analytical information using a biological recognition system based on biochemical processes (biochemical receptor). Unlike chemical sensors, which usually employ a polymeric surface containing doping agents or coated with non-biological materials, biosensors are based on biomolecules (such as enzymes, antibodies, receptors, cells, tissues, or membranes) that are contained in the active surface as a detection component. However, these devices can be considered a subset of chemical sensors based on the same transduction methods. Both of them measure a chemical or biochemical concentration, although there are biosensors that detect whole cells (Taylor and Schultz, 1996). Applications of biosensors are, for example, glucose monitoring in diabetic patients but also in industries like the fermentation industry, detection of pathogens in food, detection of papillomavirus in humans, and many others (Mehrotra, 2016).

Hydrogels

Hydrogels are colloidal structures constituted by three-dimensional networks of hydrophilic polymeric chains that form a solid matrix capable of absorbing and holding a large amount of water (until 98%) (Singh et al., 2017), performing the so-called "swelling behavior." This peculiarity makes hydrogels semi-solid systems with liquids' characteristics, like free diffusion of solute molecules, and mechanical characteristics typical of a solid material that does not flow but is elastic (Okay, 2009; Rathod and Mehta, 2015).

One of the essential characteristics of hydrogels is their ability to respond to external stimuli thanks to their swelling behavior and excellent permeability (Pinelli et al., 2020). This behavior can be tuned by adding specific functional groups to the polymers constituting the hydrogel or varying some parameters such as the crosslinking degree, mesh size, and framework ionic charge. Because of these characteristics, one of the main applications of these structures, which is of clear interest for this work, is their employment in sensing applications. Three main ways to employ hydrogels, exploiting specific peculiarities, have been highlighted in literature (Pinelli et al., 2020):

- The semi-wet and inert structure of hydrogels can be exploited using them as a host network.
- The stimuli-responsive behavior can be exploited using the hydrogel as amplification devices and analyzing properties such as swelling degree changes.
- The ability to control the diffusion behavior of the molecules through the polymeric matrix.

Hydrogels classification

Hydrogels can be classified in different ways: for example, depending on the polymer's origin, they can be synthetic or natural. However, the primary and most widespread classification divides hydrogels based on bonds' typology between chains in the cross-linking. In this classification, two groups of hydrogels are distinguished: physically cross-linked hydrogels and chemically cross-linked hydrogels.

Physical hydrogels

In physically cross-linked hydrogels, also called reversible hydrogels, polymeric chains are held together by physical interactions and molecular entanglement, which are weaker bonds than chemical ones, leading to reversible gelation. However, in recent years there has been a growing interest in these hydrogels as they do not require the use of cross-linking agents during their synthesis. These agents are often toxic compounds that need to be removed before the application of the final system. Physically cross-linked hydrogels can be prepared with different methods working on other operative conditions (Hennink and van Nostrum, 2012; Varaprasad et al., 2017). Some of them are illustrated below.

- *Heating/cooling polymer solution*: A well-known method for producing a physical hydrogel is to heat and then cool a gelatin or carrageenan solution, leading to the synthesis of helix-formations and junction zones.
- *Freeze-thawing (crystallization)*: When an aqueous solution of polymers such as PVA (polyvinyl alcohol) undergoes a freeze-thaw process, PVA microcrystals are formed. They act as physical crosslinking sites of the network.
- *Ionic interactions*: Physical hydrogels can form by adding di- or trivalent counterions to an ionic polymer in a polyelectrolyte solution. Alginate (sodium alginate) is a well-known example of a polymer that can be gelled, adding a multivalent opposite charge such as calcium ions (calcium chloride).

- *Complex coacervation*: A complex coacervate can form by mixing a polyanion (e.g., polyanionic xanthan) with a polycation (e.g., polycationic chitosan) to a gel formation.
- *H-bonding*: Physical cross-linked gel structures can be obtained through hydrogen bonding interactions. The best example is the carboxymethyl cellulose network obtained by lowering the pH with HCl 0.1 M and forming hydrogen bonds through the carboxyl group's protonation.

Chemical hydrogels

In chemically cross-linked hydrogels, the polymeric chains are held together by covalent and irreversible bonds between functional groups. These hydrogels present a relatively high mechanical strength depending on the type concerning physical hydrogels (Varaprasad et al., 2017). Some of the different available methods used to prepare chemical hydrogels are listed below.

- *Chemical cross-linking*: New molecules, the cross-linkers, can be introduced to obtain a cross-linked hydrogel. The reaction of functional groups establishes covalent bonds between polymeric chains.
- *Grafting*: Hydrogels based on grafting are prepared by polymerizing a monomer on the backbone of a performed polymer. Grafting can be activated by the reaction of a chemical agent or by radiation.
- *Radical polymerization*: Chemically cross-linked hydrogels can also be prepared from low molecular weight monomers in the presence of a cross-linking agent. Examples of free radical initiators are ammonium persulfate (APS) or potassium persulfate.

Swelling and characterization

As previously reported, one of the essential characteristics of hydrogels, even for sensing applications, is the ability to swell a high content of water. When the hydrogel comes in contact with water or another thermodynamically compatible solvent, the solvents' molecules penetrate the polymeric network. The network's meshes start expanding, allowing more liquid to penetrate (Ganji et al., 2008). The degree of swelling can be evaluated by parameters like the volumetric swelling ratio Q or the weight swelling ratio Q_M, more easily measurable. The two values can be related using the density of the polymer and water.

$$Q = \frac{V_{wet}}{V_{dry}} \tag{1}$$

$$Q_M = \frac{m_{water}}{m_{dry}} = \frac{m_{wet} - m_{dry}}{m_{dry}} \tag{2}$$

$$Q = 1 + \frac{\rho_{polymer}}{\rho_{water}} \cdot (Q_M - 1) \tag{3}$$

The subscripts *dry* and *wet* indicate the dry polymer and the swollen hydrogel, respectively, at a particular time. The swelling process is favored by osmotic forces, while it is opposed by the elastic force of the chemical or physical crosslinks that counteract the deformation. At a specific time, the two forces balance, equilibrium is reached, and no additional swelling occurs (Ganji et al., 2008). This behavior is affected by external parameters like temperature and pH and the characteristics of the polymeric network, like the polymer's nature and the functional groups of the cross-linking degree.

The Flory-Rehner theory is the most used theory to explain the swelling behavior thermodynamically. In brief, Flory and Rehner divided the free energy of a dry polymer's swelling into two contributions: the free energy of mixing ΔG_M and the elastic free energy ΔG_{el} (Flory, 1953).

$$\Delta G = \Delta G_M + \Delta G_{el} \tag{4}$$

ΔG_M can be expressed according to the Flory-Huggins equation:

$$\Delta G_M = \Delta H_M - T\Delta S_{el} = kT \cdot (n_1 \cdot \ln \nu_1 + n_2 \cdot \ln \nu_2 + \chi_1 \cdot n_2 \cdot \nu_1) \tag{5}$$

Where k is the Boltzmann constant, T is the temperature, n_1 is the number of the solvent molecules in the solution, n_2 is the number of polymer molecules (that is zero since there are no individual polymer molecules in the network structure), ν_1 is the volume fraction of the solvent, ν_2 is the volume fraction of the polymer and χ_1 is the Flory-Huggins interaction parameter, that takes into account the free energy of interaction for solvent between the polymer and the solvent. ΔG_{el} can be expressed by analogy with the elasticity of rubber in isotropic conditions.

$$\Delta G_{el} = \left(\frac{k \cdot T \cdot \nu_e}{2}\right) \cdot \left(3\alpha_s^2 - 3 - \ln\left(\alpha_s^3\right)\right) \tag{6}$$

where k is the Boltzmann constant, T is the temperature, ν_e is the effective number of polymeric chains in the network and α_s is the linear deformation that, in isotropic conditions, is equal along with the three coordinates ($\alpha_x = \alpha_y = \alpha_z = \alpha_s$). Considering that the two contributions at the equilibrium are equal, after some mathematical steps (Flory, 1953), we can derive the Flory-Rehner equation.

$$-\left(\ln(1-\nu_2)+\nu_2+\chi_1\nu_2^2\right)=\frac{V_1}{\bar{\nu}M_C}\cdot\left(1-\frac{2M_c}{M}\right)\cdot\left(\nu_2^{\frac{1}{3}}-\frac{\nu_2}{2}\right) \tag{7}$$

where ν_2 is the volume fraction of the polymer in the swollen state, χ_1 is the Flory-Huggins interaction parameter, V_1 is the molar volume of the solvent, $\bar{\nu}$ is the specific volume of the polymer, M_c is the average molecular mass between crosslinks and M is the number average primary molecular weight.

Theories as the Flory-Rehner one and experimental techniques make it possible to determine and relate the characteristic parameters of a hydrogel to each other (Peppas et al., 2006). In particular, the most important parameters used to characterize a crosslinked hydrogel network are three (Lin and Metters, 2006): the polymer volume fraction (ν_s, or ν_2 in the equations above), the average molecular weight between two crosslink points (M_c) and the mesh size (ξ).

The polymer volume fraction in the swollen state (ν_s) quantifies the amount of water absorbed in the hydrogel. It is described as the ratio between the volume of the polymer (V_p) and the volume of the swollen gel (V_g): it is also a reciprocal of volumetric swollen ratio (Q).

$$\nu_s=\frac{V_p}{V_g}=Q^{-1} \tag{8}$$

The average molecular weight between two adjacent crosslinks (M_c) quantifies the degree of crosslinking of a hydrogel. The mesh size (ξ) is a measure of the distance between two adjacent crosslinks and it is used in describing the size of the pores. It can be calculated with the following equation.

$$\xi=\nu_s^{-\frac{1}{3}}\cdot C_n\cdot\left(\frac{M_c}{M_r}\right)^{\frac{1}{2}}\cdot l \tag{9}$$

Where M_r is the molecular weight of the monomeric repeating unit, and C_n is the Flory characteristic ratio, which is a constant for a given polymer-solvent system, and l is the bond length along the polymer backbone.

Mechanical properties

A mechanical and rheological assessment is very important for any application, including sensors. The mechanical properties of a hydrogel are strongly dependent on the degree of crosslinking: increasing the degree of crosslinking, a stronger hydrogel is obtained though the structure is more brittle, and the elongation and swelling ability decrease (Das, 2013). Therefore, there is an optimal value of the degree of crosslinking that allows obtaining the compromise between mechanical strength and elasticity required by a hydrogel's specific application. The preferred mechanical properties can also be achieved by adding specific polymer, co-monomer, and crosslinkers (Bashir et al., 2020).

Hydrogels in the swollen state present a viscoelastic behavior, and they have both a viscous and elastic characteristic. While solid elastic material and viscous liquid are mathematically characterized with the Hooke's law and the Newton's law, hydrogels present a transitional behavior. They can be mechanically tested with different techniques such as compression and tension analysis, or oscillatory tests were done using a rheometer. With this instrument, two other parameters can be measured: the storage modulus G′ and the loss modulus G″. The storage modulus G′ [Pa] measures the deformation energy stored in a sample during a shear process, then released during the reformation process. Therefore, G′ represents the elastic behavior of the hydrogel. The loss modulus G″ [Pa] is instead the measure of the energy lost in the shear process, and it represents the viscous behavior of the sample (Mezger, 2006). Hydrogel is characterized by an elastic modulus that exhibits a pronounced plateau extending to time at least of the order of seconds and by a loss modulus that is smaller than the elastic modulus in the plateau region (Almdal et al., 1993).

Responsive behavior

Intelligent materials such as hydrogels, due to their characteristics previously explained, can be beneficial for many applications. Being interested in the sensing field application, as already mentioned, a fundamental characteristic worth investigating is the stimuli-responsive behavior. The nature of the stimulus can be physical (temperature, pressure, strain, light, electrical and magnetic fields), chemical (pH variations, presence of ions and molecules), and biological (presence of biomolecules or antigens). Physical stimuli influence molecular interactions, while chemical and biological stimuli generally influence the intramolecular interactions between polymer chains. In any case, the effect induced by the stimulus to the hydrogel is macroscopic. It generally can be a volume phase transition, characterized by a change in the degree of swelling (Dušek and Dušková-Smrčková, 2020), a change in shape, in size, in its optical, wettability, electrical, and mechanical properties (Echeverria et al., 2018). Particularly in volume phase transition, an enormous change of volume can be induced by a tiny stimulus variation. This can be interesting for applying hydrogel as sensors, actuators, amplifiers, and so on (Shibayama and Tanaka, 1993). For example, some hydrogels composed of thermo-sensitive polymers exhibit a transition when the temperature reaches a critical value. Other hydrogels that are based on polyelectrolytes swell or shrink when pH crosses a certain value.

Light-sensitive hydrogels present some advantages over other stimuli-responsive hydrogels. Among different stimuli, light is noninvasive. It does not require contact with the material and has low thermal effect (Unger et al., 2017). This kind of hydrogel is usually composed of a polymeric network and a photoreactive moiety. The photochromic molecule captures the optical signal

and converts it into a chemical signal through a photoreaction (photoisomerization, photocleavage, and photodimerization) (Tomatsu et al., 2011).

The redox-responsive hydrogel can reduce or oxidate the molecular constituents through a chemical or an electrochemical activation. These structures are commonly constituted of conducting polymers (e.g., polypyrrole and polyaniline). The mechanism involves the oxidation of a portion of the subunits within the polymer backbone, leading to an influx of counterions to balance the formed charges and the material's swelling (or deswelling) (Greene et al., 2017).

Analyte-responsive hydrogels can detect and recognize different molecules, including inorganic ions, carbohydrates, thiols, biomolecules, and gasses. The interaction between the hydrogels and the analyte leads to observable effects such as optical changes, swelling, shrinkage, gelation, collapse (Lim et al., 2020a), electrical resistance changes, and others. In traditional polymer systems, an analyte-responsive behavior can be achieved and tuned by incorporating functional monomers that form preferential interactions with the interest molecules. Alternatively, biomolecules with a high affinity for an analyte can be incorporated into the hydrogel to confer recognition capacity (Culver et al., 2017).

Finally, also electric current can be used to induce responses to hydrogels that are usually made of polyelectrolytes and, in the presence of an electrical field, shrink, swell, and change in shape. The result may differ depending on the different situations: for example, the hydrogel can be in contact with the electrode or not, and electrolytes may be present or not (Qiu and Park, 2001).

Some of the essential stimuli-responsive behavior will be illustrated deeper in the following section.

Hydrogel-based sensors

Thanks to all the features described above, hydrogels can be used as sensing materials to recognize a physical, chemical, or stimulus. Furthermore, due to hydrogels' peculiarities, sensors based on these biomaterials present some advantages over conventional sensors. For example, they can be used for emerging applications such as wearable sensors in health monitoring, disease diagnostic, and environmental safety (Sun et al., 2021). Almost all hydrogel sensors consist of two main parts: the hydrogel and the transducer (Van Der Linden et al., 2003). The transducer, as we said above, converts the response of the hydrogel into an analytical signal. In this section, we will explain in detail the response, as mentioned earlier mechanisms of hydrogels to different stimuli, and show some examples of hydrogel-based sensors.

Physico-chemical sensing mechanism

Among the articles in literature, we can find some overviews, such as those published by Buenger et al. (2012) and, more recently, by Pinelli et al. (2020), which explain in detail the response mechanism to a physicochemical stimulus and their application in the sensing field. Several different hydrogels are used to function as the sensing element of physical or chemical stimuli: temperature, pH, stress, pressure, humidity and presence of gas.

Temperature sensors

Temperature-responsive hydrogels are certainly among the most studied. They are composed of polymers that exhibit a temperature-induced transition between a state of preferential polymer-water interaction and a state of preferential polymer-polymer interaction (Tokarev and Minko, 2009). This transition temperature, at which it is possible to observe a phase change between the polymer and the solvent, is called critical temperature (Tcr) or volume phase transition temperature (TvPT) (Echeverria et al., 2018). Some hydrogels present phase separation above a critical point, the lower critical solution temperature (LCST), while others below a critical point, the upper critical solution temperature (UCST).

Temperature sensors need to detect the exact temperature in a variety of different conditions. For this reason, LCTS polymeric systems, which exhibit a sharp and tunable entropy driven collapse at a critical temperature, are of great interest. Poly(*N*-isopropylacrylamide) (PNIPAM), that present this characteristic, is the main polymer used to produce thermo-responsive hydrogels. The output signal can be tuned modifying the formulation of the hydrogel. In this sense two families of hydrogels, that exploit their optical properties, seem very promising: hydrogel photonic crystals (PCs) and intelligent polymerized crystalline colloidal arrays (IPCCA).

PCs (Hou et al., 2018) are materials in which the dielectric constant is varying periodically and this determines the creation of a photonic band structure that electromagnetic waves may or may not proceed depending on their wavelength. Applications of PCs in sensing take advantage of changes in this structure due to an external stimulus. The incorporation of a thermo-responsive material in PCs makes the entire system responsive to temperature changes. On the other hand, IPCCA (Li et al., 2016) are a crystal colloidal array of polymer spheres polymerized in a hydrogel matrix. This structure, like PCs, diffracts the light generating an intense color. Incorporating a temperature-sensitive polymer, IPCCA becomes an ideal candidate for temperature sensing. In fact, every temperature change induces a volume phase transition, and this produces color changes. In addition to these two families, in the last years new types of hydrogel-based sensor were developed. In literature we can find many applications of poly(*N*-isopropylacrylamide) (PNIPAM) hydrogels in combination with plasmonic nanoparticles as thermosensitive colorimetric sensors due to their low critical solution temperature close to the temperature of human body and to a significant and reversible volume transition.

However, other technologies are also used in addition to color changing sensors and optical sensors. Li et al. (2020a,b) for example developed a temperature sensor based on a modified polyvinyl alcohol hydrogel with silver nanofibers (AgNWs) that

exploit the conductivity, that it has shown to be linearly correlated to temperature increase. In fact, they demonstrated that as the electron motions become more intense and their energy becomes higher when temperature increases, they are allowed to pass through some uncontacted AgNWs. This hydrogel-based sensor showed an error range of commercial thermometers (less than 2 °C), good repeatability, good biocompatibility but poor mechanical properties. For this reason, Double-Network (DN) hydrogels, composed of two polymers, a rigid and brittle polyelectrolyte and a soft and ductile neutral polymer (Chen et al., 2015), have attracted more and more researcher due to their high mechanical strength, toughness and modulus. For example An et al. (2020) developed a temperature sensor based on multi-wall carbon nanotubes (MWCNTs) composite polyacrylamide/Fe^{3+}-polyacrylic acid DN hydrogels able to combine flexibility, thermal sensitivity and self-healing ability. The response to temperature changes of the hydrogel-based sensor proposed by Li and co-authors in their work is illustrated in **Fig. 1**.

Pressure and strain sensors

In the last years pressure and strains hydrogel-based sensors became quite popular because of the increasing interest in new technologies such as electronic skins, health monitors, and human-machine interfaces. Commonly, external stress acting on hydrogels induces a change in shape or size, or volume, and in other functional properties such as the electrical conductivity in conductive hydrogels, permeability, and viscosity (Zhang et al., 2020) due to the rearrangement of the network. These hydrogels are characterized by intrinsic flexibility, high sensitivity, and great repeatability that guarantee their execution both in single specific pressure measurement and cyclic strain evaluation.

An example of this type of hydrogel-based sensor is provided by Zhu et al. (2020). They developed an ionic conductor hydrogel synthesized with interpenetrating sodium carboxymethylcellulose micro-sheets in a polyacrylamide network. Thanks to interactions, they obtained a system characterized by great physical and mechanical robustness, high adhesion efficiency, excellent

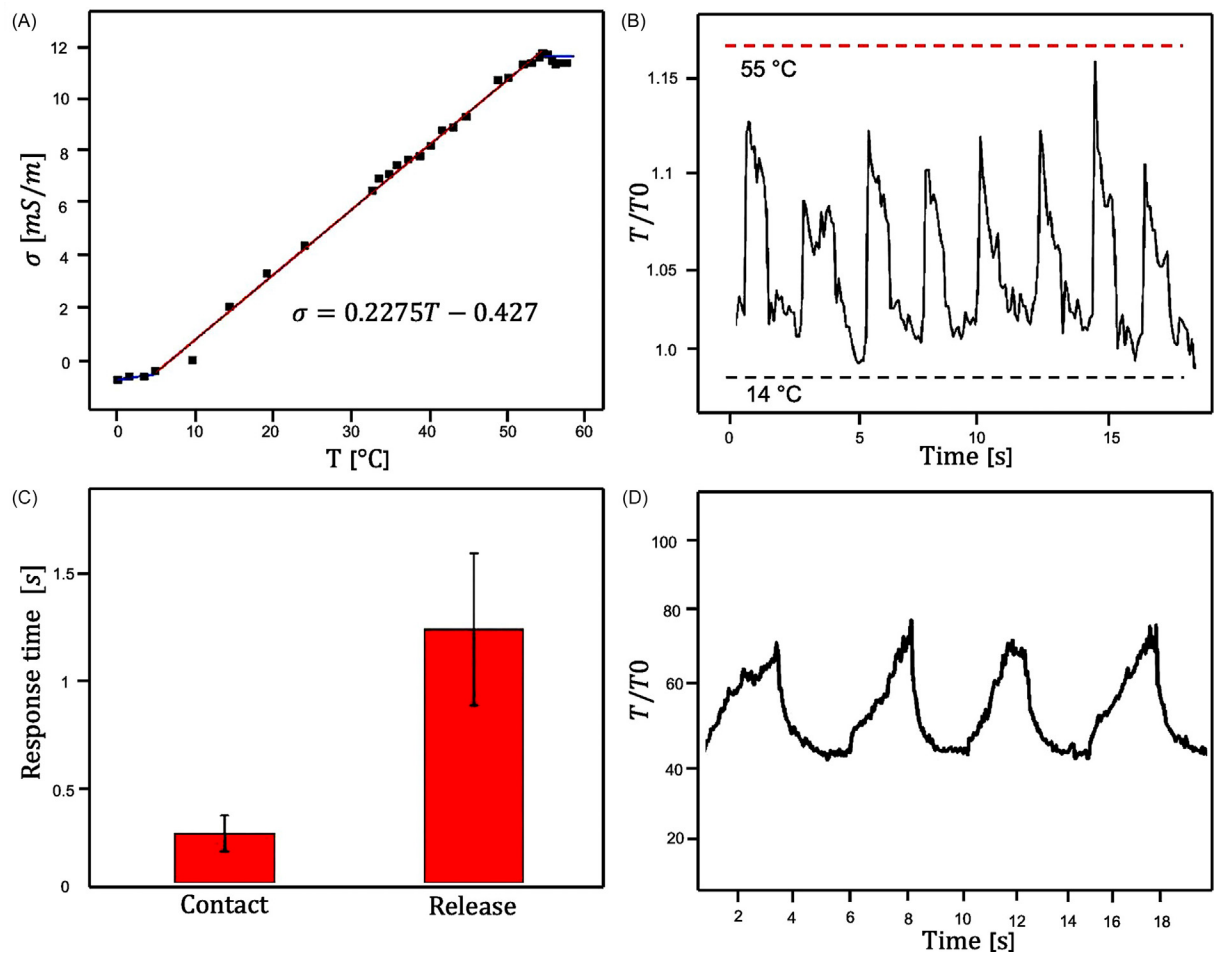

Fig. 1 (A) Linear relationship between electric conductivity of the PGN gel and temperature. (B) Current changes periodically placing the PNG gel between 14 °C and 15 °C. (C) Response time for contact (temperature increase) and release (temperature decrease) in Figure b (error bars, S.D.; $n = 3$). (D) Current changes induced by finger contact under the environment of 14 °C. Reprinted with the permission of Elsevier: Li Y, et al. (2020b) Hydrogel-based temperature sensor with water retention, frost resistance and remoldability. *Polymer* 186: 122027. doi: 10.1016/j.polymer.2019.122027.

repeatability, sensitivity, and nearly real-time response. The hydrogel was encapsulated in an elastic substrate, and Cu foil was attached for electrical connection. This hybrid hydrogel has a potential application as a wearable strain sensor that, as illustrated in Fig. 2, can monitor and distinguish different human motions, from large strain to small pressure changes due to human breath.

Zhang et al. (2019a,b) proposed another example of a hydrogel-based strain sensor. They developed composite hydrogels entrapping MXene nanosheets, which are kind of transition metal carbides or carbonitrides, in poly(*N*-isopropylacrylamide) (PNIPAM) hydrogel matrix and in physically cross-linked hydrogel. These hydrogels showed excellent mechanical properties and conductivity tests confirmed the potential application as compressive strain sensors.

pH Sensors

Another high studied category of responsive hydrogels is that of pH-responsive hydrogels. These systems are made of polymers that contain pendant acidic (e.g., carboxylic and sulfonic acids) or basic (e.g., ammonium salts) groups (Qiu and Park, 2001). These polymers containing many ionized groups are known as polyelectrolytes, classified as anionic, cationic, or amphiphilic, and they can release or accept protons in response to change of environmental pH leading to a volume phase transition. In the case of a polyanionic gel, the ionization of acid groups obtained by increasing pH (above the pK_a of the acidic groups) of an aqueous solution causes the production of fixed negative charges on polymer chains and of positive mobile charges in the solution. As a result, there is an increase in the hydrophilic nature of the hydrogel, in the number of fixed negative charges, and in the repulsion between the polymeric chains leading to a swelling of the hydrogel. Vice versa, when pH is lowered (below the pK_a of acidic groups), protonation occurs, hydrophobicity increases, the number of fixed negative charges decreases, and hydrogel shrinks (Rizwan et al., 2017). In the case of a polycationic gel instead, the response is the opposite. The technologies of the transducer that convert the non-electric swelling behavior into an evaluable signal for pH value detection can be various: changes in holographic diffraction wavelength in optical Bragg grating sensors, shift of the resonance frequency of a quartz crystal microbalance, in microgravimetric sensors, a bending of micromechanical bilayer cantilevers and deflection of silicon membranes in piezoresistive pressure sensors.

An example of a hydrogel-based pH sensor is proposed by Shin et al. (2010), who prepared a photonic crystal pH sensor polymerizing hydrogel in the interstitial space of inverse opal structure. The same authors, in another article (Shin et al., 2012), proposed an improvement of this formulation using various vinyl monomers containing acidic or basic substances: acrylic acid, vinyl phosphonic acid, vinyl imidazole, and dimethylaminoethylmethacrylic acid were respectively copolymerized with hydroxylethylmethacrylate via UV-initiated photopolymerization. They obtained four different inverse opal colorimetric sensors, which, according to

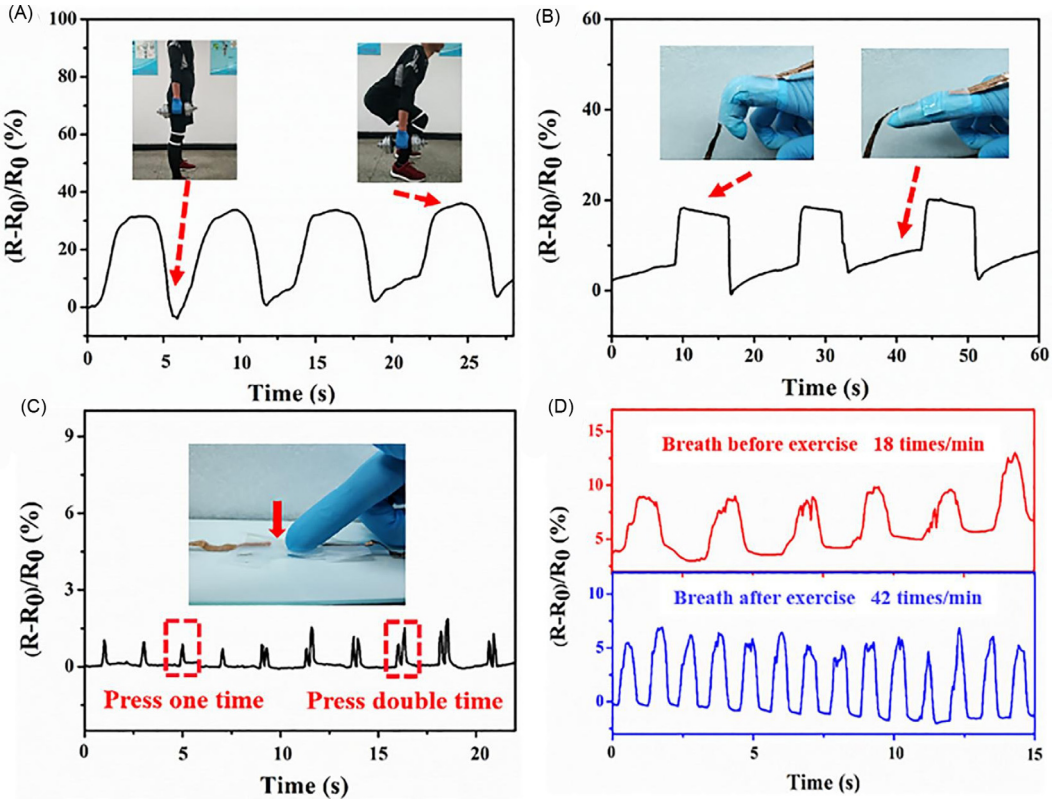

Fig. 2 Recorded resistance variations of the hydrogel system (A) adhered onto the knee when squatting and stand up, (B) adhered onto the finger when bending and straightening, (C) pressing the hydrogel one and two presses at a time, and (D) breathing air against the hydrogel before and after exercise. Reprinted with the permission of Elsevier: Zhu T, et al. (2020) A semi-interpenetrating network ionic hydrogel for strain sensing with high sensitivity, large strain range, and stable cycle performance. *Chemical Engineering Journal* 385: 123912. doi: doi:10.1016/j.cej.2019.123912.

their swelling behavior, determine different responses depending on the substituents inside the structure. This typology of hydrogel-based sensors showed good reproducibility in a wider spectrum of applications with respect to the previous formulation.

Other types of pH sensors use a bending plate transducer with a pretty different sensing mechanism. In these sensors, applying an external pH solution causes a swelling pressure (p_{sens}) from the sensitive hydrogel to the plate that deflects. Since in open-loop hydrogel-based pH sensors, the performance is often limited by the slow cooperative diffusion process, Deng et al. (2018) developed, to overcome this drawback, pH sensors with force compensation. This new sensor exploits the compensation pressure from an actuator (p_{actu}) that can suppress hydrogel swelling, accelerate the diffusion process within the hydrogel and improve the dynamic behavior of the sensor. In their work, they developed a pH-responsive hydrogel based on polyvinyl alcohol and polyacrylic acid with a weight ratio of 8:1, and a micro-actuator with a high energy density based on a thermosensitive hydrogel. This type of solution, after a formulation modification, can be applied in other sensing applications such as chemical or biochemical bending-plate-based sensors.

Some pH sensors instead use other technologies such as quartz crystal microbalance (QCM). Sannino et al. (2007), for example, realized a spin coating over QCM plates with cellulose-based hydrogels to obtain a smart hydrogel sensor able to recognize small variations of pH and ionic strength in a water solution.

Ionic sensors

To make hydrogels sensitive to a specific ion dissolved in a solution, it is necessary to functionalize them by attaching to the polymers specific groups that selectively bind to the ion. For example, a very common approach is to incorporate crown ethers into the hydrogels, which selectively form charged complexes with a variety of ions. This brings free charges in the hydrogel network, leading to hydration and swelling (Van Der Linden et al., 2003). A significant example of this procedure is provided by Zhang et al. (2018).

They developed a K^+ ion-sensitive hydrogel based on polyethylene glycol methacrylate and acrylamide copolymer (P(PEGMA-co-AM)) functionalized with 18-crown-6 ether by employing surface-initiated polymerization. The sensor for potassium detection and monitoring is realized by synthesizing this hydrogel with quartz crystal microbalances. K^+ formed a coordinate bond with oxygen atoms of 18-crown-6 ether, leading to a shift in the frequency of the microbalances. In particular, with an increase of potassium chloride (KCl), a gradual decrease of the frequency is observed. This system showed a rapid response time, high reusability, sensitivity, and selectivity to K^+ ions compared to other cations such as Na^+, Ca^+, Mg^{2+}, and NH_4^+. On the other hand, Ozay and Ozay (2013) developed a sensor for the naked-eye detection of Fe^{3+} ions. They synthesized a hydrogel using 2-hydroxyethylmethacrylate (HEMA) and acrylamide (AA) as primary monomer and N-(Rhodamine-6G)lactam-N0 acryloylethylenediamine (RH6GAC) as comonomer. They observed that, as ion concentration increased, the color intensity of the hydrogel increased. UV-analysis allowed quantification of ion concentrations (**Fig. 3**).

On the other side, there are new generation nanomaterials emerging in recent years that can become interesting tools for sensing application. Quantum dots (QD) (Reshma and Mohanan, 2019), for example, thanks to their properties such as photostability, high quantum yields, and broad adsorption bands, represent an innovative solution for fluorescent-based sensing applications. However, in order to perform fluorescence measurements, QDs need to be mixed with the target aqueous sample. Polymeric hydrogels, allowing the immobilization of the QDs without affecting their properties and permitting the penetration of analytes, represent a suitable matrix for QDs encapsulation. As reported in work provided by Zhou et al. (2018), QDs have been demonstrated to be a promising sensor probe for the detection of different heavy metal ions. They developed, for example, a ratiometric fluorescent sensor for real-time detection of Fe^{3+} ions based on QDs-doped hydrogel optical fiber. A hydrogel-based on polyethylene glycol diacrylate (PEGDA) was used to incorporate two types of QDs with two different photoluminescent wavelengths. The first one was coated with thioglycolic acid (TGA) and exhibits green emission (gQDs), while it was capped with N-acetyl-L-cysteine (NAC) and exhibited red emission (rQDs). The rQDs were selectively quenched by the Fe^{3+} ions diffusing into the matrix, while gQDs were insensitive to metal ions, exhibiting a stable fluorescent emission, and they served as reference. Ratiometric detection of the fluorescence intensities of the two QDs allowed a quantitative and selective detection of Fe^{3+} ions with a linear range from 0 to 3.5 μM.

Gas sensors

The rapid development of our society in recent years has caused an increase of pollutants produced by industry and agriculture, including carbon oxides (CO_x), nitrogen oxides (NO_x), sulfur oxides (SO_x), and ammonia (NH_3), which are seriously damaging the environment and the human health. Moreover, some gasses are considered a biomarker for human diseases: for example, NOx is a biomarker of lung infections and of bowel diseases. Therefore, gas detection has an important role in hazardous monitoring, human healthcare, and food spoilage monitoring (Guo et al., 2019). Hydrogels are a very interesting material for application in the gas detection field as they have some advantages over conventional metal oxide-based gas sensors that present some drawbacks like high working temperature and low sensitivity. In fact, they are capable of combining many features such as selectivity, responsivity, and biocompatibility. We can divide hydrogel-based gas sensors into three families: (I) hydrogels used as passive protection coating for a primary sensor/electrode, (II) hydrogels modified by gas sensitive molecules that make the whole system sensitive, and (III) hydrogels that exploit their swelling behavior for gas detection.

Hydrogels belonging to the first group mainly constitute a supporting element that can improve the performance of the real sensor due to some characteristics such as anti-adhesive and protein repellent ability. For example, Oh et al. (2006) synthesize an internal hydrogel separation layer of a planar multielectrode nitric oxide (NO) sensor. The sensor consisted of a platinized working electrode and a silver paint reference electrode coated with a thin silicon rubber gas permeable membrane. The Pt electrode

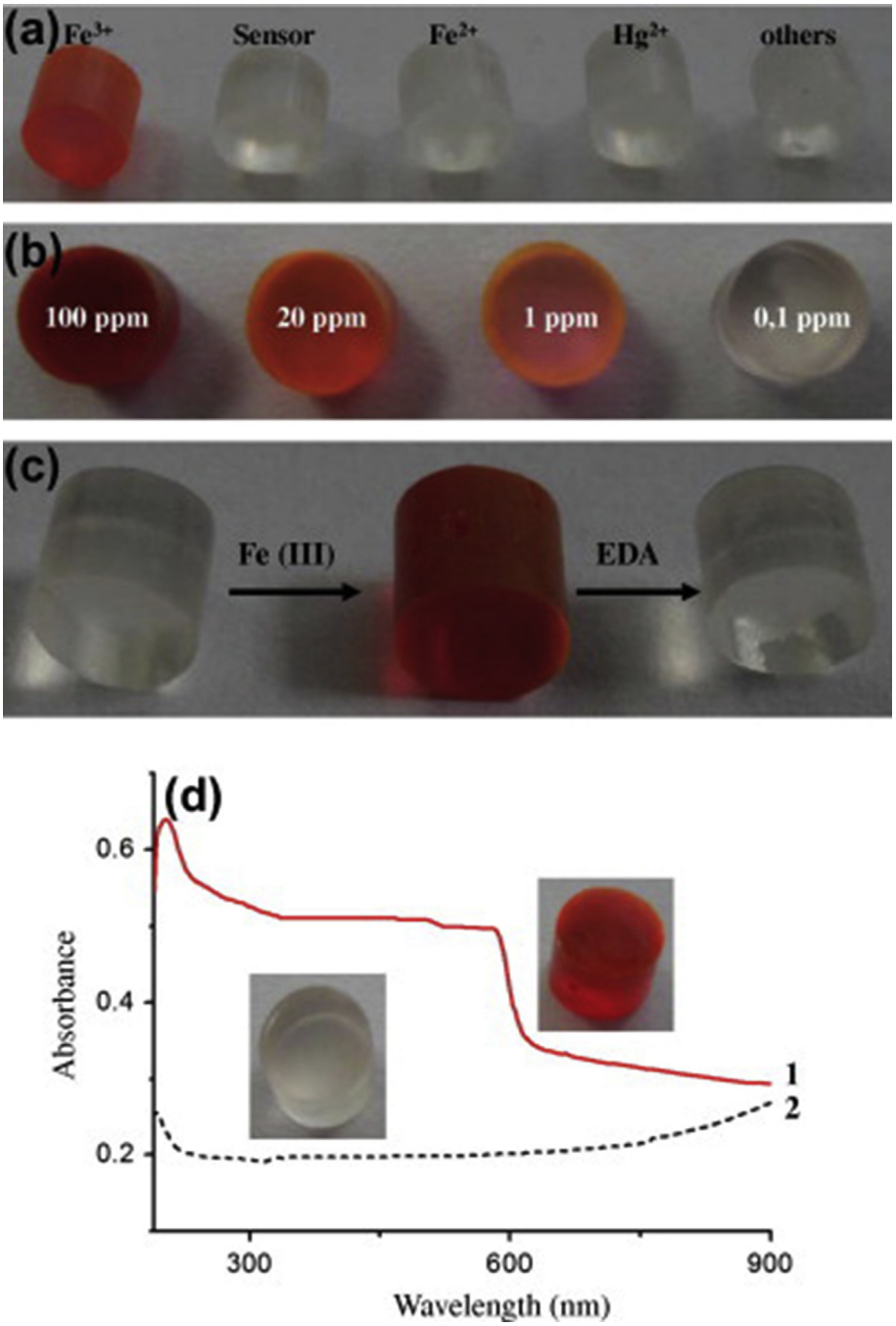

Fig. 3 Color changes of p(HEMA-co-RH6GAC) hydrogel (A) in the presence of 1 ppm in 100 mL of different metal ions, (B) in the presence of a different concentration of Fe^{3+}. (C) The ability of this hydrogel system to be re-used. (D) UV-Vis spectra of the specific initial hydrogel (1) and with Fe^{3+} (2). Reprinted with the permission of Elsevier: Ozay H and Ozay O (2013) Rhodamine based reusable and colorimetric naked-eye hydrogel sensors for Fe3+ ion. *Chemical Engineering Journal* 232: 364–371. doi: 10.1016/j.cej.2013.07.111.

and membrane are separated by an internal hydrogel layer. They demonstrated that this ultramicroelectrode sensor could be an appropriate device for determining steady-state surface NO concentration and that the hydrogel layer is able to protect the electrode. Puttasakul et al. (2019) proposed the application of a polyacrylamide (PAAM) gel as an electrochemical gas sensor for explosive vapor detection due to the high porosity showed and the ability to absorb explosive vapors. The sensor was made from PAAM, a gel on screen-printed gold electrode connected to the potentiostat through which it is possible to carry out electrochemical measurements. The authors demonstrated that the gas absorption on the system increased the electron transfer reaction. The derivative analysis of the signal was unique for each chemical, and this demonstrated the usefulness of this system in the detection of explosive materials.

The second group of the hydrogel-based gas sensor is characterized by the addiction of gas sensing molecules, including fluorescent dyes and photonic crystals. Wu et al. (2018), for example, developed fluorescent dual pH and oxygen sensors for in situ and high-throughput monitoring of oxygen respiration during microbial cell growth. For the synthesis of the hydrogel matrix, poly(2-hydroxyethyl methacrylate)-co-polyacrylamide (PHEMA-co-PA) were used. An oxygen probe derived from Pt(II)meso-tetra(pentafluorophenyl)porphine and a polymerizable pH probe derived from fluorescein were chemically conjugated to the hydrogel matrix. Hong et al. (2013) instead developed an inverse opal photonic hydrogel for CO_2 sensing, using dimethyl aminopropyl methacrylamide (DMAPMA) as a functional monomer. Since CO_2 can react with amine, they predicted that, bubbling a stream of CO_2 through a photonic gel with amino groups, may significantly shift the diffraction light.

Among the hydrogel belonging to the third category introduced above of hydrogel-based gas sensors we can distinguish sensors for CO_2 detection based on Severinghaus principle. This strategy exploits the pH changes in an electrolyte solution induced by CO_2 diffusion that can be sensed by a pH sensitive hydrogel. For example Herber et al. (2005) developed a technology for carbon dioxide detection based on pH responsive hydrogel, that is synthesized by polymerizing the monomer dimethylaminoethyl methacrylate (DMAEMA) and comonomer 2-hydroxyethyl methacrylate (HEMA). The hydrogel in a bicarbonate electrolyte solution is mounted on a micropressure sensor and covered by a gas permeable silicon membrane. Carbon dioxide diffusion through the permeable membrane induces a pH variation that causes swelling and shrinkage of the hydrogel, and the pressure variation, related to CO_2 concentration, is detected by the pressure sensor.

Wu et al. (2019) proposed a method for NO_2 and NH_3 detection based on a different mechanism. They synthesize ionic conductive polyacrylamide/carrageenan double network ultrastretchable and transparent hydrogels for gas sensing. The gas sensing measurements were carried out in a gas chamber with electrical feedthroughs. With gas diffusing into the hydrogel, the movability of K^+ and Cl^- ions is hindered, causing an increase in resistance. The variation in resistance is then related to gas concentration. This hydrogel-based sensor showed a high sensitivity and a low theoretical limit of detection, and the mechanical deformation did not exert a negative effect on the gas-sensing performance.

In literature we can also find some examples of hydrogel-based sensors composed of chemiresistive conductive polymers. Polyaniline (PANI), for example, is widely used for detection of gas molecules such as amines. Wang et al. (2014) proposed a room temperature NH_3 gas sensor including CeO_2 NPs conformally coated by cross-linked PANI hydrogel. The sensing mechanism is based on the reversible doping/dedoping process of PANI. Exposure to electron-donating NH_3 leads to the conversion of PANI from emeraldine salt (ES) to emeraldine base (EB) with the increasing of the electrical resistance. The system showed an enhanced response and a shorter detection time when exposed to 50 ppm of NH_3 which could be attributed to the p-n junction formed by the intimate contact CeO_2 core and PANI shell. The results are illustrated in more details in **Fig. 4**.

Other authors instead developed conducting polymers composite aerogels, obtained from the corresponding hydrogels, as smart responding materials for gas detection exploiting their high porosity. Bai et al. (2011) synthesized three different formulations of graphene oxide/conducting polymer hydrogels (GO/CP): GO/polypyrrole (PPy), GO/poly(3,4 ethylenedioxythiophene) (PEDOT) and GO/polyaniline (PANI). These three hydrogel formulations were prepared by in situ chemical polymerization in aqueous dispersion of GO sheets, coating them and cross-linking them with CPs via π–π, electrostatic interactions, and hydrogen bonding. Among them, lyophilized GO/PPy hydrogel showed high sensitivity towards ammonia, exhibiting, after gas exposure, an increase in electrical resistance, that can be related to the dedoping process of PPy. The high performance showed by this sensor can be attributed to its high permeability and ultrathin PPy layers.

Humidity sensors

Various industrial products such as food, pharmaceutical, natural gas, and semiconductor face damage in the presence of humidity (Bridgeman et al., 2014). For this reason, devices that measure humidity, called hygrometers, are of fundamental importance in many industries. Hydrogels, thanks to their ability to absorb water into their mashes, changing their properties, are promising materials for humidity sensors that are based on different transduction methods.

Optical-based detection via color change offers an attractive and relatively simple way for humidity detection. Sobhanimatin et al. (2021), for example, synthesized a humidity-sensitive inverse opal hydrogel by copolymerizing acrylamide, 2-acrylamide-2-methylpropane sulfonic acid (AMPS), that is the functional monomer, and N,N′-Methylene-bis-acrylamide within the interstitial space of a highly monodisperse polystyrene opal template, that was then removed. When the relative humidity (RH) increased, an increasing number of H_2O molecules were absorbed into the hydrogel, and swelling occurred. Consequently, increasing RH from 20% to 90%, changes of the refractive peak were recorded (**Fig. 5**). This system showed short response time, excellent mechanical stability, recoverability, and long lifetime (more than 1 year) without sensible degradation. Jang et al. (2020) proposed a real-time colorimetric humidity sensor that exploits plasmonic chitosan-based metal-hydrogel-metal filters. Chitosan-based hydrogel swell in response to changes in relative humidity, affecting the structural transmission color of the multilayer structure. This system was combined with a photovoltaic cell that converts the optical response of the filters to an electrical signal showing a decrease of the output current decreased when RH increased. An equation was used to describe the response and to obtain a precise measurement of relative humidity.

Another different optical hydrogel-based humidity sensor was proposed by Buchberger et al. (2019) that exploits pHEMA hydrogel thin films produced by initiated chemical vapor deposition. When in contact with humid air, the hydrogel layer increased its thickness, and the swelling degree was directly proportional to the relative humidity of the surrounding atmosphere. Optical swelling measurements were done using two different implementations both based on interference phenomena. The first one

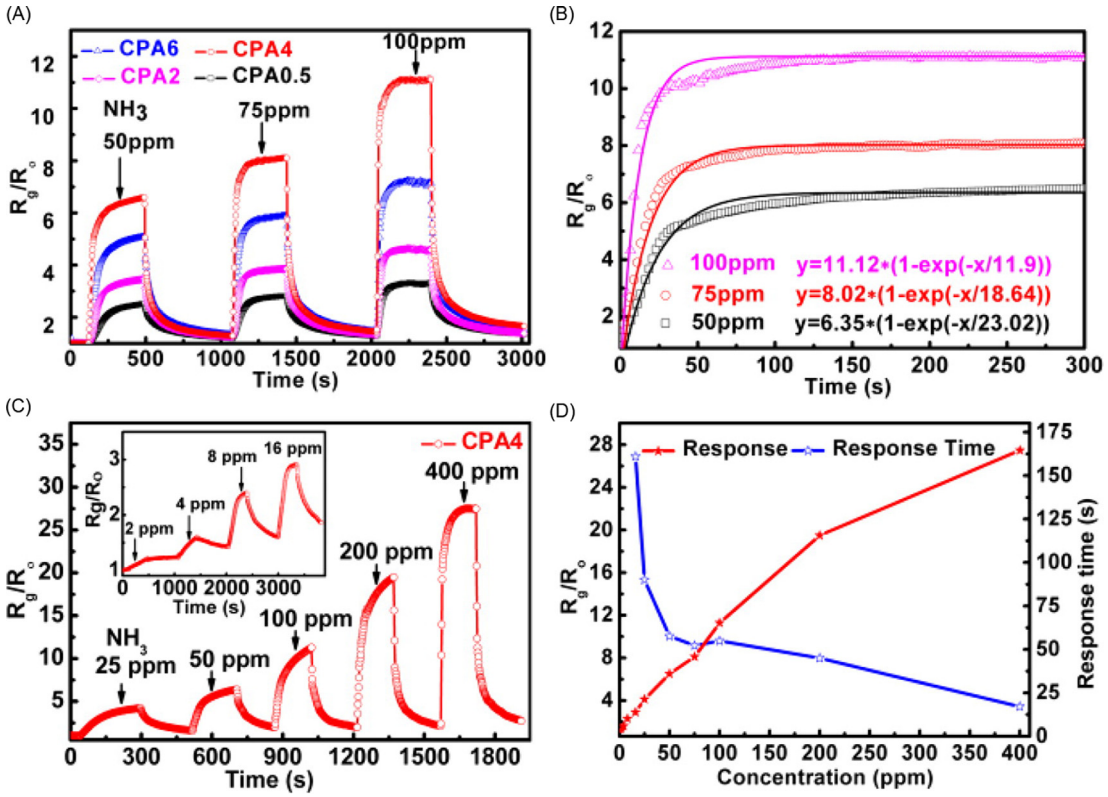

Fig. 4 (A) Response curves to different concentration of ammonia of CeO_2@PANI hydrogels produced with different ratios of CeO_2 to aniline (6, 4, 2, 0.5). (B) Fitted curves (solid lines) and experimental results (scattered points) of CPA4 to different concentration of NH_3. (C) Response of CPA4 upon sequential exposure to different concentrations of NH_3. (D) Response and response time of CPA4 to various NH_3 concentrations. Reprinted with the permission of the American Chemical Society: Wang L, et al. (2014) Enhanced sensitivity and stability of room-temperature NH3 sensors using core-shell CeO2 nanoparticles@cross-linked PANI with p-n heterojunctions. *ACS Applied Materials and Interfaces* 6(16): 14131–14140. doi: 10.1021/am503286h.

consists of a laser and a photo detector that is able to measure the relative thickness changes. The correlation between the hydrogel relative thickness and the relative humidity was described using the Flory-Rehner theory where the Flory-Huggins interaction parameter χ was empirically approximated for the actual hydrogel composition by a measurement of the two quantities simultaneously. The second implementation was realized with a broadband light source and a spectrometer that allows the recording of absolute thickness values.

Pinming et al. (2016) developed a hydrogel-based sensor that exploited a different technique. They synthesized a carboxymethyl cellulose (CMC) hydrogel membrane, and the electrical resistance was chosen as physical parameter for the transduction mechanism. The hydrogel membrane that represent the absorbing layer was prepared to start from a 2 wt% CMC solution that is spin-coated on an electrode and then crosslinked by using 3 wt% epichlorohydrin. This system was tested by varying the relative humidity from 53% to 93%. The results showed a decrease in resistance related to the increase of humidity, demonstrating the possible application of this system as sensing material.

Biochemical sensing mechanism

As already mentioned, we can define as biosensors all those sensing system that are based on biochemical process and that typically detect biological analytes, such as glucose, lactate, DNA, antibodies and others (An et al., 2017). Hydrogels, due to their hydrophilicity, large surface area and excellent biocompatibility, are promising materials for this type of application (George et al., 2020). Hydrogel-based biosensors can be divided into two families: sensors based on molecular interactions and "living" sensors where cells and bacteria are immobilized in the hydrogel and generate the signal used for sensing. In the following paragraph we describe these two categories in more detail.

Sensors based on molecular interactions

Enzyme-substrate interaction

Enzymes are highly specific biocatalysts that typically speed up biochemical reactions in living organisms, lowering their activation energy (Robinson, 2015). They act on biomolecules called substrates and they form with them, in the first step of the reaction,

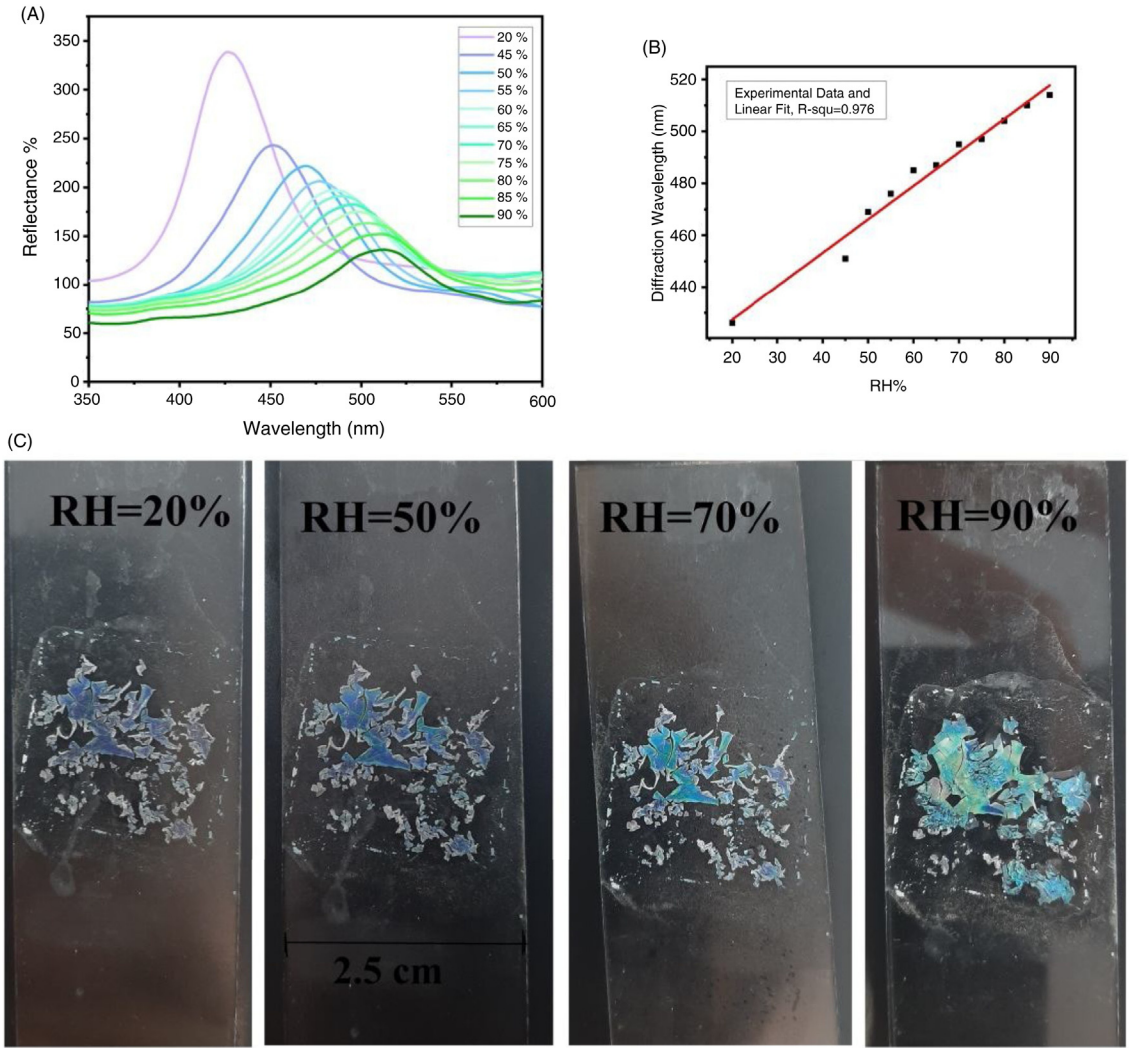

Fig. 5 Responsive behavior of the inverse opal hydrogel sensor under different relative humidity. (A) Corresponding reflection spectra of the hydrogel sensor in the 20% RH to 90% RH range. (B) Linear relationship between maximum reflection peak positions and RH. (C) Photograph of the hydrogel sensor at different relative humidity. Reprinted with the permission of Elsevier: Sobhanimatin MB, Pourmahdian S and Tehranchi MM (2021) Fast inverse opal humidity sensor based on acrylamide/AMPS hydrogel *Materials Today Communications* 26: 101997. doi: 10.1016/j.mtcomm.2020.101997.

a complex that represents the transition state. After the reaction, the products are released, and the enzyme returns to its initial functional conformation.

Enzyme kinetics may be used for precise determination of analyte concentrations. Regarding this, a widely used and consolidated theory is the one of Michaelis and Menten, that is based on the two reaction stages explained above. They demonstrate that, if the substrate concentration is sufficiently high, the biocatalyst is saturated, and the reaction rate is only determined by the rate of conversion from the substrate to the products. This results in a pseudo-first order kinetic of the reaction with respect to the concentration of the enzyme, that can be expressed with the following equation.

$$r = \frac{k_{cat} \cdot [E_0] \cdot [S]}{K_m + [S]} \tag{10}$$

where r is the rate of the reaction, k_{cat} is the rate constant of the catalyzed reaction, K_m is the Michaelis-Menten constant which is the substrate concentration required for an enzyme to reach one-half its maximum reaction rate, comprises k_{cat} and the rate constant for the enzyme–substrate complex formation, and $[E_0]$ and $[S]$ are respectively the starting concentration of the enzyme and the concentration of the substrate. In reality, in the enzyme-substrate reaction, more complex reactions schemes occur that involve multiple binding and allosteric rearrangements. However, Eq. (10) is a good mathematical description of the process and it shows how enzymatic activity can be used for the determination of analyte concentration.

Compared to other enzyme immobilization means, hydrogels have showed higher sensitivities because of the large number of hydroxyl groups in the matrix that offer a biocompatible microenvironment for retaining the natural configuration of the enzyme. In the following paragraphs we are going to describe different applications of hydrogel-based sensors that exploit the enzyme substrate interaction.

Alcohol detection

Enzymatic biosensors are one of the most used technologies for alcohol detection and, among them, hydrogel-based sensors are of great interest for the reasons stated above. For example, Burrs et al. (2015) compared four different matrixes for the encapsulation of alcohol oxidase (AOX): hydrogels based on chitosan, on poly-*N*-isopropylacrylamide (PNIPAAM), on silk fibroin and on cellulose nanocrystals (CNC). Chitosan and PNIPAAM showed the highest sensitivity and fastest response time. These two hydrogels can be exploited in the future as biocompatible and non-toxic materials for biosensing applications.

Chinnadayyala et al. (2014) proposed an innovative enzymatic biosensor fabricated by immobilizing ferrocene entrapped alcohol oxidase (FcAOx) and horseradish peroxidase (HRP) in a sol-gel chitosan film on a multi-walled carbon nanotube (MWCNT) modified glassy carbon electrode through layer-by-layer technique. The biosensor showed a linear response and a good sensitivity and stability. In **Fig. 6** shows a schematic representation of the synthesis and of the functioning of this hydrogel system.

Ammonia and urea detection

This type of hydrogel-based sensors, which exploit the enzymatic interactions, can be used for several relevant applications such as implantable urea sensors, that allow a continuous monitoring of renal and hepatic functions. Quinn et al. (2019) developed an urea senor based on a pH-responsive hydrogel consisting of polyelectrolyte multilayer microcapsules containing a SERS-sensitive pH reporter. Urease and bovine serum albumin (BSA) modified 4-mercaptopyridine(MPy)-AgNPs were immobilized in the alginate hydrogel matrix. The system was able to monitor the urea concentration through pH sensing, as urea hydrolysis by urease caused an increase of the pH throughout the hydrogel, and an alteration of the SERS response at 4 Mpy. Erfkamp et al. (2019) synthetized a pH-sensitive poly(acrylic acid-co-dimethylaminoethyl methacrylate) hydrogel for urea detection. The functionalization with urease enzyme made the hydrogel able to swell in the presence of urea, according to the aforementioned mechanism. The swelling pressure of the hydrogel is transformed via a piezoresistive pressure sensor into a measurable output voltage.

Glucose detection

Diabetes mellitus is a disease that is affecting an increasing number of patients leading to a growing demand for smart glucose sensing device. In the last years an increasing interest has been directed towards continuous glucose monitoring that, unlike point measurements, provides a comprehensive blood glucose profile, which can be used to predict and avoid hypoglycemia as well as hyperglycemia (Yu et al., 2020). The most conventional method to detect glucose levels exploits the enzyme glucose oxidase (GOX), a flavoprotein that catalyzes the oxidation of β-D-glucose, using molecular oxygen, to produce hydrogen peroxide and D-glucono-

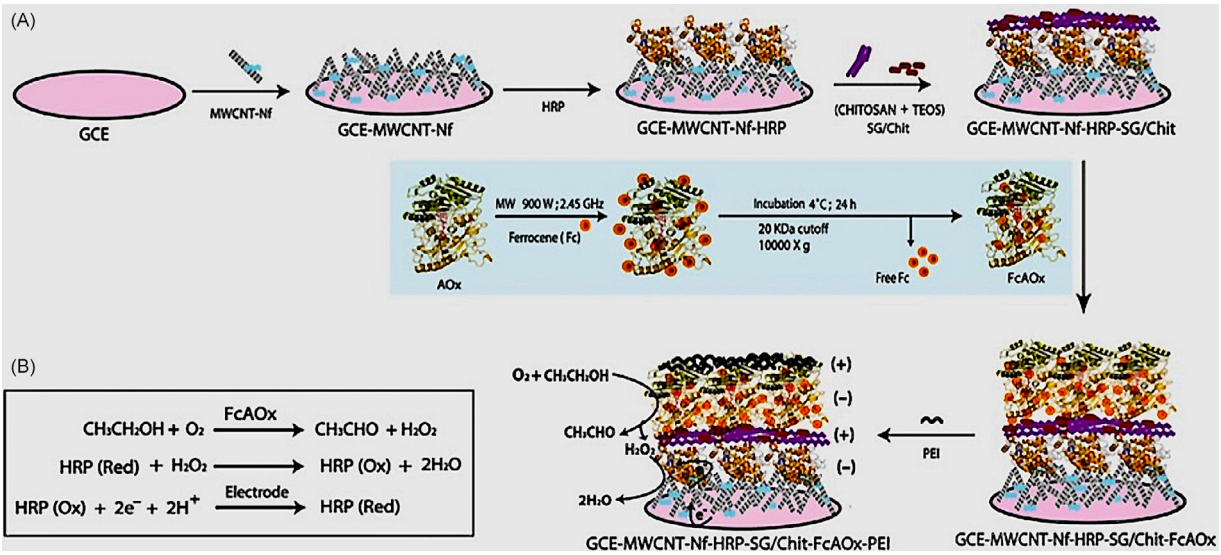

Fig. 6 (A) Schematic representation of the bienzyme electrode fabrication. (B) Main reactions catalyzed by FcAOx and HRP at the electrode surface. Reprinted with the permission of Elsevier: Chinnadayyala SR, et al. (2014) A novel amperometric alcohol biosensor developed in a 3rd generation bioelectrode platform using peroxidase coupled ferrocene activated alcohol oxidase as biorecognition system. *Biosensors and Bioelectronics* 55: 120–126. doi: 10.1016/j.bios.2013.12.005.

delta-lactone (Ferri et al., 2011), that hydrolyze in gluconic acid. When the enzyme is immobilized in a pH-responsive hydrogel, the decrease of the pH induces the matrix to swell in response to the oxidation of the detected glucose.

Mugweru et al. (2007), for example, used a poly(ethylene glycol) diacrylate (PEG-DA) hydrogel network to entrap both a redox polymer and glucose oxidase. The sensor arrays were fabricated on gold electrodes on flexible polyimide sheets. The enzyme catalyzed the oxidation of glucose and then exchanged electrons with the redox polymer in the hydrogel. The catalytic current is proportional to glucose concentration.

Kim et al. (2016), instead, exploited an optical technique for the glucose detection. They synthesize a hydrogel sensor based on a copolymer consisted of acrylamide and fluorescent monomers of fluorescein and rhodamine B, in which GOX was immobilized. The matrix was pH responsive and could change its fluorescent color with the pH changes, caused by glucose oxidation induced by the action of GOX. This work provided an easy and promising strategy for the fabrication of a reusable glucose sensor based on naked-eye detection.

Unruh et al. (2015) compared sensors based on three hydrogels: a poly(2 hydroxyethyl methacrylate) (pHEMA) homopolymer and 2 poly(2-hydroxyethyl methacrylate-co-acrylamide) (pHEMA-co-AAm) copolymers. In these three hydrogels they entrapped glucose oxidase, catalase an oxygen-sensitive benzoporphyrin phosphor. In vitro and in vivo tests demonstrated excellent sensitivity and rapid response to the glucose levels of the sensors. Among the three hydrogels, pHEMA-co-AAm proved to be the best matrix.

Antibody-antigen interaction

Sensors based on antibody-antigen interactions, called also immunosensors, are devices that detect the immunochemical complex formation between an specifical couple antibody-antigen, through the action of a transducer (Gizeli and Lowe, 1996). The signal obtained is proportional to the analyte concentration. Hydrogels represent a promising matrix for the immobilization of antibodies (or antigens) through different methods, such as chemical conjugation and copolymerization between antibody antigen-binding fragments and the hydrogel.

The biochemical signal produced by the antibody-antigen interaction is converted to an analytical signal by different transduction technologies: for example, the quartz crystal microgravimetry with dissipation (QCM-D) is one of the most used. This method quantifies the decrease of the resonant frequency of quartz crystals when the mass increase due to the binding between the immobilized antibody and the antigen. Similarly, the surface plasmon resonance (SPR) is an established optical surface-sensitive technique for the detection of biomacromolecular interactions. This method uses evanescent waves to examine the surface and to detect changes in refractive index determined by analyte binding, allowing real-time measurements. Other signal-transduction methods are electrochemical immunoassay, electrochemiluminescence, and colorimetric immunoassay wherein changes in electrical properties, chemiluminescence and changes in color are measured, respectively (George et al., 2020).

An example of antibody-antigen based biosensor is provided by Lim et al. (2020a,b). They reported the synthesis of a bioconjugated polyacrylamide-based hydrogel (HBPAAm hydrogel) that responds to the presence of hepatitis B core antigen (HBcAg) by a weight change in the hydrogel. The structure is made of the cross-linked acrylamide (AAm) polymer chains pre-conjugated with the HBcAg and its antibody, anti-HBc. In the presence of free HBcAg, the immobilized HBcAg-(anti-HBc) complexes, that governed the swelling degree, are disrupted, inducing the hydrogel to swell. Due to its short response time, good specificity and reusability, this hydrogel has a great potential in the biosensing field.

Photonic crystals (PCs), as we have reported, represents an attractive solution in sensing applications. Choi et al. (2013), for example, proposed a specific and label-free method for the naked-eye detection of immunoglobulin G (IgG) antibody using a photonic crystal hydrogel. The hydrogel structure, realized with poly (ethylene glycol)-diacrylate (PEG-DA) and used as backbone for the PCs, showed high capacity for biomolecule immobilization, great probability of interacting with the target ligand, and sensitivity. Protein A was immobilized on the structure and, when interaction with the specific antibody (IgG) took place, the color of the device, initially green, changed to dark orange. Moreover, the device showed different bandgap shift, allowing to quantify the molecule interactions. The detection mechanism is illustrated in **Fig. 7**.

Nucleotide and DNA interaction

Various functional DNA structures that can respond to different stimuli, including ions, small molecules, proteins, nucleic acids, and cells, have shown to be viable materials for biosensing applications. Among these materials, DNA hydrogels, with their ability to change their swelling volume, crosslinking density, and optical or mechanical properties in response to external stimuli, have attracted particular research interest (Li et al., 2020a,b).

Generally, in DNA-based hydrogels a synthetic polymer is employed as the scaffold and an analyte binding, and functional DNA cross-linker as the sensor. After the recognition of the respective target, the cross-linker dissociates inducing the hydrogel to swell and to change some of its properties and thus generating a signal of the presence of the analyte (Gačanin et al., 2020).

Mao et al. (2017) proposed a portable, sensitive, specific, and visual detection method for various molecules based on DNA crosslinked hydrogel and on gold nanorods (AuNRs). This hydrogel is based on aptamers, DNA oligonucleotides catalyzing certain chemical reactions, that represent the target-responsive units incorporated in the matrix. In addiction glucoamylase, an enzyme that catalyzes the transformation of amylose into glucose, is encapsulated for molecular recognition and signal amplification. Gold nanorods (AuNRs) were used as multicolor readout circuit for analyte quantification: the color variation was correlated to the concentration of the targets. Colorimetric detection, however, presents some drawback such as low sensitivity and semiquantitative nature of the analysis.

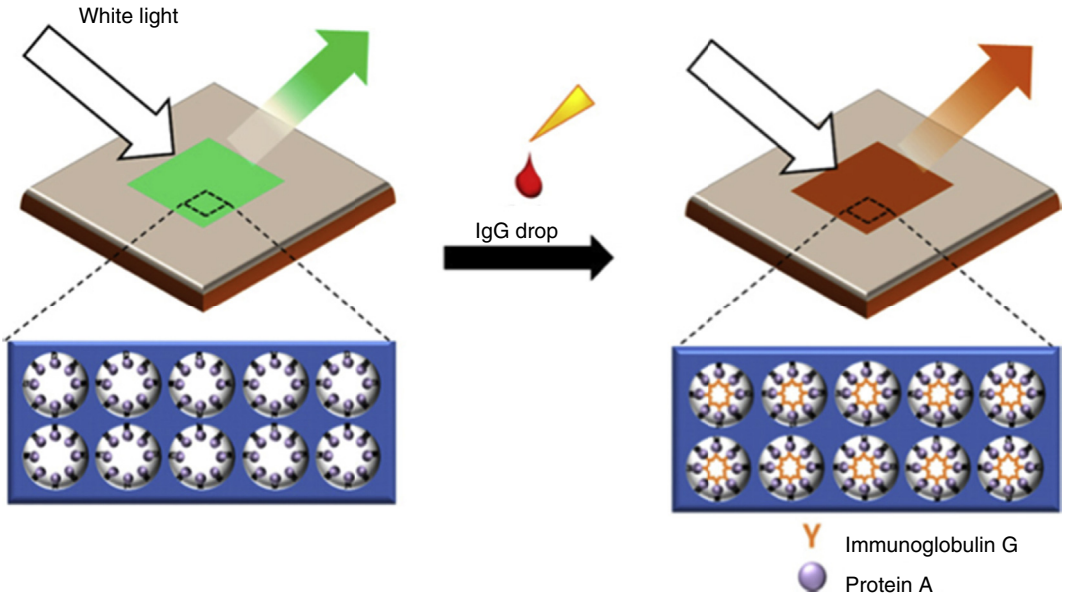

Fig. 7 Mechanism of detection of IgG of hydrogel-based biosensor proposed by Choi and co-workers. IgG can be detected by observing color changes in dry conditions. When the protein A immobilized on the nanoporous structure interacts with the specific antibody (IgG), the color of the system changes from green to dark orange. Reprinted with the permission of Elsevier: Choi E, et al. (2013) Label-free specific detection of immunoglobulin G antibody using nanoporous hydrogel photonic crystals. *Sensors and Actuators, B: Chemical.* Elsevier B.V., 180: 107–113. doi: 10.1016/j.snb.2012.03.053.

An important alternative is represented by electrochemical biosensors. An example of this solution is provided by Liu et al. (2018), who developed a device based on hybrid DNA hydrogel entrapped on indium tin oxide/polyethylene terephthalate (ITO/PET) electrode for the detection of miR-21, a microRNA that represents a biomarker for the lung cancer screening. The hydrogel was based on DNA-grafted linear polyacrylamide and ferrocene-tagged DNAs as the recognition probes, and it was immobilized on ITO electrode treated with 3-(trimethoxysilyl)propyl methacrylate. The high sensitivity and stability have shown that this electrochemical DNA hydrogel biosensor can be promising for early clinical cancer diagnosis.

Another significant example is provided by the work of Wang et al. (2020), who developed a sensor for miRNA detection fixing a DNA hydrogel at the end of a capillary. The sensor is based on hybridization between miRNA targets in a solution and DNA probes which leads to an increase of the permeability of the hydrogel. Thus, miRNA can be quantified by a naked-eye measurement of flow-through distance in the capillary tube of the solution.

Sensors based on living cells

Sensing methods based on living cells present some advantages such as the ability to detect a wide range of substances, amenability to genetic modifications, and broad operating pH and temperature conditions. Hydrogels are an advantageous solution for the immobilization of microorganisms due to their high water content and the three-dimensional polymer network, which can be engineered to provide mechanical and chemical stability, biocompatibility and selective permeability (Jen et al., 1996), allowing gas exchange and transport of nutrition to the cells. These characteristics make hydrogel an ideal matrix for the cultivation of bacteria, genetical engineered cells, tissues, and other types of cells for the application in living sensors.

Bacteria

Bacteria exhibit positive or negative response to different environmental conditions, such as the presence of nutrients or toxins (Bjerketorp et al., 2006). For this reason they have been largely used in living sensors for pollutants detection (Tavakoli and Tan, 2017). Zhang et al. (2019a,b), for example, proposed a long-term valid system for toxicity test, based on the effects induced by heavy metal ions, such as Hg(II), on bacterial viability and enzymatic activity. *Escherichia coli* bacteria were encapsulated in a polyvinyl alcohol hydrogel through freeze-thaw approach to achieve long-term viability and enzymatic activity and to improve the portability of the system. Toxic effects of Hg(II) in aqueous samples influenced the viability and enzymatic activity of *E. coli*. Hg(II) titration leads to a colorimetric response, that is correlated to the concentration of ions (**Fig. 8**).

Elcin and Öktem (2020) instead developed a whole-cell bacterial biosensor for arsenic detection exploiting a fluorescent response. They utilized as bioreporter an *E. coli* strain genetically engineered by introducing green fluorescent protein (*gfp*) as reporter gene, and they immobilized these microorganisms in agar hydrogel and in alginate beads. The authors demonstrated that, changing two different medium compositions, this system can be used for recognition of both arsenite and/or arsenate, the two most abundant species of arsenic. This sensor has shown a detection range which includes typical permissible arsenic

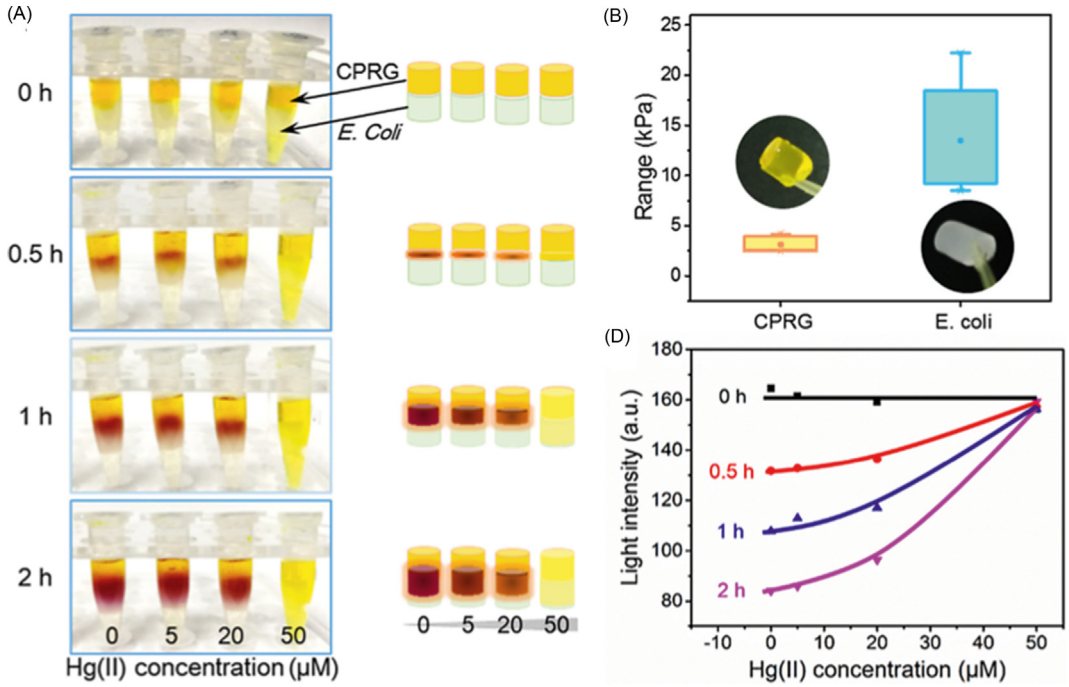

Fig. 8 Visual (A) and quantitative (D) analyzes of hydrogel-based toxicity test with different Hg(II) concentrations. (B) Cartoon illustration of color evolution of the samples in (A). (C) Mechanical properties of CPRG and *E. coli* hydrogels. Reprinted with the permission of Elsevier: Zhang Y, et al. (2019a) Acute heavy metal toxicity test based on bacteria-hydrogel. *Colloids and Surfaces A: Physicochemical and Engineering Aspects* 563: 318–323. doi: 10.1016/j.colsurfa.2018.12.016.

concentrations in drinking water, and it could be a promising device for a specific, sensitive and low-cost monitoring arsenite and arsenate in water.

Different methods for bacteria encapsulation are proposed in literature. Alehosseini et al. (2019), for example, encapsulated the sensitive strain *Bifidobacterium pseudocatenulatum* CECT 7765 in agarose-based hydrogel particles, exploiting novel technique called "oil-induced biphasic hydrogel particle formation." This method presents some advantages over other techniques that allow to obtain viability levels required for commercial applications: the formation of a continuous layer surrounding the bacteria and the optimal combination of materials.

Cells

Hydrogels, thanks to the already mentioned peculiarities, and thanks to their structural similarity to the macromolecular-based cellular microenvironment in human body, called extracellular matrix, can have multiple applications in biosensors that exploit encapsulated cells or tissues.

In the last years, for example, the development of food and beverage industries has led to a growing interest in artificial biosensor systems that can allow to investigate the kinetic characteristics of taste receptors and that can mimic the physiological functions of human tongue for standardized taste inspections. In literature we can find different works on this topic like the one provided by Qiao et al. (2015). The authors developed a taste biosensor based on receptor-ligand interaction fixing taste-bud tissues of SD rats to a glassy carbon electrode using a sodium alginate-starch gel. They entrapped the tissues between two nuclear microporous membrane to make a sandwich-type sensing system and they measured the response current induced by capsaicin and gingerol stimulating the corresponding receptors. This device has shown high sensitivity, wide linear range, and low detection limits, which make it suitable for taste biosensing applications and for the determination of binding and dissociation constants of pungent substances with their receptors.

Another type of sensing device based on living cells immobilized in a hydrogel is proposed by Jiang et al. (2017) in their work. They developed an electrochemical method based on mast cells for the detection of bacterial quorum signaling molecules, *N*-acyl-homoserine lactones (AHLs), that can be utilized for a preliminary evaluation of the toxicity of food-borne pathogenic bacteria. Rat basophilic leukemia (RBL-2H3) mast cells were immobilized in a sodium alginate/graphene oxide hydrogel fixed on gold electrodes. The *Pseudomonas aeruginosa* quorum-sensing molecule, N-3-oxododecanoyl homoserine lactone (3OC12-HSL), was used as AHL representative, and the electrochemical response of cells was analyzed with electrochemical impedance spectroscopy (EIS). The results indicated that cellular activities were influenced by the AHLs. In this case, 3OC12-HSL induced a decrease in the electrochemical impedance signal that is proportional to the exposure dose. This system exhibits good sensitivity, reproducibility, stability, and low detection limit. A schematization of this system is reported in Fig. 9.

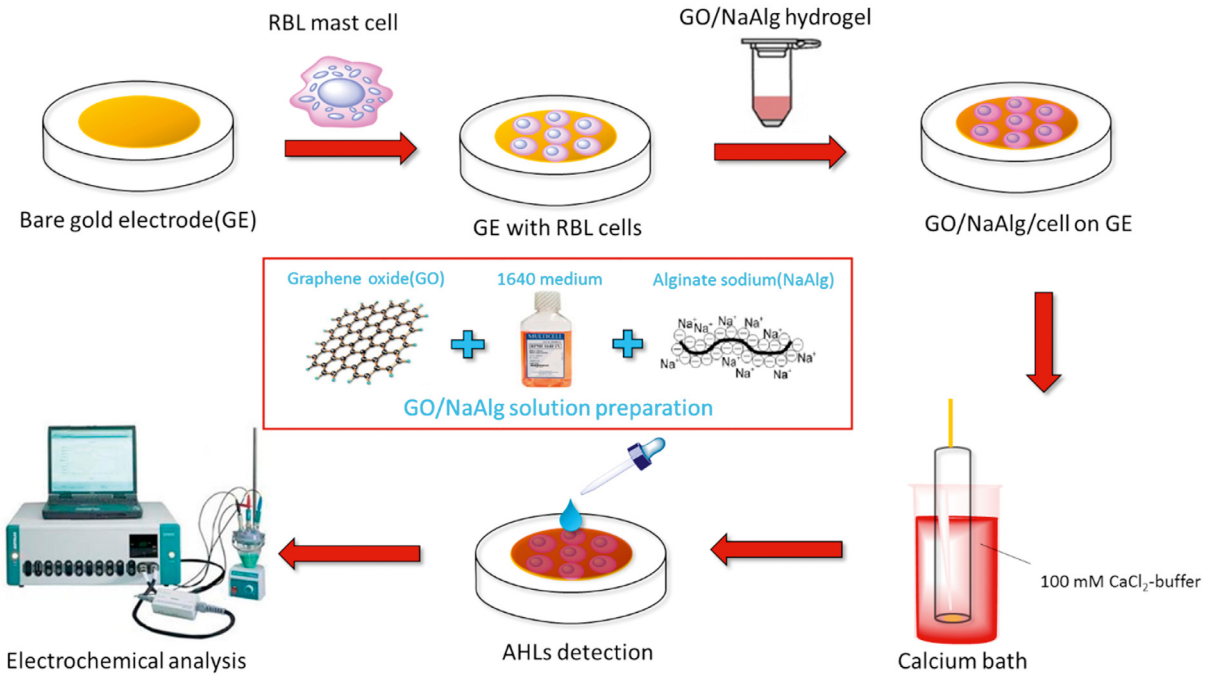

Fig. 9 Schematic representation of the preparation of RBL-2H3 mast cell sensor and process of AHLs detection. Reprinted with the permission of Elsevier Jiang D, et al. (2017) Preliminary study on an innovative, simple mast cell-based electrochemical method for detecting foodborne pathogenic bacterial quorum signaling molecules (N-acyl-homoserine-lactones). *Biosensors and Bioelectronics* 90: 436–442. doi: 10.1016/j.bios.2016.09.096.

Conclusions

As it should be clear to the reader, hydrogels have acquired great importance and consideration in the field of sensor in the last decades. The features and characteristics of these biomaterials are ideal for different applications and guarantee their use in multiple fields, from bio-medical systems to environmental employments. The possibility to tune and proper formulate hydrogels to obtain specific and responsive systems guarantees to these devices great versatility and adaptability that is a pivotal characteristic for a sensor device. This versatility is confirmed by the wide range of fields in which nowadays hydrogels-based sensors are employed. In the next years the diffusion of these devices will for sure increase thanks to the efforts to conjugate already existing sensors with innovative hydrogel-based systems.

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