ADVANCED FUNCTIONAL HYDROGEL BIOMATERIALS BASED ON DYNAMIC B-O BONDS AND POLYSACCHARIDE BUILDING BLOCKS

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ABSTRACT: Dynamic covalent chemistry applied to polymers has attracted significant attention over the past decade. Within this area, this review highlights the recent research on polysaccharide-based hydrogels cross-linked by boronic-acid moieties, illustrating its versatility and relevance in biomaterials science to design self-healing, multiple stimuli-responsive, and adaptive biointerfaces and advanced functional devices.

1. INTRODUCTION

Hydrogels are defined as three-dimensional (3D) polymer networks that display hydrophilic groups, and thus are capable of absorbing and retaining considerable amounts of liquid maintaining their form under their own weight without affecting significantly their 3D structure. Interestingly, their soft, rubbery texture, similar to that of human tissues, in combination with their high biocompatibility and huge versatility - in form and dimensions, has placed hydrogels as key elements in a wide range of biotechnological applications in the fields of tissue engineering, soft robotics for bioelectronics, or drug delivery, among others.[1–3] Regarding their composition, hydrogels based on natural polymers and, especially, polysaccharides[4,5] and peptides[6], have been attracting a lot of interest because of their biodegradability, low production cost and toxicity, and abundance of resources.

Recently, several research avenues in the field of polymer science are focused on the development of hydrogels as advanced biomaterials. Hence, not only are hydrogels designed to fulfil basic requirements (*i.e.* processability through simple and cost-effective manufacturing

strategies and synthetic routes, compatibility with biological tissues, mechanical strength, high permeability to various solutes and high ionic conductivity) but, in addition, exhibit superior performance and cutting-edge properties. In particular, properties such as self-healing,[7] multiple stimuli-responsiveness,[8] and adaptive macroscale properties (shape-memory, stretchability, and reprocessability),[9–11] enable their use for real-world applications.[12]

As the structure of physically cross-linked hydrogels is unstable under small environmental changes and present limited robustness, while the irreversible nature of chemical cross-links prevents their use in shear-thinning and self-healing applications, hydrogels based on dynamic covalent interactions have emerged as an attractive alternative to reach such high-value features.[13] Indeed, in comparison with non-covalent bonds (*i.e.* hydrogen bonds,[14,15] van der Waals interactions,[16] π-π stacking,[17] metal–ligand coordination,[18,19] electrostatic interactions,[20] or host–guest interactions[21]), dynamic covalent chemistry exhibits higher stability and affords reversibility under specific conditions or stimuli.[22] The range of dynamic covalent chemistry that has been exploited to produce healable polymers includes nucleophilic substitutions, imine chemistry, Diels–Alder reactions, disulfide exchange chemistry, thiol-Michael exchange, transthioesterifications, boronic esters and boronates, Si–O exchange in siloxanes and silyl ethers, among others.[23]

Briefly, the dynamic bond is a class of bond that can selectively, reversibly break and reform, under equilibrium conditions, without irreversible side reactions.[24] Dynamic covalent networks are influenced by external factors (such as temperature, water content, concentration, or the presence of Lewis bases, among others) and their components easily assemble and disassemble according to physicochemical cues. Due to their nature, dynamic bonds permit stress relaxation, material flow and higher stability, thus combining the advantages of both physically and

chemically cross-linked hydrogels, allowing self-healing gels to restore their functionalities and structures after damage.[25] The bonding breakage and reformation occurs either through the associative or the dissociative bond exchange mechanism. During the associative bond exchange mechanism, breakage and reconstruction of the dynamic bond takes place simultaneously, maintaining a constant cross-link density. Contrarily, in the dissociative bond exchange mechanism, the bond of complementary species firstly breaks and then reforms at new sites, as a result of a reduction in cross-link density, which allows topological rearrangements.[26]

Among the wide range of possibilities regarding dynamic covalent chemistry, this review provides an overview of the chemistry of organoboron species with dynamic B–O bonds implemented to enhance the properties of polysaccharide-based hydrogel systems for advanced applications. Bapat *et al.* recently reviewed the design of healable/reprocessable bulk polymer networks containing dynamic B–O bonds;[26] however, they excluded the discussion of hydrogels and organogels. And, although several reviews focus on the design of hydrogels for biomedical applications using dynamic covalent boronic esters,[27,28] whereas PVA-boronate organogels have become recently popular as low-impact cleaning tools for painted surfaces,[29–31] a specific analysis of polysaccharide-based hydrogel systems was required. Indeed, we consider this area of biomaterials science as an emerging one owing to the growing number of publications in the last years, as well as the impact of those, which present biomaterial devices with innovative features that are achieved through the combination of the dynamic covalent chemistry applied and the selection of biocompatible natural polymers.

In the neutral form, boronic acids display a trigonal planar sp^2-hybridized boron, which is bonded to an alkyl or an aryl group and two hydroxyl groups, and primarily act as Lewis acids, due to the vacant p-orbital on the boron center. Condensation reactions between boronic acid-

based polymers and their derivatives is a common approach found in the literature to form networks with boronate esters as linkages (Scheme 1). Such reactions are usually carried out under mild conditions and in basic aqueous media or anhydrous organic solvents. Indeed, boronic acids have been extensively explored on account of their excellent ability to interact reversibly with diols, forming boronate esters, the most common interaction occurring with *cis*-1,2- and *cis*-1,3-diols, forming five and six membered rings, respectively.[32] The stability of the boronate ester bond (*i.e.* its formation and dissociation, which can occur both in aqueous and organic media, under mild temperature, and without the need of catalysts) highly depends on both the pK_a of the boronic-acid pair and the pH value of the environment. Reaction kinetics are fastest in aqueous basic media, where boron is present in its anionic form. When the pH is equal or above the pK_a of the acid, a negatively charged tetrahedral structure facilitates its reaction with hydroxyl groups and, consequently, the ester formation occurs. In contrast, near the physiological pH, the diol–boronic acid interaction is not favored, while it is completely cleaved under highly acidic conditions. In addition, the binding affinity between a diol and a boronic acid is also affected by diol acidity, solution composition, and the dihedral angle of the incoming diol.[27]

Boronate and boronic esters are considered "dynamic covalent" structures because of the kinetically controlled dynamic exchange between the free (*i.e.* free diol and boronic acid, reactants) and bound species (*i.e.* boronate ester, products). Hence, on the basis of this process, which is relatively facile and results from the low-energy transition state between reactants and products, boronate esters undergo dynamic rearrangement constantly. Consequently, materials based on B–O dynamic bonds are able to reform bonds around a damaged zone, thus repairing

their functional properties,[33] even within an atypically wide pH range with boronate ester-cross-linked hydrogels capable of self-healing behaviour at neutral and acidic pH.[34]

Scheme 1 Formation of boronate ester by a condensation reaction.

Why have boronic acid-containing systems been the focus of attention recently? First of all, the high reactivity between boronic acids and diols, in addition to the multitude of boronates that are synthetically available, allows for the formation of versatile systems with a wide range of potential applications. Indeed, Nakahata and Sakai defined boronic acids as "functional cross-linkers" and highlighted their contribution to produce hybrid and composite functional nanomaterials, among other systems.[35] Not only that, but B–O dynamics bonds can be combined with other reversible covalent bonds, to yield multi-responsive networks.[36] Also, the pK_a values, and thus the exchange rate of boronic ester bonds, can be controlled by conveniently selecting the chemical structure of the neighboring substituents.[37] For instance, Brooks *et al.* investigated various boronic acids and other organoboron compounds to determine their pK_a and their binding constants with the biologically relevant diols including sorbitol, fructose, and glucose.[38] Moreover, the impact of the boronic-acid exchange reactions on the dynamics of hydrogels was recently reported by Yesilyurt *et al.*, who demonstrated the utility of mixtures of kinetically unique covalent crosslink dynamics to tune the time-dependent mechanical response of bulk hydrogels.[39,40] Briefly, they designed, synthesized, and applied poly(ethylene glycol) (PEG)-based shear-thinning and self-healing hydrogel networks prepared using reversible covalent interactions between phenylboronic acid (PBA) derivatives and *cis*-diols,[39] and later by using

two different PBA derivatives with unique diol complexation rates, 4-carboxyphenylboronic acid and o-aminomethylphenylboronic acid.[40] However, most importantly to the biomaterial field, the breakdown of boronic-acid containing polymers releases generally boric acid, which was assessed to be not particularly toxic.[41] Hence, the use of boronic-acid compounds as biomaterials has been proven to be highly encouraged because of the lack of cytotoxicity and their high stability when applied to *in vivo* environments.[42] Furthermore, biologically relevant compounds, such as saccharides, glycoproteins, or dopamine, are susceptible to boronate ester formation, thus supporting the use of boronic acids for biotechnological purposes.

Even though diols are the preferred route to obtain boronate esters, other substrates, such as random copolymers with single alcohol groups within the functional side chains,[43] can act as platforms for the design of mechanical enhanced and self-healing hydrogel biomaterials. In fact, this approach has been recently exploited to a great extent, thus producing significant work on the area.[44–53]

Herein, we summarized the latest advances on boronic acid-based hydrogels as functional biomaterials with enhanced properties that include in their composition polysaccharide units. This review firstly covers recent impactful developments in this area from a general point of view, considering alginate, hyaluronic acid and other natural-derived polymers. Then, attention is turned to chitosan-based systems and their applications, which offer unique possibilities and have attracted growing interest among the research biomaterial community. Overall, the main goal is to illustrate how the versatility of the B–O dynamic covalent chemistry, in combination with natural polymers, leads to potential biomaterial products suitable to translation into clinical set-ups upon meeting application-specific design criteria. Challenges and potential future developments are also discussed.

2. GENERAL OVERVIEW: POLYSACCHARIDE-BASED HYDROGELS

Polysaccharides consist of macromolecules of more than 10 monosaccharides joined by glycosidic linkages, with molecular weight values raging from tens of thousands to even millions. These materials are produced by a wide range of species (*e.g.* microorganisms, algae, plants and animals) and display interesting properties, such as antioxidant, hepatoprotective, hypoglycemic, antibacterial, anti-inflammatory, and immunological activities.[54] These environmentally-friendly materials satisfy several key properties as biomaterials, which include affordability, structural support, and promotion of cell attachment, proliferation, and differentiation.[5]

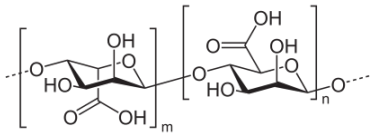
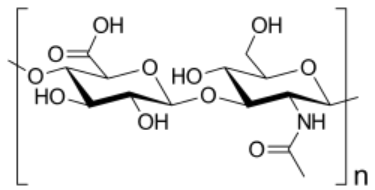
Table 1 lists the main polysaccharides cited in this work with their features.[55] Most polysaccharides can form hydrogels due to their intrinsic properties. For instance, sodium alginate spontaneously forms gels in the presence of divalent cations through electrostatic interactions, while others, such as hyaluronic acid (HA), laminarin, or cellulose, often require chemical modifications to introduce functional groups that are then able to cross-link the polymeric network. Regarding the formation of hydrogels crosslinked by boronic acid ester bonds, it is important that the polysaccharide structure is easily accessible for chemical reactions which, ultimately, introduce the crosslinking moieties of interest, as well as additional physicochemical or biological cues.[54] Not only that, but displaying high water solubility further facilitates the introduction of boronic acid derivatives in aqueous environments under mild conditions, whereas the degradation profile of the resulting polysaccharide-based system also needs to be taken into account when designing the biomaterial hydrogel to match the requirements of the specific application. Indeed, some polysaccharides render hydrogels that are enzymatically degradable, which leads to the potential controllable degradation of the

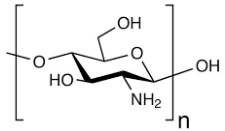
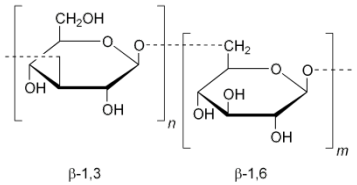
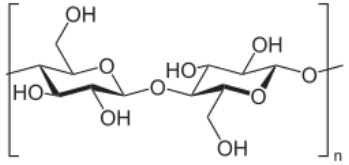
biomaterial *in vivo*.[56] Besides, the properties of polysaccharide-based hydrogels depend on their composition and structure, with factors such as type of sugar, linkage, molecular weight, chain conformation, or sulfate content affecting the relationship between structure and function, including bioactivity. Therefore, since all these elements play a significant role, it is important to determine them properly. Finally, the use of natural-based materials addresses the effort made by technology and industry players of using more sustainable sources instead of petroleum-derived ones to produce recyclable and commercially competitive products.

Because of their properties, polysaccharide-based materials are expected to play a key role in future biomedical technology and specific medical applications. Among those, the following have attracted growing attention, tissue engineering, wound healing, drug delivery, adhesive and antibleeding products, cell delivery, and angiogenesis, among others.[57] In general, the tunable structure and networked morphology of polysaccharide hydrogels promote functions that are vital for such bioapplications. For instance, drug release in physiological fluids is facilitated by hydrogel swelling, controlled in turn by the crosslinking density, with the cargo being delivered depending on the different release rates of each system.[58] For an active, on-demand delivery, the system needs to respond to an external stimulus at the desired time at the specific location. In general, the use of hydrogels for this application results in efficient drug targeting at low cost. Moreover, the porous nature of hydrogel-based wound dressings allow gases to be exchanged efficiently at the wound interface, while keeping moisture and temperature constant, as well as displaying barrier protection towards bacterial infection.[59] For tissue regeneration purposes, polysaccharide-based hydrogels behave as valuable scaffolds on account of their reticulated structure, which mimics the native extracellular matrix, as well as their tunable viscoelasticity, high water content, high permeability for oxygen and essential nutrients, and bioactivity, which

overall promotes new tissue formation.[60,61] Noteworthy, although challenging, strategies exist already to enhance the initial weak mechanical properties of some systems (*i.e.* inferior mechanical strength, limited ductility, and poor recoverability) to render them fully functional biomaterials for a wide range of mechanical microenvironments.[62] In addition to these features, polysaccharide-based hydrogels are capable of displaying a more advanced performance if careful attention is placed to the design strategy. Indeed, when cross-linked by boronic-acid moieties, their versatility and relevance in the biomaterial field increases by displaying stretchability, shape-memory, and self-healing, as well as injectability and environment sensitivity to pH and/or temperature, which can further facilitate their bioapplication.

Table 1 List of the main polysaccharides cited in this work with their features.[55]

Polysaccharide	Chemical structure	Source	Ionic nature	Water solubility / Degradability	Crosslinking strategy	General properties of derived hydrogels
Alginate (salt of alginic acid)	(1-4)-linked β-D-mannuronic acid and α-L-guluronic acid units 	Microbial (brown algae) and soil bacteria	Linear, anionic	Dissolves slowly in water, forming a viscous solution; Uncontrollable degradation profiles	Electrostatic interactions: divalent cations interact with the carboxylic groups to produce 'egg-box'-shaped structured hydrogels	Low cytotoxicity / Easy chemical modification through carboxylic groups / Purification process required / Weak mechanical properties
Hyaluronic acid	Glucuronic acid and N-acetyl glucosamine. linked via alternating β-1,4 and β-1,3 glycosidic bonds 	Linear, non-sulfated glycosaminogly can present in connective, epithelial, and neural tissues. Obtained from rooster combs and *Streptococcus bacterium*	Anionic	Water-soluble, but highly viscous in solution; not resistant to enzymatic degradation	Chemical modification to introduce functional crosslinking groups.	Easy modification of its chemical structure / Enhanced processability / Injectable / Biocompatible / Weak mechanical properties
Chitosan	β-1,4-linked 2-amino-2-deoxy-D-glucose	Partial alkaline deacetylation of chitin (shrimp, crustacean shells)	Cationic (at acidic pH-values)	Insoluble in aqueous solutions above pH 7; In dilute acids (pH 6), the free amine groups are protonated and the molecule becomes soluble;	In physical gels, sol–gel transition through intermolecular interactions of a hydrophobic nature -based on its pH-dependent	Hydrophilicity / Accessible for chemical reactions (covalent gels)/ High annual production / Great accessibility of chitin / pH-dependent solubility / Processing under mild conditions / Non-toxic /

				Biodegradable	solubility/insolubility	Antibacterial activity / Weak mechanical properties
Laminarin	β(1→3)-glucan with β(1→6)-branches 	Polysaccharide of glucose found in brown algae.	Neutral	Water-soluble; hydrolysis is catalyzed by enzymes (laminarinase)	Chemical modification to introduce functional crosslinking groups.	Bioavailability / Abundant / Weak mechanical performance / Excellent therapeutic properties
Cellulose	β-D-glucan units linked by (1→4) glycosidic bonds 	Cell walls of plants, mainly in stalks, stems or trunks / Bacterial origin (*Acetobacter xylinum*)	Neutral	Fibrous, tough, water-insoluble; Poor degradation both *in vitro* and *in vivo*	Chemical modification of cellulose derivatives, which are used as starting materials	Most widespread polymeric material in nature / High degree of crystallinity / High strength in the wet state / Biocompatible / Not biodegradable in the human body
Gelatin	Heterogeneous mixture of proteins of high average molecular masses present in collagen	Animal source: extracted by boiling in water relevant skin, tendons, ligaments, and bones.	Neutral	Soluble in hot water; *in vivo* degradability of gelatin hydrogels depends on their water content	Cooling-induced crosslinking: reorganization of the peptide chains to form a secondary electrostatic network through tertiary coils	Tasteless, odorless, colorless / Brittle / Thixotropic response (increasing viscosity under stress) / Bioavailable / Cytocompatible

2.1 Alginate-containing hydrogels

Alginates, which are refined from brown seaweeds, have been already successfully applied as a mold-making material in dentistry and prosthetics, as well as in the food, pharmaceutical, textile and biomedical industries and, therefore, it is not surprising the role they play during the design of advanced functional hydrogels based on polysaccharides. Specifically, for tissue engineering applications, alginate has been chosen as hydrogel precursor in cartilage, bone, skin, liver and heart regeneration approaches.[55]

Back in 2014, Meng *et al.* explored novel shape memory hydrogels on the basis of dynamic phenylboronic acid (PBA)–diol ester bonds formed by PBA-grafted alginate (Alg–PBA) and poly(vinyl alcohol) (PVA).[63,64] The shape of the hydrogel was stabilized by alginate-Ca^{2+} cross-links, which display a slower rearrangement relative to the experimental times evaluated, whereas the reversible B–O dynamic bonds were in charge of memorizing the temporary shape, which was pH-controlled and took place within minutes with a recovery ratio of 100%: temporarily deformation occurred at pH 6, while fixation at pH 10.6. Then, the hydrogel shape was reverse to its original form by either reducing the pH or by soaking in a saccharide solution.

Later, Hong *et al.* developed a highly simplified single polymeric component hydrogel that consisted of an alginate-boronic acid conjugate (alginate–BA) utilizing intrinsic *cis*-diol existing along alginate backbones. In this case, the dynamic equilibrium between the *cis*-diol and boronic acid hydroxyls rendered the material with rubber-like viscoelastic properties and a wide range of superior features, which included high stretchability, self-healing (up to 98% healing efficiency), shear-thinning, pH- and glucose-sensitivity, adhesiveness, and reshaping properties, owing to reversible inter- and intramolecular interactions. As a result, subcutaneous implantation of this hydrogel showed low toxicity and lasted longer when administered orally for *in vivo* mucosal

adhesions.[65] Indeed, bioadhesives are currently being developed to provide adhesion moieties as tissue sealants, wound dressings, or hemostatic agents in biomedical applications, as well as to improve assembly in soft actuators and robotics. In this emerging research area, it has been reported that a boronic acid-tethered alginate polymer meets for the first time all the requirements for hydrogel attachment and assembly as polysaccharide glue.[66] Specifically, the boronic acid "*cis*-diol" moiety exhibits adhesive properties similar to catechol cis-diols in mussel adhesive proteins.

In the search of other "smart" and advanced functionalities for biotechnological applications (*e.g.* electronic skin, soft robotics or actuators), Le and co-workers reported a triple shape memory double-network (DN) hydrogel resulting from the polymerization of acrylamide in the presence of a supramolecular network, that is Alg–PBA and PVA.[67] The subsequent contact with alkaline solution introduced reversible PBA–diol ester bonds. In fact, the two non-interfering supramolecular interaction chemistries (dynamic phenylboronic (PBA)–diol ester bonds and the chelation of alginate with Ca^{2+}) were responsible for the outstanding shape memory feature of the system (Figure 1). More recently, a similar approach was applied to produce a multiresponsive hydrogel with shape memory and self-healing properties corresponding to three types of common triggers: moisture, multivalent cations, and pH.[68]

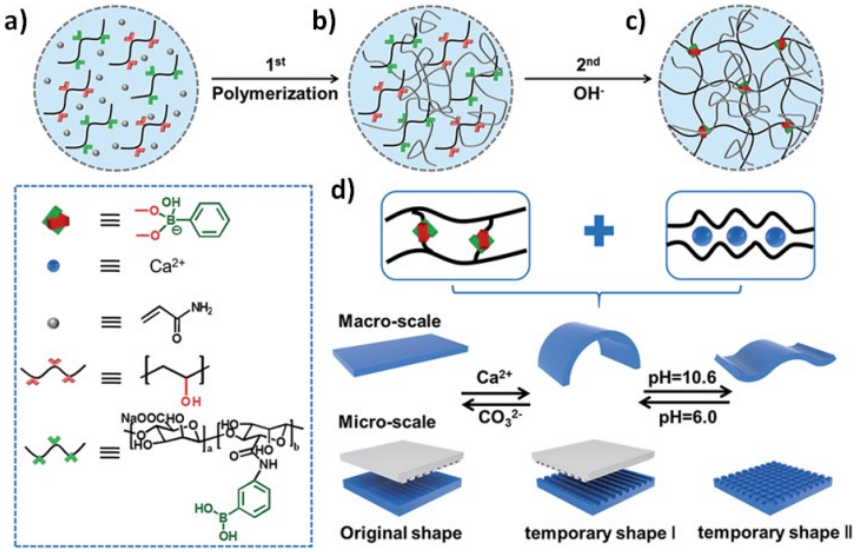


Figure 1 Schematic illustration of stretchable supramolecular hydrogels with a triple shape memory effect. a–c) Acrylamide is polymerized in the presence of Alg–PBA and PVA, then the supramolecular network is formed *via* immersion into alkaline solution to generate dynamic PBA–diol ester bonds. d) The reversible PBA–diol ester bonds and the chelation of Alg/Ca^{2+} endow the hydrogel with triple shape memory behaviour at both the macro-scale and micro-scale. "Stretchable Supramolecular Hydrogels with Triple Shape Memory Effect" by X. Le, W. Lu, J. Zheng, D. Tong, N. Zhao, C. Ma, H. Xiao, J. Zhang, Y. Huang, and T. Chen is licensed under CC BY 3.0 (ref. 67).

Targeting a different application, namely drug delivery at the inflammation region, PBA was grafted to the side chain of the alginate polymer to yield a highly specific dual-responsive hydrogel as promising wound dressing with low pH and high reactive oxygen species (ROS)-responsiveness.[69] Furthermore, antibacterial and anti-inflammatory activity was achieved by incorporating the corresponding drug-loaded micelles, which were composed of HA, into the

composition. Overall, the whole formula of this stimuli-responsive hydrogel included natural-based polymers. In a similar work, the boronate ester groups cross-link Alg–PBA to dextran, a diol biopolymer, thus resulting in a multilayer build-up responsive to hydrogen peroxide, a very promising stimulus for targeted drug delivery to diseased tissue.[70]

Certainly, multistimuli-responsiveness has been the focus of several works. For instance, glucose-responsive multilayer capsules were prepared by layer-by-layer deposition of an alginate derivative and polyvinylpyrrolidone (PVPON). Interestingly, the concentration-dependent glucose responsiveness was reached via the incorporation of phenylboronic acid moieties inside the alginate chain.[71]

Pettignano *et al.* reported the facile preparation of a multistimuli-responsive, self-healing, injectable and biocompatible soft biohydrogel exclusively from a boronic acid-modified alginate without the need for any external diol source and/or divalent cations (usually Ca^{2+}).[32] In addition to displaying good biocompatibility upon encapsulation of cells, which were able to survive gel injection and self-healing processes, the system exhibited extraordinary elasticity. Aware of the necessity to obtain more stretchable and tough hydrogels through different approaches,[9] the viscoelastic fluid-like behaviour of Alg–PBA esters was thoroughly studied to show that even modest changes in alginate concentration and pH have dramatic effects on the rheology of these systems.[72] Therefore, B–O dynamic covalent chemistry also offers the possibility to easily vary the flowability of the resulting system, which might be of practical relevance in specific applications, such as pharmaceutics, food industry or 3D printing manufacturing processes.

As a final note of the versatility of applications that result from the synergy between natural polymers and dynamic covalent chemistry, alginate was also a key component in nanogels

designed by a green, in situ fabrication strategy, which combined silver, poly(3-aminophenyl boronic acid), and sodium alginate, as a colorimetric nanoprobe for H_2O_2 detection in water.[73]

2.2 Hyaluronic acid-containing hydrogels

Even though alginate is one of the polysaccharide of choice in most of the recent publications, other natural polymers and plants derivatives have also been exploited as suitable biomaterials. For instance, as a main component in the human body, HA has become an attractive polysaccharide for engineering hydrogels for cell and tissue engineering, as well as the cosmetic industry. Indeed, taking into consideration the soft nature of the resulting biomaterials, current research envisions them as soft matrices for cartilage, heart, and neuronal regeneration.[55]

Auzély-Velty and co-workers have advanced rapid in this area of research along the last year.[74–77] Firstly, they studied the relationship between the properties of boronate ester cross-links and the mechanical behaviour of the resulting HA-based networks.[74] To that end, the HA backbone was modified with two different arylboronic acids, on the one hand, and with three different saccharide units, on the other. After the mechanistic study, it was shown that depending on the boronic acid derivative/sugar pair, the viscoelastic properties of boronate-crosslinked HA hydrogels can be tuned to better mimic, for instance, the dynamics of cellular microenvironments. Later, the same group reported for the first time self-crosslinking hydrogels based on HA modified with benzoxaborole (BOR) derivatives through the direct BOR–HA diol complexation at physiological pH,[75] while other HA-based dynamic covalent hydrogels were also formed by a facile route: phenylboronate ester cross-links bridged phenylboronic acid-grafted hyaluronic acid (HA–PBA) with sugar derivatives, maltose[78] or fructose.[76] Finally, in a subsequent work, they reported the design of the first dynamic nanogels for drug delivery

purposes made exclusively of polysaccharides modified with phenyl boronic acid groups or sugar moieties, namely HA–PBA, dextran-fructose and dextran-maltose (Figure 2).[77] The highly versatile nanoassembly, controlled by the formation of boronic ester cross-links, can be tuned by changing the sugar moiety and adjusting the pH.

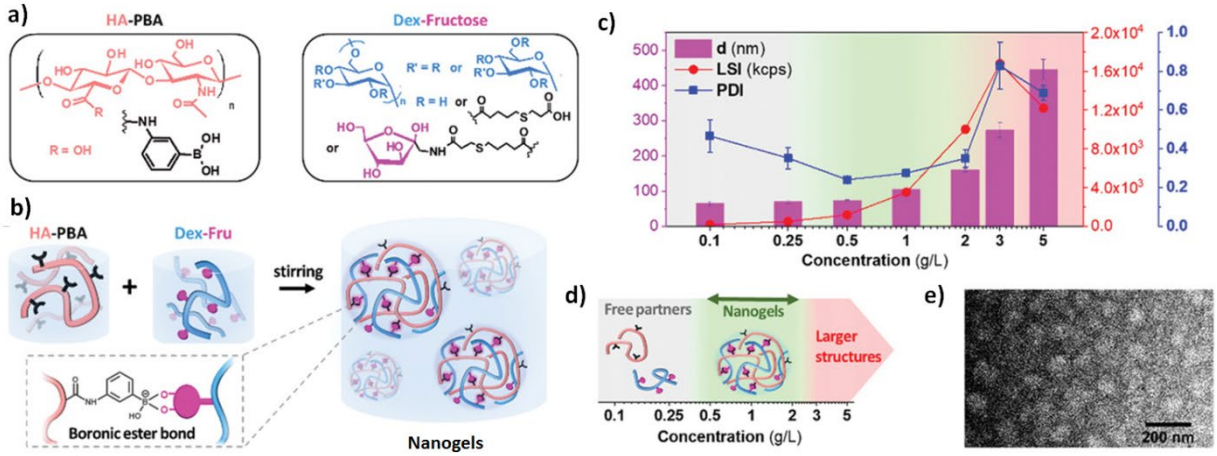


Figure 2 a) Chemical structures of HA–PBA and Dex–Fru. b) Principle of nanogel formation upon creation of boronic ester cross-links between partners. c) DLS measurements of mixtures of partners at different concentrations displaying values of hydrodynamic diameter (*d*), scattering intensity (LSI), and the polydispersity index (PDI). d) Schematic representation of the structure formed upon increasing partner concentration. e) Transmission electron microscopy image of nanogels at 1 g L^{-1} in PBS. Reprinted with permission from ref. 77 Copyright 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Following a synthetic approach analogous to Alg–PBA, Shi *et al.* prepared an injectable and self-healing hydrogel by dynamically cross-linking HA–PBA and PVA.[79] The resulting

biomaterial was presented as a H_2O_2/reactive oxygen species (ROS) responsive drug delivery system. Indeed, encapsulated neural progenitor cells (NPC) were viable and protected from ROS *in vitro* induced damage when H_2O_2 was present in the medium. Finally, the viscoelastic properties of the hydrogel, which were fully characterized, could allow its application as bioink for 3D bioprinting.

2.3 Other biopolymer-containing hydrogels

Nature has become a great source of inspiration and, in fact, it provides us with an incomparable pool of degradable biopolymers to choose from. For instance, laminarin, a low molecular weight, marine-derived branched polysaccharide, has started to attract some attention as a consequence of its availability and abundance, as well as its excellent therapeutic properties.[80] Indeed, Amaral *et al.* proved how the chemical modification of laminarin with PBA was possible and its cross-linking with PVA within seconds under physiological conditions produced a hydrogel biomaterial with advanced functionalities.[81]

Another biodegradable natural source that has been exploited in conjunction with dynamic boronic ester cross-linking is cellulose, the most widespread polymeric material in nature and widely applied as wound dressing for deep dermal burns, in addition to tissue regeneration (cartilage and skin).[55] Specifically, the hydrogel based on phenylboronic acid-modified carboxymethyl cellulose/PVA was applied for controlled release of doxorubicin (DOX), which showed a successive slow release profile.[82] Moreover, as a distinctive feature, the presence of ionized carboxyl groups rendered the hydrogel conductive. Other works are based on the same principle,[83] while rapidly self-healing nanocomposite hydrogel systems were obtained after introducing nanofibrillated cellulose[84] or rigid tannic acid-coated cellulose nanocrystal motifs into a PVA–borax dynamic network.[85,86] Targeting especific applications, such as cartilage

regeneration[87] or focal combination chemotherapy,[88] Balakrishnan *et al.* employed cellulose and gelatin to prepare *in situ* gelling hydrogels via dual cross-linking methods: borate–diol complexation of periodate oxidized carboxymethyl cellulose with borax and the subsequent Schiff's reaction of its aldehyde groups with the amino groups of gelatin.

An indispensable macromolecule for the human body, heparin, a negatively charged polysaccharide belonging to the glycosaminoglycan family, has been the centre of a wide number of investigations eager to produce analogous heparin-mimicking polymers and hydrogels.[89] As an example, Ren *et al.* developed a heparin-based hydrogel through the formation of boronate–maltose ester crosslinks to dynamically deliver the insulin-like growth factor IGF-1.[90]

Finally, we direct the reader to a few examples were other natural sources are exploited to produce hydrogels networks based on B–O dynamic covalent bonds, namely guar gum[91] and, even though no polysaccharide is applied, guanosine,[92] a purine nucleoside, and bioactive plant-derived polyphenols.[93]

3. FOCUS ON CHITOSAN-BASED HYDROGELS

Chitosan (CS), the second most abundant natural biopolymer after cellulose, is a broadly used linear amino polysaccharide, with superior biological and physical properties (*i.e.* self-assembly capacity, pH-responsiveness, biocompatibility, and biodegradability, as well as chelating, complexing, antioxidant, and film-forming properties). Indeed, such features have made CS the biopolymer of choice in numerous and varied applications, such as tissue engineering, wound dressing, drug delivery, anticorrosion, organo- and heterogeneous catalysis, polymer industry,

among others.[94] Hence, considering all the above, we have reviewed chitosan-based hydrogels more specifically in the current section.

CS, which is a random copolymer of D-glucosamine and *N*-acetyl-glucosamine, is obtained by the *N*-deacetylation of another polysaccharide, chitin.[95] When the degree of deacetylation exceeds 50%, the amino groups of chitosan are protonated at a pH lower than 6.2, which transforms the polymer into a water-soluble electrolyte, capable of interacting with negatively charged molecules.[95,96] On the other hand, under neutral or basic pH environments, the amino groups are deprotonated and engage in the formation of intermolecular and intramolecular hydrogen bonds with the hydroxyl groups, thus allowing the construction of poorly water-soluble hydrogel networks.

The plethora of amino and hydroxyl groups on the CS backbone endow the polymer with biodegradability and biocompatibility, while its hydrogen donor ability is responsible for its good electrical conductivity and good interaction with different ions; besides, good antimicrobial properties have also been reported.[95] Therefore, its chemical structure, as well as the fact that it is a basic polysaccharide, have contributed to its increased commercial interest, compared to other natural polymers, such as cellulose or alginate.[97] Indeed, CS represents an extremely versatile biopolymer for chemical modifications since, in addition to dynamic boronate ester bonds, imine bonds or Schiff-base linkages,[98,99] which occur between amino groups and aldehydes, are also used to modify chitosan.[100] Because of all that, CS is considered an ideal candidate for the preparation of dynamic covalent hydrogels that display pH-responsiveness and self-healing properties.[101]

3.1 Tissue engineering applications

Zhao *et al.* reported the design of dual-loaded smart hydrogels as bioactive wound dressings for diabetic ulcer, with loaded insulin and fibroblasts as model drug and cells.[102] The starting components of the system included phenylboronic-modified CS (CS–PBA), PVA and benzaldehyde-capped poly(ethylene glycol). Overall, the hydrogels promoted neovascularization and collagen deposition, thus enhancing the wound-healing process of diabetic wounds. Earlier, the same group had demonstrated the synthesis of dually responsive injectable hydrogels by combining the pH responsive imine bond and glucose responsive phenylboronate ester together (CS–PBA) (Figure 3).[103] Indeed, the responsiveness of the boronate ester bond is of highly relevance in the design of responsive delivery systems (see next subsection).

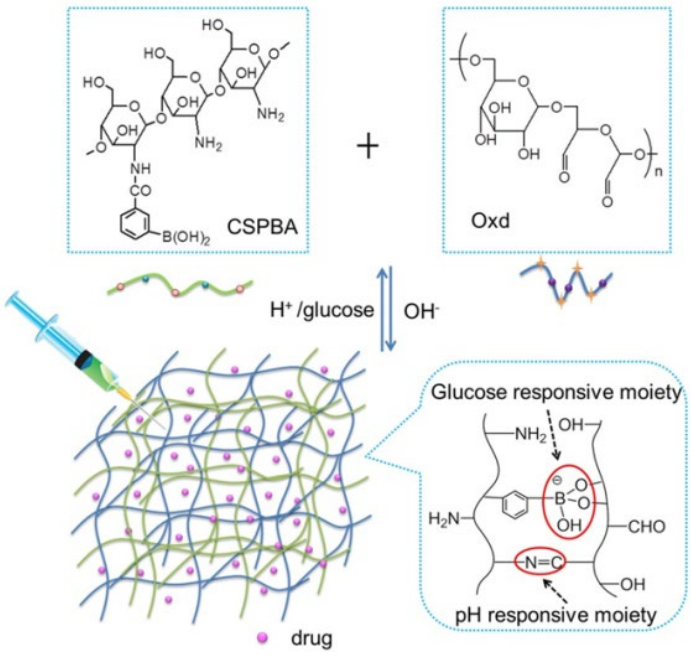


Figure 3 Illustrative synthesis of the CS–PBA/Oxd hydrogel. Reprinted with permission from ref. 103 Copyright 2015 Wiley Periodicals, Inc.

2-formylphenylboronic acid (2-FPBA), a non-toxic cross-linking agent, was applied to dually cross-link CS-based hydrogels. Specifically, 2-FPBA formed imine bonds with CS and hydrogen bonds with the OH groups of the boronic moieties.[104] The dynamic structure of the iminoboronate unit rendered hydrogels with good mechanical properties and reorganization according to various environmental stimuli, while the hydrogen bonding helped to further stabilize the supramolecular structure. Based on the anticancer and antifungal activity of the iminoboronates and the boric acid, respectively, these hydrogels were envisioned to treat yeast vaginitis. In fact, their antifungal activity was proved by inhibiting both the growth of two different *Candida* strains which are responsible for vulvovaginitis infections and the formation of their pathogenic biofilms.

Articular cartilage regeneration was the target application of a series of biocompatible, self-healing and multiresponsive (to glucose concentration and temperature) hydrogels based on the ester formation between lactose-modified CS (L-CS) and boric acid, using mannitol as a competitor in order to achieve gel homogeneity.[105] Here, the mechanical performance of the L-CS−boric acid network, in conjunction with the well-known bioactivity of L-CS, evidenced the interesting role that the resulting system can play as bioactive scaffolds and mechanic-transducers for intracellular signaling. More recently, Thibault *et al.* have investigated the potential use of a CS-PBA/bioglass composite material to repair bone tissue, improved adhesion being achieved through the development of boronate ester bond with carbohydrate molecules present on the surface of cells.[106] In another example, injectable and sprayable hydrogels were produced via a one-step procedure, which included O-carboxymethyl chitosan (CMCS), tannic acid (TA) and 1,4-benzenediboronic acid (BDBA).[107] In this case, as the authors showed, the balance of interactions between all three components (*i.e.* hydrogen bonding and dynamic

boronate ester formation) is essential to construct the hydrogels for hemostasis purposes. Indeed, the antibleeding properties of the hydrogel were tested on a mouse model and compared to other methods. Excellent hemostatic effects were observed owing to their rapid gelation (~10 s), biocompatibility, as well as self-healing, injectable, and sprayable abilities.

3.2 Responsive delivery applications

As reported by Stubelius *et al.,* boronic acid derivatives have been incorporated in polymeric systems both as a stimuli-responsive functional group and as a targeting ligand. Indeed, it reacts with several chemical markers of disease, such as ROS, adenosine triphosphate (ATP), glucose, and at reduced pH, but it also acts as ligands for diols, such as sialic acid, which make boronic acid-containing materials promising carriers for responsive delivery systems.[108]

Back in 2011, Wu *et al.* reported the glucose sensitivity of PBA-containing copolymers based on CS.[109] On the basis of this property, many groups have focused on studying and developing insulin delivery systems.[110,111] For instance, different hydrogels of poly(acrylamide-co-3-acrylamido PBA-*co*-CS grafted maleic acid) were synthesized using poly(ethylene glycol) diacrylate (PEGDA) as a cross-linker to serve for glucose sensing and insulin delivery.[112] In response to glucose concentration, the hydrogel displayed swelling-shrinking behavior: at low glucose concentration the hydrogel shrank because of the 2:1 boronate-glucose binding, while it swelled at high glucose concentration because of 1:1 boronate-glucose complexation. More recently, several CS-based hydrogels that make use of the dynamic boronate ester bond have been prepared, tested and used as carriers for glucose-responsive insulin release. These materials, which exploited the exceptional performance of the PBA glucose-responsive system, displayed advanced features, such as high insulin loading capacity, function under physiological

conditions, satisfactory glucose adsorption, and controlled-rate release of insulin, among others.[113–116] Similarly, the preference of borate ions to form a complex with glucose was exploited to produce films based on CS and PVA that disintegrated by a glucose-triggered mechanism to release anticancer drugs.[117,118]

Interestingly, Li *et al.* exploited the benefits of a double-crosslinked dynamic network hydrogel, with enhanced mechanical properties (G' = 5.7 kPa) and mucoadhesive ability, to deliver the antitumor drug DOX.[119] In comparison to other delivery system, the reported biocompatible and self-healing hydrogel constructed by simultaneously cross-linking PVA and glycol chitosan via borate ester and imine linkages, achieved a superior performance when used in an *in vivo* mouse model, without provoking inflammation or tissue damage, thus proving its biosafety and safe implantability, as well.

With the aim of improving delivery efficiency, boronate ester dynamic chemistry has been applied recently to nanomaterials.[108] For instance, boronic acid-rich CS nanoparticles where designed to deliver DOX to 3D multicellular spheroids and tumors on the basis of the reversible and rapid reaction of PBA groups with sialic acid residues in tumor tissue to form boronate esters, which increased the residence time and uptake at a target site.[120] Another tumor-targeting hydrogel was designed by using a lactose-modified CS that contained PBA moieties and a HA derivative modified with dopamine moieties. This yielded a pH- and hyaluronidase-responsive nanogel that allowed for the controlled delivery of DOX and NO inside the tumor cells.[121]

3.3 Technological applications

It is a fact already that more and more electronic devices are being designed for a potential integration into the human body for health purposes. To that end, biodevices need to be efficient,

as well as biocompatible and with long term applicability. Matching the mechanical properties of biological tissues, soft electronic devices rely on "smart" hydrogels with either shape memory behavior or reversible actuation for sensor, actuation, or artificial muscles applications.[122] However, the design of robust, stretchable, self-healing, and biocompatible hydrogel electronics and devices represents a critical challenge in the emerging field of soft materials, electronics, and devices.[123] For this reason, although few examples can be found in the literature, dynamic covalent chemistry, and specifically boronate ester formation, represent a potential solution to overcome this issue.[124] For instance, a hydrogel with triple shape memory properties was obtained by combining the formation of reversible Schiff base bonds between the amino groups of CS and aldehyde groups of oxidized dextran, which was applied to memorize temporary shapes, with the chelation effect of various metal cations which fixed other temporary shapes.[125]

A great example of the immense possibilities that combining natural polymers with dynamic covalent chemistry offer is found in the work recently published by Zhou *et al.*[126] They reported a multi-responsive luminescent hydrogel prepared by mixing phenylboronic acid-modified gelatin, catechol-modified carboxymethyl chitosan, 3,5-dinitrosalicylic acid, and Eu^{3+} ions through a facile heating-cooling process, which resulted in an interpenetrating polymer network. Firstly, the coordination of Eu^{3+} ions and ligands rendered the hydrogel highly fluorescent. Moreover, such luminescence was a reversible phenomenon to four different stimuli, which included temperature, acid/base, redox, and salt. Interestingly, the multiple responsiveness was exploited as a method to encrypt and decrypt information for applications such as anticounterfeiting and data security protection (Figure 4). Not only that, but the system also displayed naked eye sensing of glucose, shape memory, self-healing based on dynamic bonds, enhanced mechanical properties based on salt responsiveness, and antibacterial activity. Hence,

the overall combination of features allow for the application of the hydrogel in anti-counterfeiting materials, optical devices, and flexible sensors, in addition to biomedicine.

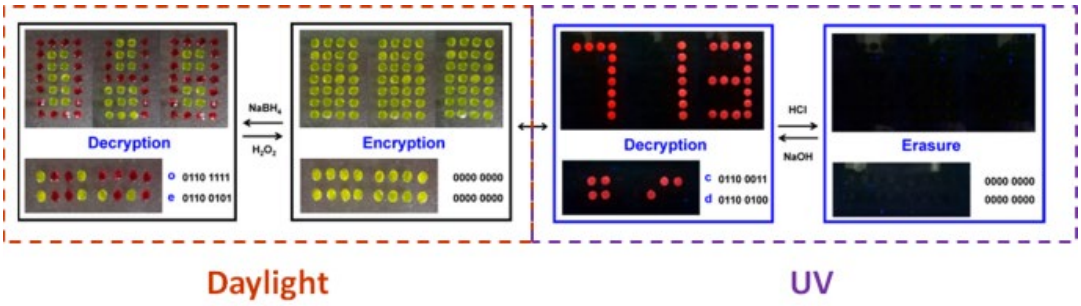


Figure 4 Photographs of number- and binary-coded hydrogel disc arrays with the encryption, decryption, and erasure processes. Reprinted with permission from ref. 126 Copyright 2020 American Chemical Society.

Another area of research that is showing great promise is the design of artificial electric skin, which strongly adheres to the human body while detecting different responses, for biomedical prosthetics, human/machine interfaces, wearable devices and soft robotics. Wang *et al.* reported an ionic gel skin as shape-adaptable and skin-friendly sensor for human motions based on the *in situ* polymerization of (3-acrylamidophenyl) boronic acid and acrylamide in the presence of chitosan containing catechol groups.[127] In this work, it is evident how the reversible cross-linkers of H-bonding and dynamic covalent bonds not only do endow the gels with strong adhering strength on different surfaces and rapid self-healing, but also with large stretchability and plasticity (Figure 5).

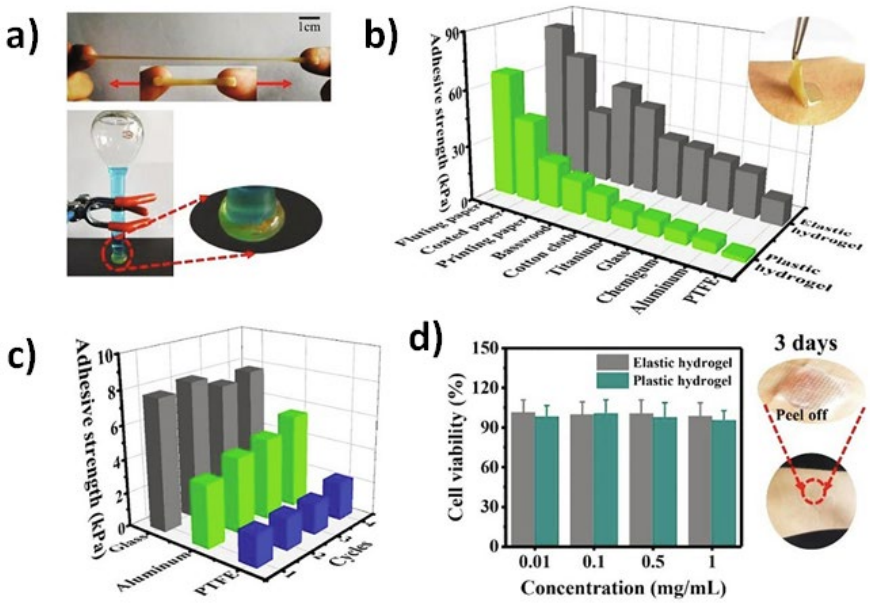


Figure 5 Adhesion characterization of plastic gel and elastic gel: (3-acrylamidophenyl) boronic acid and acrylamide in the presence of chitosan containing catechol groups. a) Adhesion to skin to withstand 400% deformation (Top) and to glass to prevent liquid leakage (Bottom). b) Adhesive strength to various substrates. c) Adhesion stability of plastic gel during cyclic adhering and detaching. d) Biocompatibility evaluated by MTT cytotoxicity and 3 days' skin test. Reprinted from Chem. Eng. J., 398, P. Wang, D. Pei, Z. Wang, M. Li, X. Ma, J. You, C. Li, Biocompatible and Self-Healing Ionic Gel Skin as Shape-Adaptable and Skin-Adhering Sensor of Human Motions, 125540, Copyright (2020), with permission from Elsevier (ref. 127).

Other technological applications might include the improvement of paper adhesive properties to produce high value products. Zhang *et al.* developed self-assembly, multilayer, thin films based on the ester formation between CS–PBA and PVA.[128] The construction of the layer-by-layer assembly was controlled by pH adjustment, thus taking advantage of the pH sensitivity of the boronate ester bond. Indeed, the next generation of adhesives designed on the basis of

dynamic chemistry and biopolymers can aid numerous applications in soft material science beyond biomedicine.

CONCLUSIONS AND FUTURES PERSPECTIVES

The studies reported herein indicate the wide range of potential biomaterial hydrogels and advanced functional applications that can be obtained when combining natural polymers and dynamic covalent chemistry, thus producing 'smart' systems that respond to external stimuli and interact with the surrounding environment. Indeed, boronic ester bonds provide a versatile approach to assemble responsive hydrogel networks. Moreover, fine control over the material properties is achieved by playing with the chemistry of the reversible bond, as well as the network topology. Interestingly, despite the still incomplete knowledge of the boronic ester chemistry itself, the role it plays in producing advanced soft matter is validated by the number of reported systems and the range of possibilities considering its application.

Among the different uses reviewed, the rational design of responsive delivery systems stands out. We consider that dynamic boronic ester bonds can undoubtedly advance in this area. For instance, the possibility to inject, following a minimally invasive procedure, a self-healing hydrogel to the site of interest that also interacts with biological inputs and responds accordingly by releasing in a controlled manner molecular therapeutics, represents a not so far scenario. Hence, from a biomedical point of view, the incorporation of boronic acid moieties to natural polymers, and especially into CS, as glucose-responsive units has been extensively investigated to engineer successful insulin delivery systems. However, even though glucose is the most widely studied biological trigger, efforts are being placed in considering other agents, such as pH or sugars, to obtain a more specific release.

The formation of boronate esters (*i.e.* the stability of the reaction between diols and boronic acid) is highly dependent on the pH, which influences the self-healing efficiency and the mechanical properties of the resulting system. However, although this could be a disadvantage since biological environments are found at neutral pH (cells at pH higher than 8 might die), we have seen how recent research overcame this issue obtaining self-healable systems that encapsulate cells and display excellent cytocompatibility. Overall, dynamic scaffolds and 3D cell culture systems are being developed to modulate cell attachment and other functions, investigate cell-cell interactions, or act as sacrificial templates. In contrast, an aspect that still requires some research effort is the combination in one system of both self-healing and robustness properties to improve the stability of hydrogels with boronic esters as cross-linkers. Hence, despite their uses in cell culture applications, both *in vitro* and *in vivo*, this aspect still requires some development.

Finally, an interesting challenge remains from a technological perspective. Indeed, although some examples have been reported, the immense range of possibilities that wait for polysaccharide-based hydrogels incorporating dynamic covalent chemistry will undoubtedly produce advanced electronic wearable devices, biosensors or actuators. Moreover, the already known properties, such as self-healing, adaptability, or shape-memory, could be coupled with enhanced electronic and ionic features if electrically conductive materials are embedded into the hydrogel network. Finally, these technological devices could benefit from the adhesive properties that are intrinsic to some natural polymers, thus avoiding the taping of wearable devices to human skin.

Overall, as researchers further exploit the knowledge gained through chemistry and apply it to biomaterials science, hydrogel devices with advanced functional properties can

revolutionize the fields of tissue engineering and drug delivery, as well as pave the way to biotechnological applications in humane/machine interfaces.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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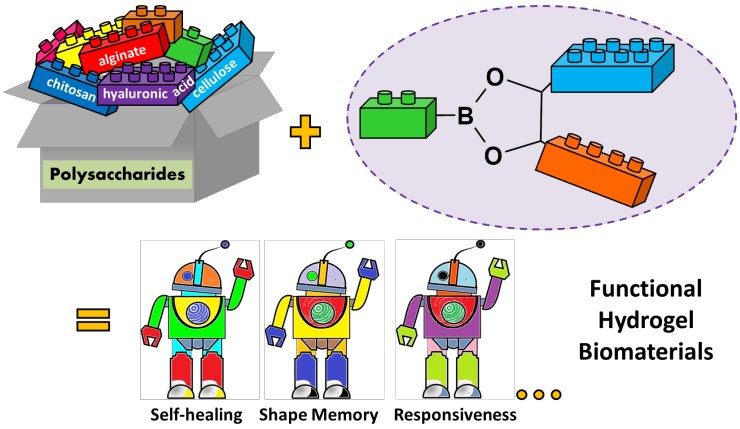

Dynamic covalent B–O bonds and polysaccharide building blocks: a versatile and relevant emerging research field to design advanced functional hydrogel devices.