Materials Today Chemistry 26 (2022) 101222

Contents lists available at ScienceDirect

Materials Today Chemistry

journal homepage: www.journals.elsevier.com/materials-today-chemistry/

Advanced hydrogels based on natural macromolecules: chemical routes to achieve mechanical versatility

C. Mortier [a, b, ***, d], D.C.S. Costa [a, **, d], M.B. Oliveira [a], H.J. Haugen [b], S.P. Lyngstadaas [b], J.J. Blaker [c], J.F. Mano [a, *]

[a] Department of Chemistry, CICECO – Aveiro Institute of Materials, University of Aveiro, Campus Universitário de Santiago, 3810-193, Aveiro, Portugal
[b] Institute of Clinical Dentistry, University of Oslo, Norway
[c] Department of Materials & Henry Royce Institute, The University of Manchester, Manchester, M13 9PL, UK

ARTICLE INFO

Article history:
Received 22 June 2022
Received in revised form
21 September 2022
Accepted 22 September 2022
Available online xxx

Keywords:
Hydrogel
Double networks
Dual-crosslinked networks
Interpenetrating networks
Biomacromolecules

ABSTRACT

Advances in synthetic routes to chemically modify natural macromolecules such as polysaccharides and proteins have allowed designing functional hydrogels able to tackle current challenges in the biomedical field. Hydrogels are hydrophilic three-dimensional systems able to absorb or retain a large volume of water, prepared from a low percentage of precursor macromolecules. The typical fragile elastic structure of common hydrogel formulations often limits their usage. Three main fabrication strategies involving several compounds or multimodified materials known as double networks, dual-crosslinked networks, and interpenetrating networks have been explored to impart mechanical strength to hydrogels. Widely investigated for synthetic polymers, these approaches allow obtaining added-value hydrogels with a large spectrum of mechanical properties. Advances in the development of such hydrogels with biomacromolecules as main constituent materials have enabled the fabrication of hydrogels with improved key properties for medical use, including biocompatibility, controlled release of active substances and tailored biodegradability, while exploring sustainable sources. This review describes recent advances in the use of proteins, as well as natural and semi-synthetic polymers for the fabrication of hydrogels for biomedical applications. Structures processed *via* double network, dual-crosslinked, or interpenetrating network strategies are reviewed, and emphasis is given to the type of chemical modifications and reactions, as well as the covalent and non-covalent interactions/bonds involved in those mechanisms.

1. Introduction

Hydrogels for biomedical purposes have been widely investigated over the past two decades. Those have mostly been obtained using synthetic polymers [1], such as polyacrylamide (PA) [2] or polyvinyl alcohol (PVA) [3]. A plethora of mechanical behaviors can be obtained using different synthesis approaches leading, for example, to high-toughness structures compatible with high stretchability [4], or soft hydrogels often correlated with self-healing and/or injectability properties. This wide range of mechanical properties is ascribed to the possibility of easily modifying synthetic monomers, as well as to controlling and assessing their polymerization rates. However, uncertainty about the lack of biodegradability and biocompatibility of most synthetic systems remains [5,6]. Additionally, the petroleum origin of synthetic polymers constitutes a drawback regarding their sustainability. Some natural macromolecules possess inherent biodegradability in physiological conditions, well-reported cytocompatibility, and even antimicrobial properties. Therefore, their integration into biomedical hydrogel compositions could prevent postimplantation rejection and infections. Coming from usually under-used and discarded human, animal, or plant by-products, the use of these biomaterials contributes to maintaining the biomass system with a cyclic usage of materials along their lifespan. From a processing standpoint, the frequent hydrophilicity of nature-derived molecules often avoids or drastically reduces the usage of organic solvents during chemical modification reactions or gelation

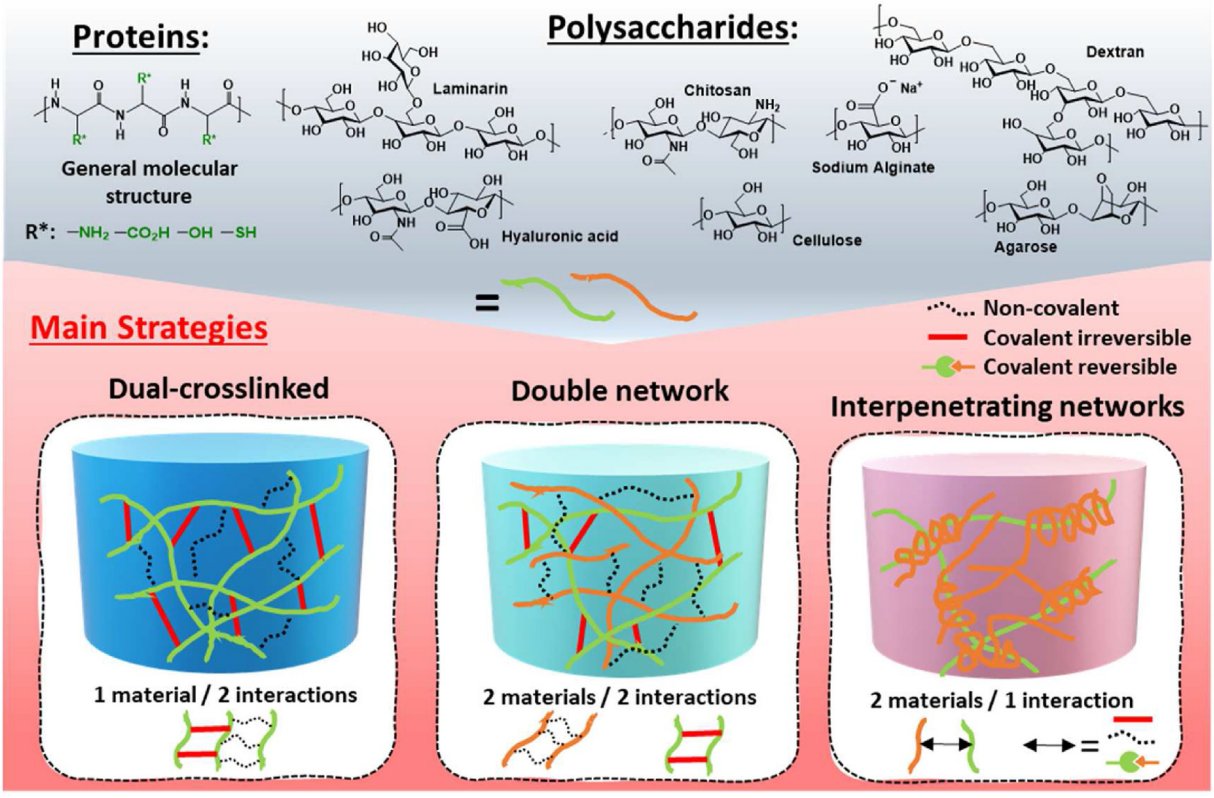
* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: claudio.mortier@ua.pt (C. Mortier), doracosta@ua.pt (D.C.S. Costa), jmano@ua.pt (J.F. Mano).
[d] Equal contributions.

https://doi.org/10.1016/j.mtchem.2022.101222

processes. The chemical modifications of natural macromolecules have permitted the increase of key hydrogel features such as adhesiveness and toughness [7] or self-healing [8]. However, both wide-ranging modifications and respective characterization of natural macromolecules still constitute a significant challenge when compared with well-reported chemical functionalization and characterization of synthetic polymers. Currently, a main challenge for natural-based hydrogel fabrication lies in the search for materials that enable achieving mechanical properties like the ones previously obtained using synthetic materials, while maintaining the expected high biocompatibility and biodegradability of natural ones (Scheme 1).

A straightforward analysis of the mechanical properties of hydrogels is often focused on stiffness, culminating simply in the division between stiff and soft structures. However, considering the movements associated with the healthy function of most tissues and organs, the functional response of hydrogels to high deformations and their ability to recover their properties after several cycles of mechanical stimulation are more closely correlated with what might be real mechanical stimulation during medical use. This performance also correlates with the opposing concepts of brittleness and toughness, while associated with adequate stiffness properties. In fact, recapitulating the peculiar behavior of several animal tissues – such as bone, cartilage [9], skin or tendon – characterized by the ability to be cyclically deformed and recover their initial properties in a time-dependent viscoelastic manner is a goal that has been sought by several authors dedicated to the design of hydrogels. Despite the wide range of mechanical and viscoelastic properties showcased by human tissues, it is notable that most tissues rely on self-assembled common constituents, namely collagens, glycosaminoglycans, and inorganic particulates (in bone and dentin) [10]. This can be seen as an inspiring premise to use finely modified and assembled polymeric biomolecules to allow for different hierarchical scales of covalent and non-covalent bonding, enabling the achievement of hydrogels with tissue-like mechanical response.

Soft hydrogels are usually fabricated from one component with single or multiple chemical modifications [11,12]. Structures with a low elastic modulus are often associated with properties as injectability and self-healing capability, rendering them suitable for three-dimensional (3D) printing [13]. Such systems are usually evaluated using rheological measurements, permitting the assessment of parameters such as the storage and loss modulus: G' and G", respectively [14]. At this scale, the concept of cohesion is especially relevant, referring to the viscoelastic properties represented by the internal strength inside the hydrogel and between the different entities composing the hydrogel [15]. For strong hydrogels, mechanical properties are generally evaluated under compression or tensile stresses. The processing of tougher hydrogels usually requires the use of more than one network, especially when natural materials are involved. Gong et al. [16–18] pioneered the development of a new class of hydrogels associating one brittle/strong network combined with another soft/elastic one to form a double network (DN) system. In these systems, two networks formed by different types of chemical interactions coexist in the same hydrogel, although they are independent from each other. Most of the previous strategies leading to tough hydrogels followed the principles of DNs or took inspiration from the concept. Interpenetrating networks (IPNs) hydrogels, on their turn, are composed by two or more networks interacting non-covalently, with mechanical strength remaining generally on the high number of weak interactions with a low enthalpy for each interaction [19]. The two networks react between each other, which is the main distinctive point when compared to DN approaches. Finally, hydrogels involving a single network able to create two types



Scheme 1. Main biomacromolecules used and the general approaches for hydrogel fabrication.

of bonds are termed dual-crosslinked (DC) [20]. Recently, these concepts have been investigated using natural compounds as a main component, leading to satisfactory mechanical properties, namely in achieving materials covering all the spectra of mechanical behavior, such as high deformability, toughness and cyclic recovery, hence keeping up with the current developments in hydrogel processing science. This allows for the targeting of advanced biomedical applications such as tailored drug delivery systems [21], wound healing multi-layer topicals for severe burns [22] or venous/diabetic ulcers [23–25], bone repair substitutes [26] or skin and cartilage regeneration [27,28].

Adhesiveness, explored in more detail in section 4.2, has elicited high interest in the materials science and biomedical engineering communities. The fabrication of highly adhesive systems depends on an adequate balance between the adhesive and cohesive properties of the developed materials [15]. Whereas the term 'adhesion' refers to the ability of a material to directly adhere to an external substrate, the concept of 'cohesion' is associated with the intermolecular bonds within the bulk of the material. The role of the cohesion system has been proven to be extremely important in preventing the self-disintegration of adhesive materials due to low intermolecular forces within the materials when compared with the material–substrate adhesive forces. Therefore, the establishment of networks comprising different levels of disruption forces within the same materials could be paramount to processing highly effective biological glues. Adhesive materials, in the form of hydrogels, have been explored in the biomedical field as self-fixating devices, as well as glues to counter hemorrhagic phenomena. One peculiarity associated with the development of adhesives for medical use is their requirement for performance under hydrated/moisture conditions. Therefore, researchers in the field have directed significant research effort into chemistries based on mussels and other living organisms capable of naturally establishing strong adhesions in wet environments [29].

The main sources of biomacromolecules available in nature are polysaccharides and proteins [30,31]. Polysaccharides are composed of chains of repetitive monosaccharide units linked by glycosidic bonds [32]. Polysaccharides contain available functional groups such as amines, carboxylic acids, and hydroxyls for chemical modifications. On the other hand, proteins are described as a mix of amino acids such as lysine and glycine [33] and are classified by their structure organization level as primary, secondary, tertiary, and quaternary [34–37]. These complex structures make proteins harder to modify, which has made the application of DN and DC approaches more challenging than with polysaccharides. Moreover, proteins are also more sensitive to pH and temperature [38] than polysaccharides are, which could induce precipitation or aggregation. For example, Baler et al. [36] studied bovine serum albumin-based hydrogels at various pH values, and observed two forms: 1) a compact structure so-called *N* form, and 2) a more open structure, so-called *F* form, enabling a better aggregation of bovine serum albumin units leading to the formation of a non-covalent hydrogel. At physiological pH, most proteins are negatively charged [39,40], hampering ionic interactions with negatively charged species or enabling their occurrence without inducing gelation. However, negative ionic species interfere with several physicochemical parameters of proteins, such as surface tension, solubility, stability and denaturation, impacting their conformations, described as the Hoffmeister effect [41,42]. Such variation of the conformation can be explored as an advantage to enhance mechanical properties. For instance, gelatin – one of the most used proteins for hydrogel manufacturing – has the capability to form tougher hydrogels after a cycling temperature process [43,44].

In this review, recent strategies reported to develop hydrogels for biomedical applications will be addressed with a focus on DN, DC, and IPN approaches using mainly polysaccharides and proteins as raw materials. Across all strategies addressed in this review, an extensive focus is on the main biomacromolecules used for hydrogel development. Emphasis is given to the reactions most frequently used to modify these biomacromolecules, leading to specific types of networks: dynamic or static, from weak/ionic interactions to strong types of bonding, and how all these interactions could coexist to form innovative systems.

2. Photopolymerizable natural networks

Photopolymerization of modified biomacromolecules, most commonly under UV light exposure, is commonly used due its fast reaction and suitable combination with cells for biological purposes. Chemical modification with vinyl moieties and the frequent use of biocompatible photoinitiators do not affect either the stability or the content of the initial biomacromolecules. Photopolymerized natural networks constitute one of the most frequently used strategies to obtain DN hydrogels, generally combined with a second step such as soaking (with molecules that enable the establishment of a secondary network) [45] to achieve advanced hydrogels.

Polysaccharides have been intensively used in photopolymerized systems. Chitosan (CHT), comprising native properties such as low immunogenicity, antifungal and antibacterial activities, wound healing effect, and hydrophilicity [46], has often been considered a promising candidate for the fabrication of advanced hydrogels [47]. CHT is constituted of *N*-glucosamine units with a variable degree of acetyl groups in the 6-amine position and can mainly be obtained by partial deacetylation of chitin [48]. Chitin is fully acetylated, inducing poor solubility in aqueous media, which constitutes an obstacle for chitin-based biomaterials development. Typically, if the degree of deacetylation (DDA) is beyond 50%, this polysaccharide is termed CHT; otherwise, the name chitin is used [49]. CHT is the only polysaccharide that has a positively charged skeleton that is directly proportional to the DDA. The DDA affects the cell response; for example, after primary human osteoblasts seeding on CHT sponges of high and low DDA, Sukul et al. [50] observed that lower DDA induced an increase in the secretion of osteoprotegerin and sclerostin as compared with higher DDA. CHT-positive charges below its pKa (*ca.* 6.4) are commonly used to generate electrostatic networks with negatively charged species such as sodium phytate or sodium tripolyphosphate [51]. Costa et al. [52] combined two kinds of CHT in the same hydrogel – the first one by covalent bonding and the second one by electrostatic interactions – resulting in a hydrogel with high compressive strength (*c.a.* 20 MPa) and ability to cyclically recover from deformation. Independently of the electrostatic interactions, the covalent network showed stiff but brittle mechanical properties, which are the typical properties needed for the fabrication of the first precursor networks of DN hydrogels. Photosensitive moieties could be grafted onto CHT by peptide coupling or through direct substitution with methacrylic anhydride [53]. Moreover, CHT does not require a high degree of methacrylation [54] (around 15–20%) to form a hydrogel. Using similar strategies based on the combinations of electrostatic and methacrylated networks, alginate (Alg) is one of the most used natural polymers. Alg is a natural polysaccharide extracted from brown algae (*Laminaria hyperborean* or *Laminaria digitata*) [55] composed of an alternation of (1,4)-linked α-L-guluronate, called G-blocks, and β-D-mannuronate, called M-blocks. One advantage of Alg is the possibility to create rigid structures through the chelation of the G-block (composed by 4–6 carboxylate groups) with calcium cations [48,56]. Many strategies can be used by controlling the molecular ratio between Alg G-blocks and calcium cations [57], which affect the rigidity and

elasticity of the hydrogel. Gao et al. [58] reported a degree of Alg methacrylation up to 61% used on a dual-crosslinked hydrogel. In this strategy, the UV exposure was performed before the calcium crosslinking step, which allowed for targeting different biomedical applications, such as hydrogel fibers, exhibiting a relatively high tensile stress of 6 MPa for 140% elongation, and adding the possibility for cell encapsulation. Hyaluronic acid (HA) is also an interesting starting material when modified with photocrosslinkable motifs [59,60], mainly due to its good water solubility at pH 7 and its ability to form high-water content hydrogels [61,62]. With the development of medical 3D printing, injectable methacrylated natural polymer solutions [63] have been widely researched to print, for instance, biocompatible bone and tissue prostheses. For this application, cellulose – an abundant polysaccharide composed only by D-glucose units [64,65] – is commonly used. Ni et al. [66] mixed a methacrylated hydroxypropyl methylcellulose (HPMC-MA) with a silk fibroin (SF), forming an injectable solution (Fig. 1). Formulated with bone marrow mesenchymal stem cells (BMSCs), the precursor solution could be printed with the desired shape. Laminarin – which is another polysaccharide extracted from algae [67] – has also been modified with vinyl groups to obtain hydrogels with stiffness tuneable by UV exposure [68].

Gelatin and collagen are the most used proteins for the fabrication of hydrogels, including those with advanced mechanical properties [34–70]. Modifications with photosensitive moieties are commonly used to set up covalent networks in DC or DN approaches [71,72], in addition to the self-organization property of their quaternary structure. For example, Liu et al. [73] studied the soaking of methacryloyl gelatin (GelMA) into a highly concentrated tannic acid (TA) solution to produce a hydrogel with high compressive strength, exhibiting a compressive modulus of 200 kPa and a maximum compressive stress of 4.5 MPa. The acidic properties of TA did not seem to affect the biocompatibility of hydrogels and allowed for good adhesion to skin tissue without sutures. Strategies involving systems combining natural polymers and proteins – both methacrylated – have been considered. GelMA has been widely investigated to manufacture biocompatible scaffolds mimicking the extracellular matrix, and it has been combined with methacrylated polysaccharides, such as CHT [74], for the development of injectable hydrogels with wound defect filling ability, or HA [75] leading to satisfactory mechanical properties and drug screening applications. Even if the gain in terms of stiffness is not negligeable, such strategies showed a lack of resistance at high compression or tension; therefore, a posttreatment, such as soaking with TA [76], was necessary to enhance the mechanical properties. Zhang et al. [77] investigated a system with three components with methacrylated CHT and GelMA with degrees of substitution 26 and 68%, respectively, coupled with polyhedral

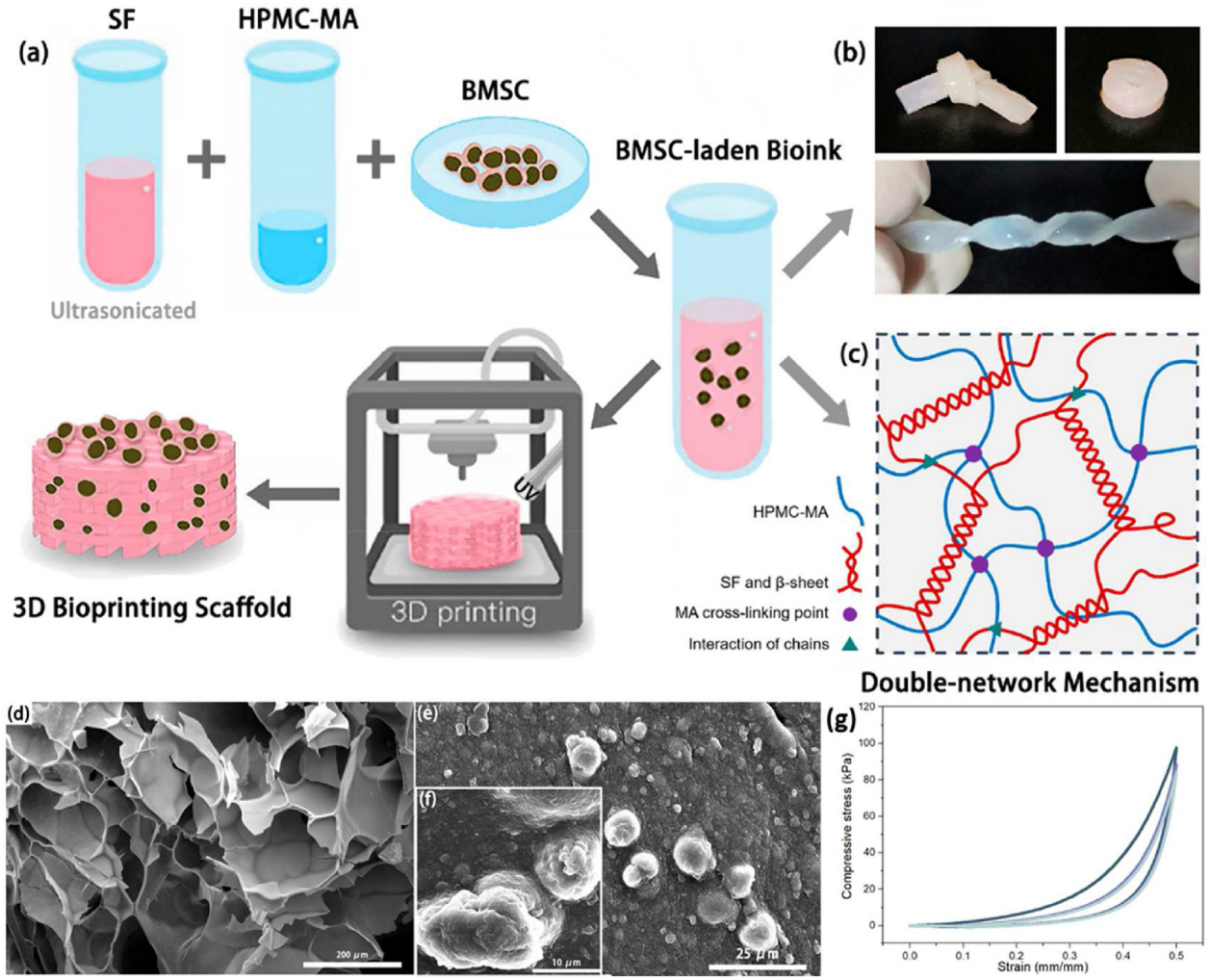


Fig. 1. Fabrication of an SF/HPMC DN hydrogel. (a) The process of bioprinting SF/HPMC scaffold, (b) the actual view of SF/HPMC hydrogel, (c) DN mechanism of the SF/HPMC hydrogel, (d,e,f) SEM images of HPMC-MA/SF loaded with BMSC, and (g) compressive strain vs strain cycling curves of HPMC-MA/SF. Adapted from Ref. [66] with permission, copyright 2020 ACS.

oligomeric silsesquioxane. The latter is composed of an inorganic cluster structure increasing the mechanical properties while enabling the maintenance of biodegradable behavior. Finally, blood-derived [78] proteins such as rich platelet lysates [79] have also been widely used in methacrylated networks to produce soft scaffolds suitable for cell culture. However, so far, there are no advanced DC or DN approaches involving such proteins.

3. *In situ* hydrogel formation based on natural macromolecules

Although significant advantages are obtained using methacrylated networks, either synthetic or natural, they require a fabrication process through (i) the transformation of modified biomacromolecules previously obtained *via* a full-synthesis process followed by (ii) polymerization through exposure to light or radical reaction. Such multistep synthesis and fabrication approaches present a drawback for the production and commercialization of the resulting hydrogels. Nevertheless, other types of reactions between natural networks involving other types of chemical modifications allow for the fabrication of a final hydrogels in one single step or even spontaneously *in situ* conditions (Table 1). The high density of reactive groups such as amine, carboxylic, or hydroxyl natively present in many biomacromolecule structures facilitates the establishment of many networks. This pathway allows for targeting properties such as stimuli responsiveness, reversibility of soft/tough hydrogel properties, and achieving transient injectability [80].

3.1. Fully polyelectrolyte associations

DN and IPN may be used for advanced hydrogel structures using only electrostatic forces to connect different networks, generating non-covalent crosslinked biomaterials [100]. The mixture of high density of positive and negative charges allows to reach IPN by ionic interactions. Such strategies can be controlled by the pH, directly affecting the number of charges in the biomacromolecules structures, and leading dynamic responses for soft hydrogels with drug delivery applications. A useful example of natural compounds to highlight this strategy is the combination of a positively charged CHT and negatively charged Alg to establish an initial stable electrostatic network [101]. Tang [81] and co-workers mixed CHT and Alg – positively and negatively charged, respectively – which enabled directly obtaining the first network based on polyelectrolyte assembly. The DN was subsequently achieved by ionic crosslinking, by soaking in a calcium chloride bath to trigger the

Table 1
Examples of full natural-based hydrogel formulations.

Constituent macromolecule(s)	Strategies and main chemical routes	Main properties – applications	Ref.
CHT	DC photopolymerization + hydrogen bonding or electrostatic interactions	High mechanical strength, recovery from strain – cell encapsulation, drug screening	[52]
Alg	DC photopolymerization + hydrogen bonding or electrostatic interactions	Microfibres, injectability, scaffold production – cell encapsulation	[58]
CHT/Alg	DN hydrogen bonding or electrostatic interactions	High compressive properties, self-healing, injectability – heavy metal ions removal, electronic devices, waste treatment	[81]
CHT	DN covalent bonds + hydrogen bonding or electrostatic interactions	High mechanical properties – cytocompatibility, super-absorbent electronic devices	[82]
Modified gelatin	DC Schiff bases/Michael addition + hydrogen bonding or electrostatic interactions	Soft hydrogel, injectability, adhesion properties – wound closure, antimicrobial, drug delivery	[83]
Alg/gelatin/CMC	Multinetwork photocrosslinking + Schiff bases	Soft hydrogel, injectability – wound dressing material	[84]
CHT/Dextran	DN Schiff bases + oxidation + hydrogen bonding or electrostatic interactions	Soft hydrogel, injectability, Self-healing, Adhesive properties, pH sensitive – wound dressing	[85]
CHT/Me-cellulose	IPN Schiff bases + thermal treatment	Release of bioactive molecules, soft materials, dynamic hydrogel, self-healing – test for cosmetic applications	[86]
HA/micelle	IPN/DN Schiff bases + hydrogen bonding or electrostatic interactions	Adhesive properties, soft hydrogel, self-healing – wound dressing	[87]
HA	IPN boronate ester	Injectability, cytocompatibility, self-healing – cell encapsulation	[88]
Alg/EGCG	DN boronate ester + oligomerisation	Conductive hydrogel, self-healing, stretchability, – biocompatibility, implantable device	[89]
Silk/gelatin	DN enzymatic bond + thermal rearrangement	High mechanical properties – bone regeneration, biodegradation	[90]
Alg/gelatin	DN enzymatic bond + hydrogen bonding or electrostatic interactions	Soft hydrogel – 3D cell culture, drug screening	[91]
Alg	DC click reaction + hydrogen bonding or electrostatic interactions	Soft and tough hydrogel, self-healing, injectability – biocompatibility, cell encapsulation	[92]
Dextran/gelatin	IPN click reaction	Soft hydrogel, injectability – drug release	[93]
HA/collagen	IPN bisulfide bridge + click reaction	Injectability – drug release, cartilage-filling biomaterial	[94]
HA	DN photopolymerization + host–guest interactions	Soft/tough dynamic hydrogel, shear-thinning – cytocompatibility, dynamic cell culture	[95]
CMC/CD/agarose	DN host–guest interactions + thermal rearrangement	Soft hydrogel, injectability, self-healing, photo switchable, reduction-responsive – drug-release systems	[96]
CHT/gelatin	DC/DN pseudo polyrotaxane system/hydrogen bonding or electrostatic interactions/structural rearrangement	Shear thinning, self-healing, soft hydrogel, injectability – bioink applications	[97]
Multi-modified CHT	DN photopolymerization + hydrogen bonding or electrostatic interactions	Tough hydrogel, injectability – tissue adhesion, antibacterial activity	[98]
Multi-modified CHT	DC click reaction + hydrogen bonding or electrostatic interactions	Soft hydrogel, injectability, self-healing, pH sensitivity – controlled crosslink density, thermodynamic properties, anti-EDTA performance	[99]

formation of the complex Alg G-block reaching a compressive strength of 70 kPa at 70% maximum deformation. Gierszewska et al. [102], instead, took advantage of the ability of CHT to be ionically crosslinked using salts such as tripolyphosphate. CHT can be studied with both negative and positive charges using carboxymethyl chitosan (CMC-CHT), which can also enhance its water solubility [103]. Depending on the pH of the media, CMC-CHT can behave differently, with the capability to interact with positive and negative charges. In an interesting approach resembling an IPN, Lv et al. [104,105] used a pH gradient from 2.7 to 6.5 and showed that CMC-CHT and Alg could be first ionically crosslinked through electrostatic interactions. Similar strategies involving proteins – which may be the key to enable cell adhesion and biomaterials degradability by cells – and other polysaccharides are also an option: Ng et al. [43] mixed CHT and gelatin at an acidic pH; then, an increase in pH induced the formation of negative charges on gelatin to trigger the electrostatic gelation between positively charged CHT and gelatin. Yan et al. [106] used the versatility of CMC-CHT in a DN hydrogel combined with agar gel and coordinated with ionic copper. A posttreatment using EDTA, able to chelate copper, allowed for the selective removal of the electrostatic interaction between CMC-CHT and copper and the switch to a softer agar-based hydrogel.

3.2. Covalent dynamic and stiff natural networks

To surpass the low reactivity of some components, a variety of strategies are based on the addition of small molecules. Those may be either administered to the system as free components (usually called crosslinkers) or grafted into polymeric chain, to reinforce the biomacromolecules basic networks. Hydrogel strategies involving small biocompatible molecules used as linkers and biopolymers/proteins have been widely explored to establish covalent networks [107]. These small molecular weight molecules permit a higher number of connections between biomacromolecules chains which increase artificially the molecular weight and therefore can lead to a better organization of networks. For instance, Wang et al. [108] used an SF/cellulose system, first covalently crosslinked using epichlorohydrin under $NaOH/H^+$ generating covalent bonds between the hydroxyl available functions of both cellulose and silk. By bubbling CO_2 inside the precursor hydrogel, cellulose chains reaggregated and formed a strong network by hydrogen bonding and entanglement of its chains. Sacco et al. [109–111] used the pH sensitivity of boric acid to connect a modified CHT with lactose using a DC approach. Section 3.2.2 provides more details about this pathway; however, here, the focus is on the diol function of lactose grafted on CHT, creating reversible links with boric acid. Genipin – a covalent linker of amine groups – is also a popular crosslinker used in hydrogel preparation strategies, especially for components possessing a large number of amines, such as gelatin [112] or CHT. For instance, Azevedo et al. [82] covalently bound two types of CHT using a double-syringe device in a DN approach. Genipin covalently bound the amine groups of both CHTs, and additional non-covalent interactions through iron complexation enabled ultra-tough biomaterials to be realized, with a maximum strength of 1.05 MPa at 90% compression. Other very well-established crosslinking strategy is based on EDC/NHS, which constitutes an easy way to bond natural networks due to their ability to establish covalent bonds between amine and carboxyl groups. Such approach was explored by Zhu et al. [113] to develop a multicomponent system involving bacterial cellulose (BC), Alg, and poly-γ-glutamic acid (PGA), in which EDC/NHS agents were used to activate carboxylic groups from BC and PGA and form an initial covalent network. In a second step involving Ca^{2+} soaking, the remaining Alg was ionically crosslinked. It is assumed that the high presence of free carboxylic and amine groups generates a dense network of hydrogen bonding capable of hardening the whole hydrogel. An original DN approach from Guo et al. [83] showed that TA could also be used to chemically modify gelatin using a basic medium and air bubbling (Fig. 2). Such TA-modified gelatin (Gel-TA) was introduced in a double-syringe system and simultaneously poured with silver nitrate, inducing the formation of the gel by contacting the amine composing the surface of the skin by (1) a reversible covalent bond *via* Schiff base (see 3.2.1) and (2) an irreversible covalent bonding *via* Michael addition (see 3.2.4). The tensile mechanical properties showed to be satisfactory for wound healing purposes, similar to surgical sutures, with a maximum supported stress of 6.6 MPa at 111% elongation.

3.2.1. The schiff base approach

Several biomacromolecules possess available amine functional groups susceptible to reactions with aldehydes to generate reversible bonds known as Schiff bases [114]. Such bonds are the product of condensation between primary amines and reactive carbonyl groups by nucleophilic addition driving to a hemiacetal intermediary state finishing by a dehydration step. Depending on the atoms linked to the amine, these bonds are characterized by imine, oxime, or hydrazone groups. Stable at physiological pH, Schiff bases can return to their initial state with pH variation and have been used to develop dynamic systems such as self-healing hydrogels or drug delivery systems [115]. Gelatin with its large number of nucleophilic amines is a useful platform to investigate Schiff base systems. For instance, Xu et al. [84] studied the modification of gelatin through beam polymerization, inducing the formation of aldehyde groups by self-oxidation on the terminal amino side chain residues of gelatin. This newly generated aldehyde spontaneously reacted with the remaining amines of the gelatin to form covalent crosslinks using the Schiff base approach. All polysaccharides possessing vicinal diols can also be oxidized by cleavage with periodate species into their dialdehyde derivatives; examples include cellulose [116], Alg [117], dextran [85] or starch [118]. For instance, Zheng et al. [119] first performed the oxidation of microfibrillated cellulose using $NaIO_4$ and then used the available amines of gelatin to trigger the formation of a Schiff base through an IPN hydrogel. CHT, whose backbone also constitutes an important source of amines depending on DDA, enables the generation of stable and dense imine bonds for Schiff base hydrogels [86]. For example, Yan et al. [120] used a two-syringe system, containing in one a mix of glycol-CHT/$CaCl_2$ and in the other a mix of Alg/dialdehyde-PEO molecules. When the two solutions were poured simultaneously, the formation of a tough DN hydrogel with an electrostatically crosslinked Alg and a covalently linked CHT by Schiff base was obtained. Another polysaccharide that has been shown to be an interesting platform for such an approach achieving DC and DN hydrogels is HA [121,122]. In fact, Yang et al. [87] investigated a multicrosslinked DN hydrogel with three chemical modifications on HA (Fig. 3): (1) an oxidated HA (OHA), (2) on this OHA, dopamine (Dop) moieties were added (resulting in an OHA-Dop), and (3) on another HA, amine synthons were grafted (resulting in a HA-ADH). The two systems were intimately associated during a double injection, inducing the formation of hydrogen bonding, aromatic interactions, and Schiff bases. By adding aldehyde terminated with Pluronic F127 micelles, the hydrogel was reinforced, enabling it to reach a maximum compressive strength of 5.7 MPa under a displacement of 80%, which can fit the motion of skin for potential use in wound-healing fields. Regarding the synthesis of aldehyde derivatives of natural compounds, it is also important to mention that enzymatic strategies [123] can be used to transform amines into aldehydes. This subject is discussed below in section 3.2.3.

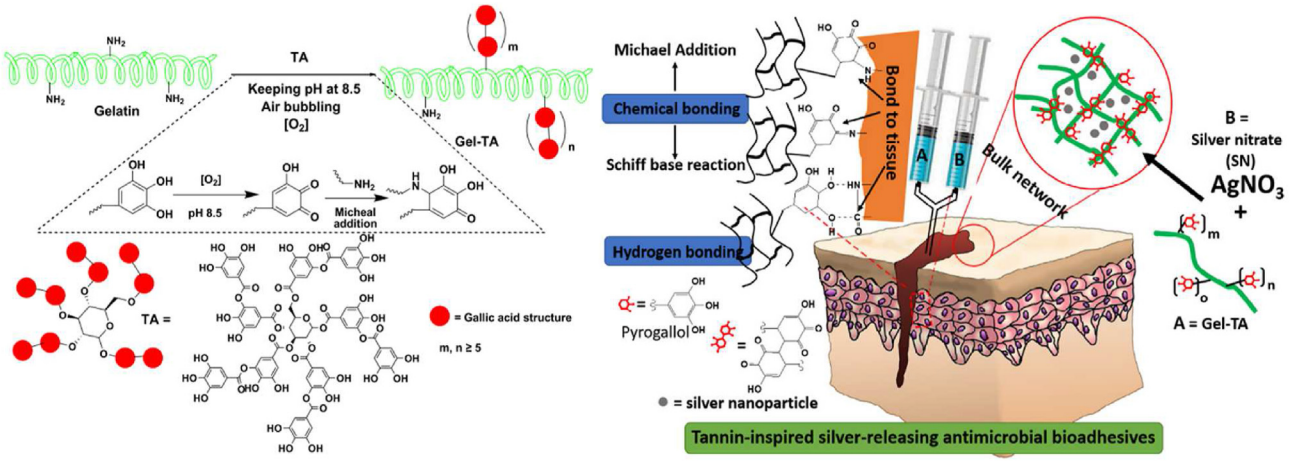


Fig. 2. Schematic representation of a DN approach mixing gelatin modified with TA (Gel-TA), enabling chemical crosslinking *via* Michael addition or Schiff base and non-covalent interaction. Adapted from Ref. [83] with permission, copyright 2018 Elsevier.

3.2.2. Boronate ester bonding approach

Boronate ester formation involves a reversible covalent bond between a trigonal boronic acid and a 1,2 or 1,3-diol species [124]. This bond has dynamic behavior, and its stability is governed by the pKa of the directly implicated bonds, such as the type of diol and/or boronic acid. Acidic media tend to pull the equilibrium to the acid side (acyclic structure), whereas a neutral/basic medium favors the formation of the ester (cyclic structure). Reversible boronic acid chemistry [125] is an alternative to Schiff base systems, with better control of reactivity. Along with Schiff base hydrogels, there has been significant interest in producing injectable and self-healing hydrogels [126,127]. PVA, composed by an alternation of such diol motifs, was studied [128] to connect natural polymers such as laminarin [129], modified by boronic acid moieties. Regarding natural polymers, boronate ester strategies are particularly interesting because some of these molecules, including Alg, possess native diol motifs, avoiding extra modification steps [130]. Hong et al. [131] modified Alg with boronic acid by EDC/NHS coupling at pH 5.5. Then, the obtained boronic acid Alg was simply dissolved in PBS at pH 7.4 to trigger the boronate ester reaction with the diol motifs of the same Alg, leading to a self-healing and stretchable adhesive DC hydrogel, opening the way to other applications such as biocompatible glues [132]. To have better control of the boronate ester bonding and, consequently, the mechanical behavior of the hydrogels, Figueiredo et al. [88,133], followed an IPN approach with an independently modified HA with phenylboronic acid and with various derivatives of sugars with diol motifs such as fructose (Fig. 4). After mixing, the resulting hydrogels, linked by different boronate esters, exhibited a variation of the pKa, enabling the researchers to obtain hydrogels with different mechanical behaviors, ranging from soft to 'strong'. Indeed, depending on the bonding strength between fructose and several boronic acids both grafted to HA, the pKa vary induces a different elastic modulus with, for instance, a G′ of 424 Pa for the formulation HA-phenylboronic acid/HA-fructose and a G' of 156 Pa for the formulation HA-benzoboroxole/HA-fructose. Additionally, the reversibility feature of the boronate ester enabled switching from a viscoelastic hydrogel to a tougher hydrogel.

Another strategy using boronate ester bonding consists of linking natural polymers and biomacromolecules, such as biocompatible polyphenols (TA, ellagic acid, or epigallocatechin [EGCG]), which possess a high number of hydroxyl moieties [134]. Choi et al. [89] combined a boronic acid-Alg with oligomerized EGCG (OEGCG) constituting a network itself and the mixture of both, results on a *quasi*-IPN system. Using the available 1,3-diol functions onto the OEGCG, boronic acid-Alg reacted to form boronate ester. The obtained hydrogels, like other boronate ester hydrogels, showed not only self-healing ability and stretchability but also conductivity due to the delocalized system from the EGCG and granted biocompatible features to implantable devices for drug delivery on demand. The boronate ester approach could also be combined with other crosslinked systems to build DN hydrogels. For example, Amaral et al. [135] studied a cell-laden injectable hydrogel based on Alg and laminarin modified with 3-aminophenylboronic acid reacting with the Alg diol motifs. After bioprinting, the resulting hydrogel was crosslinked by Ca^{2+} to form the DN system by electrostatic interaction with Alg carboxylate. Working under physiological conditions, MC3T3-E1 preosteoblasts, L929 fibroblasts, and adenocarcinoma MDA-MB-231 cell lines were loaded inside the hydrogel at 37 °C, and *in vitro* cytocompatibility was observed with cells remaining viable for up to 14 days.

3.2.3. Enzymatic chemical reactions

Enzymatic reactions [136–138] leading to irreversible covalent networks can be a suitable choice when high mechanical behaviors (*i.e.,* high resistance to the breaking, stretchability or high percentage of recovery) are targeted. These strategies generally involve an amide reacting with an amine species, resulting in a strong covalent bond catalyzed by an enzyme [139]. Such strategies are particularly interesting with proteins that have a significant free amine, lysine, or carboxamide moieties composing their complex structures. For instance, using an SF/gelatin system [140], Jiang et al. [90] first crosslinked SF by adding a mix of Horseradish peroxidase (HRP) and H_2O_2 [141]. SF was modified with tyramine moieties – which were catalyzed by HRP/H_2O_2 – to generate C–*O*–C bonds between phenolic rings. Then, a saline soaking step was performed to induce the self-organization of gelatin chains by hydrophobic interactions. This DN strategy combining two types of crosslinking – enzymatic and salt-assisted – led to the formation of gels with high compression mechanical properties, exhibiting high stretchability ~200% (maximum elongation) and elastic modulus of 0.13 MPa. The tyramine moiety [142,143] is widely used in enzymatic strategies combined with HRP enzyme catalyzed by H_2O_2. For example, after a modification of HA with tyramine moieties, Jooybar et al. [144] produced an injectable hydrogel combined with platelet lysates for cell activity support. Another enzyme, transglutaminase [145,146], widely used in the agri-food industry, can chemically crosslink a large range of proteins depending mainly on

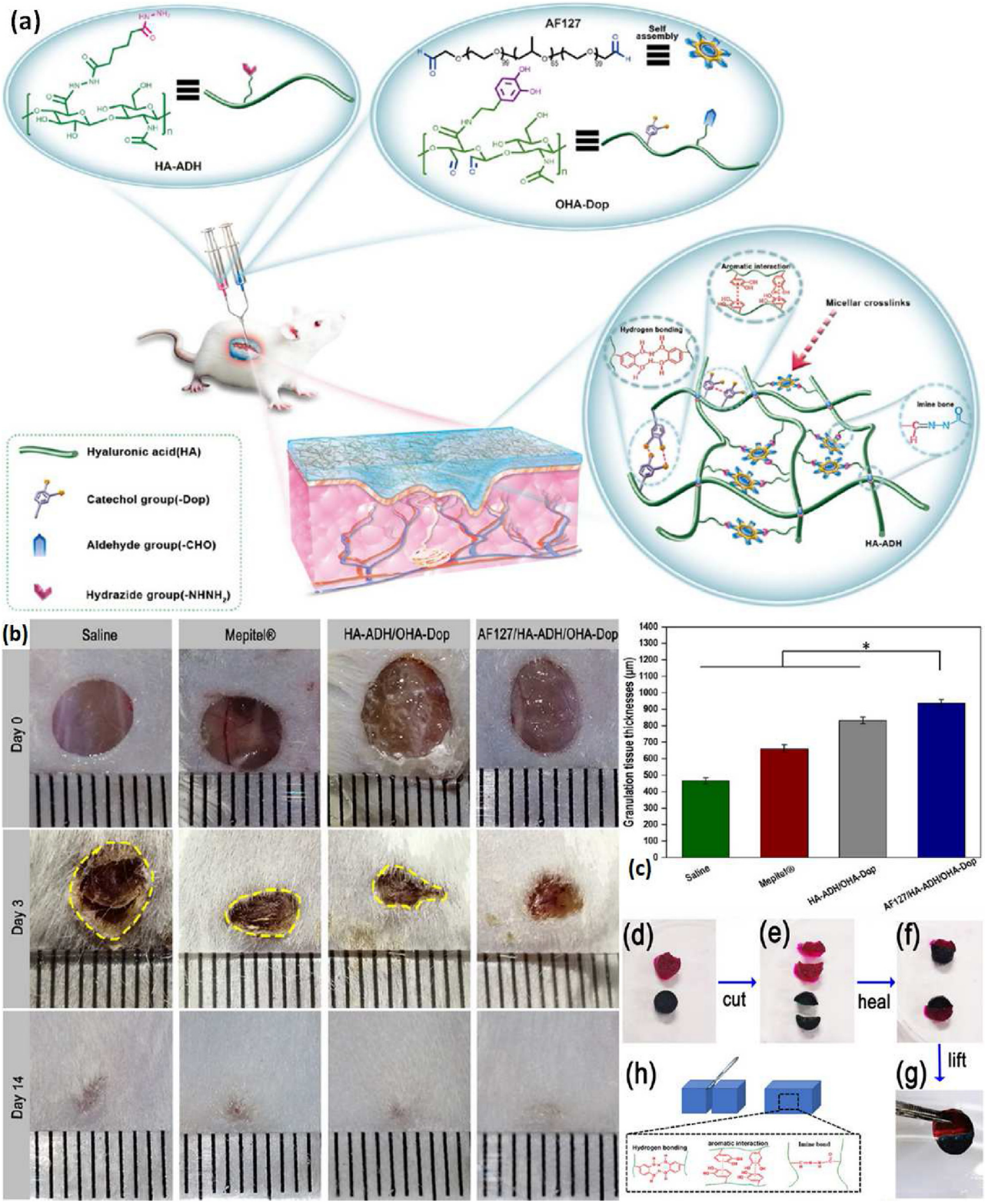


Fig. 3. (a) Schematic representation of the injectable and multicrosslinked DN AF127/HA-ADH/OHA-Dop hydrogel preparation and the application in full thickness skin wound healing; (b) gross appearance of wounds from day 0 to day 14 for Saline, Mepitel, HA-ADH/OHA-Dop, and AF127/HA-ADH/OHA-Dop hydrogel treatment groups; (c) statistical graph of granulation tissue thickness at day 14 post-treatment; (d–g) macroscopic self-healing performance of the AF127/HA-ADH/OHA-Dop hydrogel: Two disk-shaped hydrogels (stained with rhodamine B and trypan blue, respectively) were cut into two pieces, respectively. Then, the four pieces of alternate colors were combined into two integral blended hydrogel disks, which could be lifted after several minutes; (h) schematic diagram of self-healing mechanism. Adapted from Ref. [87] with permission, copyright 2020 ACS

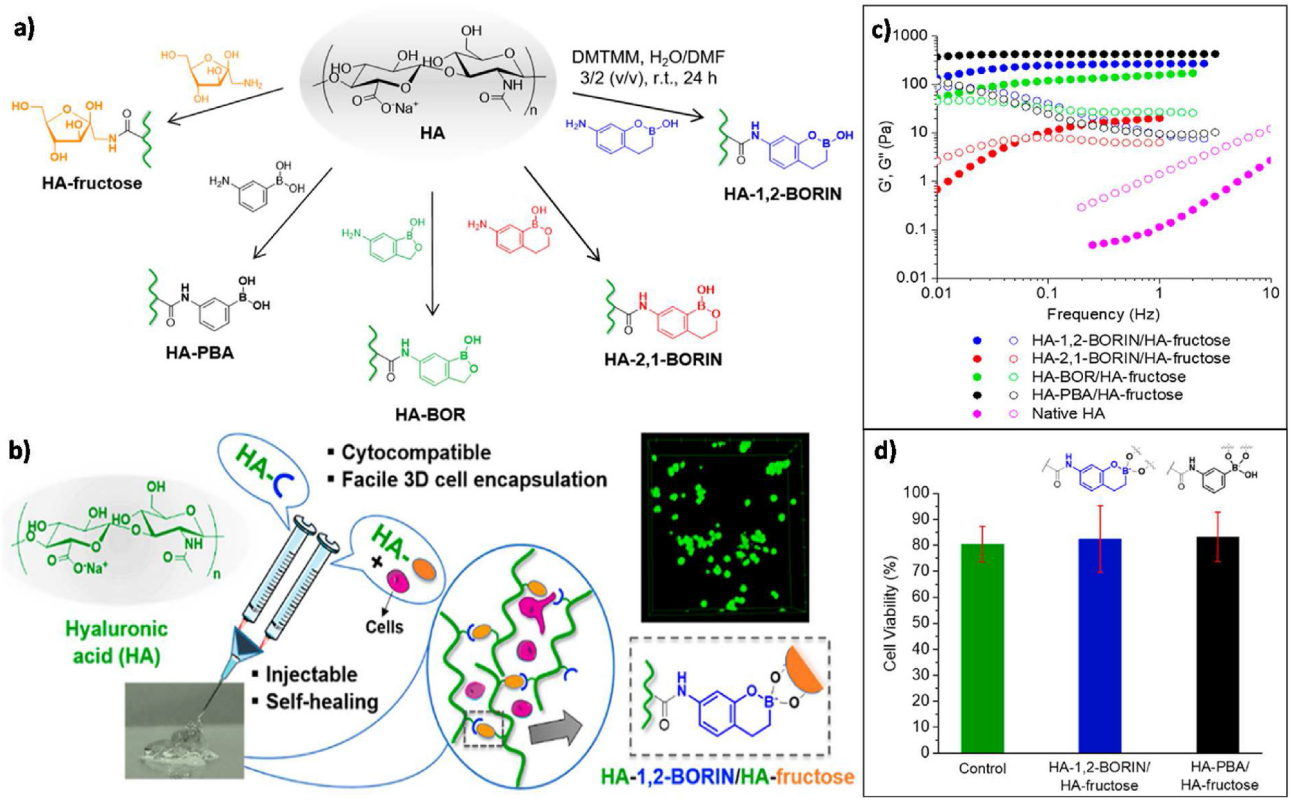


Fig. 4. (a) Strategy pathway from HA to form HA derivatives; (b) double-syringe process of hydrogel formation; (c) dynamic rheologic behavior of HA networks based on boronic acid/fructose crosslinks (G′, filled symbol; and G″, empty symbol), ratio molar of 1 for each formulation; (d) cell viability test assays. Adapted from Ref. [88] with permission, copyright 2020 ACS.

the percentage of available amine groups. The enzymatic coupling reaction occurs between γ-carboxamide groups of glutamine and, generally, ε-amino groups from lysine residues [147], resulting in the ε-(γ-glutamyl)lysine peptide bonds formation. Association with biopolymers is also possible [148], Chen et al. [91] studied a DN gelatin/Alg system, where gelatin was first crosslinked by transglutaminase, followed by soaking in a $CaCl_2$ solution to ionically crosslink Alg. This hydrogel constituted a suitable candidate for a 3D extrusion based on a bioprinting process for cell delivery because SH-SY5Y cells were encapsulated inside the hydrogel and grown efficiently during 5 days in culture.

3.2.4. "Click" reactions

An alternative to irreversible covalent bonding relies on 'click' chemistry strategies, in which Diels-Alder, Huisgen cycloaddition, Thiol-ene, and Michael addition reactions are the most used pathways [149–151]. Combining modified natural macromolecules such as HA [152], gelatin and/or CHT [153–155], using smaller molecules as linkers, such as linear or branched PEG species grafted with a diene species, is one of the most used 'click' reaction strategies. Strategies based on reactions between electron donor species and electron acceptor species are the pillar of 'click' reactions and can be applied to other chemical pathways. For example, an alkene or alkyne species can react with a thiol to form strong covalent bonds through a thiol-ene/yne reaction [156], which can be combined with natural polymers [157] and proteins to form hydrogels. Ghanian et al. [92] investigated a DC approach involving Alg modified with furan moieties by EDC/NHS coupling in a preliminary reaction. The hydrogel was obtained through a Diels-Alder reaction with a tetra-maleimide-modified 4-arm PEG, exhibiting relatively high compressive properties with a maximum strength of 0.45 MPa at 76% compression. Likewise, two natural compounds can be linked using this strategy; for example, Piazza et al. [93] grafted furan moieties into a dextran backbone using a DMAP/DCC coupling reaction and 'clicked' it into a gelatin modified with maleimide moieties. Another 'click' reaction example is an inverse electron demand Diels-Alder coupling reaction between the norbornene and the tetrazine, a rich electron donor species [158,159]. This strategy can be performed at RT and, more importantly, in aqueous media [160,161]. This chemical pathway could be used with natural polymers [159] and proteins [162] and has been proven to have lower toxicity for tetrazine compared with furan derivatives.

In a DC approach, Yao et al. [94] modified HA with thiol and maleimide groups separately using EDC/NHS coupling. By simple mixing, two crosslinks occurred with the formation of reversible disulfide bonds (between two thiol functions) and a thiol-ene reaction (between thiol and maleimide groups). Another option consists of the use of alkynes instead of alkenes; for example, Pérez-Madrigal et al. [163] combined Alg and modified thiolated HA in a DN approach. Initially, the thiolated HA reacted with a modified alkyne-PEG, yielding the first network, and then, the precursor hydrogel was immersed into a $CaCl_2$ solution to ionically crosslinked Alg. Mechanical tests on such hydrogels exhibited breaking at 70% without the Ca^{2+} crosslinking and a sustainability to compression at 95% for the hydrogel that was crosslinked with Ca^{2+}. A similar approach was used with modified maleilated CHT and thiolated HA, followed by an ionic crosslink of the CHT positively charged with anionic salt [164]. Due to the relatively low strength of such bonds, this strategy is particularly used to prepare soft hydrogels for drug delivery although they did not show high resistance.

IPN between proteins and natural polymers [165] have also been widely investigated due to the large number of amine groups available to graft thiol or double-bonded derivates. Such coupling strategy involves a thiol function activated generally *via* a radical initiator leading to an intermediary specie with a $S^{\bullet}$ reacting with an alkene group. This reaction is described as a cyclic coupling mechanism allowing high yield, lack of side products and a compatibility with aqueous medium which constitute an interesting point for biocompatible hydrogel fabrication. Li et al. [166] connected two networks of HA and collagen [167] through thiol-ene reaction. HA was modified with thiol groups using cysteine at RT, whereas collagen was modified with maleic anhydride. After mixing, the gelation occurred over a minute at 37 °C, at pH 7. Taking advantage of the strong ionic crosslinking between Alg and calcium cations, Trujilo et al. [168] modified an Alg backbone with norbornene groups [169] and covalently interconnected it using dithiothreitol or thiolated derivatives to establish an initial network. Additionally, fibronectin, which is an extracellular matrix protein, was modified with maleimide groups and connected with norbornene-Alg derivatives through a thiol-ene reaction using thiolated linkers such as dithiothreitol [170]. Original strategies combining host–guest (see part 3.3.1) and thiol/norbornene groups could be designed to introduce reversibility into the system [171].

Another type of 'click' reaction that could be used to covalently connect two networks is the 1,3-dipolar cycloaddition derived from the Huisgen reaction between an alkyne and an azide group [172]. Initially, this reaction was not preferred because of the copper dependency during the catalytic process [173], which is not compatible with biomedical purposes. To avoid the metal catalytic process and open the way to the synthesis of biocompatible hydrogels, several strategies have been studied. Among them, the reaction of an azide with a ring-strained alkyne, also called 'strain-promoted azide-alkyne cycloaddition' [174], has been studied. This reaction, popularized by Bertozzi et al. [175], is based on an alternative mode of biorthogonal reactivity through a copper-free [3 + 2] cycloaddition reaction. Taking advantage of the instability of strained cycloalkynes to decrease the activation energy, the reaction with an azide group was triggered to form the triazole ring. Triazole rings act as linkers to graft a broad range of materials, including natural polymers [176,177]. For example, Truong et al. [178] modified CHT with an azide group and used it along with a tri-branched PEG with a strained alkyne at the tail of each PEG arm. Under mild conditions, the azide-CHT and the tri-branched alkyne PEG reacted without any metal catalyst, forming an injectable hydrogel within an hour. This system has shown suitability as a 3D scaffold for human mesenchymal stem cell (MSC) encapsulation. Currently, the most used moiety in the copper-free cycloaddition strategy is dibenzocyclooctyl (DBCO) [179,180], or cyclooct-1-yn-3-glycolic acid (CGA) [181], which can be easily grafted to natural polymers through simple peptide coupling by EDC/NHS activation.

The use of a copper-free cycloaddition reaction in DC/DN and IPN approaches has not been fully developed; most of the hydrogels with these covalent bonds are soft and lead to injectable systems. For instance, Fan et al. [182] connected two networks of CHT and HA through a 'click' chemistry process using modified HA azide and a CHT modified with an oxanorbornadiene moiety, which reacted like an alkyne to form a triazole linker. To deal with the complexity of such a system but also the advantages of its use and compatibility with natural compounds, in 2018, Takemoto and co-workers [183] reported a study on an IPN connected by strain-promoted azide-alkyne cycloaddition reaction involving a DBCO-branched Alg (bAlg-DBCO) and functionalised cells (C2C12) with azide moieties (Fig. 5). This study paved the way to new thinking about biomaterials development using living material through a sustainable process [184].

3.3. Supramolecular hydrogels

Limiting the gelation steps in hydrogel fabrication for rapid translation into medical devices is a key point for researchers and hospital personnel. For this purpose, self-assembled and supramolecular systems have an important role because of the capability of the hydrogel to form spontaneously, without the addition of further chemicals or catalysts. Based only on non-covalent and weak interactions such as hydrogen bonding, van der Waals, hydrophobic, and π-π stacking [185,186], such strategies constitute a high challenge with natural DN, DC, or IPN in which many chemical groups are involved and could destabilize these bonding. Nevertheless, many strategies involving highly or multimodified biomacromolecules allow enough of these supramolecular interactions to be obtained, achieving structured organization for soft drug delivery systems or dynamic 'smart' hydrogels. So far, mechanical properties with tough features have only been achieved through combination with stronger covalent bonds.

3.3.1. Host–guest interactions

The concept of a molecular machine popularized by the 2016 Nobel Prize in Chemistry inspired many researchers around the world to develop dynamic systems based on supramolecular interactions. Host–guest strategies [187,188], belong to this category, in which two systems interact with each other by a mechanism of reversible trapping. One molecule, called the 'guest', gets trapped inside another, called the 'host', *via* weak interactions. This strategy relies on the ability of these molecules to interact efficiently, and it depends also on the diameter of the 'host' molecules which must fit to the steric feature of the 'guest'. Additionally, the chemical affinities (hydrophobic, hydrophilic) of the two entities also must be compatible. The reversibility of the bonding depends mainly on the 'guest' molecules which must be capable of changing its steric environment inducing its release of the 'cage' molecules by an external stimulus such as UV and pH. Natural-based hydrogels bonded by such mechanism mainly concern soft hydrogels with self-healing and injectability properties. Tough hydrogels can be achieved, but this generally requires an association with synthetic polymers such as PA [189,190]. α,β,γ-cyclodextrin (CD) molecules are often used for supramolecular cages as the 'host' component [191], able to trap the 'guest' moieties, which are generally low-weight molecules. These low-molecular-weight-trapped species generally have the ability to change their space conformations by stimuli (*i.e.* pH, wavelength, charge), inducing the breaking of weak interactions, permitting release from their 'cage'. Burdick and collaborators [192,193] highlighted the potential of host–guest interactions through HA-based hydrogel systems, allowing for shear-thinning and injectability features after the grafting of CD and adamantane (Ada). Additionally, a methacrylated HA [95] was added to this network to develop a DN system achieving high mechanical properties, presenting an elastic modulus of 85.7 kPa with a fracture strain of 86.5% in compression. A fully non-covalent crosslinked hydrogel could also be considered. Kim et al. [96] studied a DN system constituted by a self-assembled agarose network mixed with a CMC modified with azobenzene moieties as guest molecules, trapped by a double host used to link azobenzene-grafted CMC. The resulting hydrogels exhibited multiple functionalities such as self-healing and photo switchability due to the *cis*/*trans* conformation of its azobenzene-grafted moieties, and the mechanical studies showed a maximum elongation of 4.57 kPa at 231.9%. The use of two β-CD linkers has been enhanced by varying the number of host or guest molecules. For example, Fan and co-workers [194] synthesized a β-CD-network composed of several β-CDs connected in a series and associated with CMC in an IPN system. After the synthesis of the β-CD network, positively charged

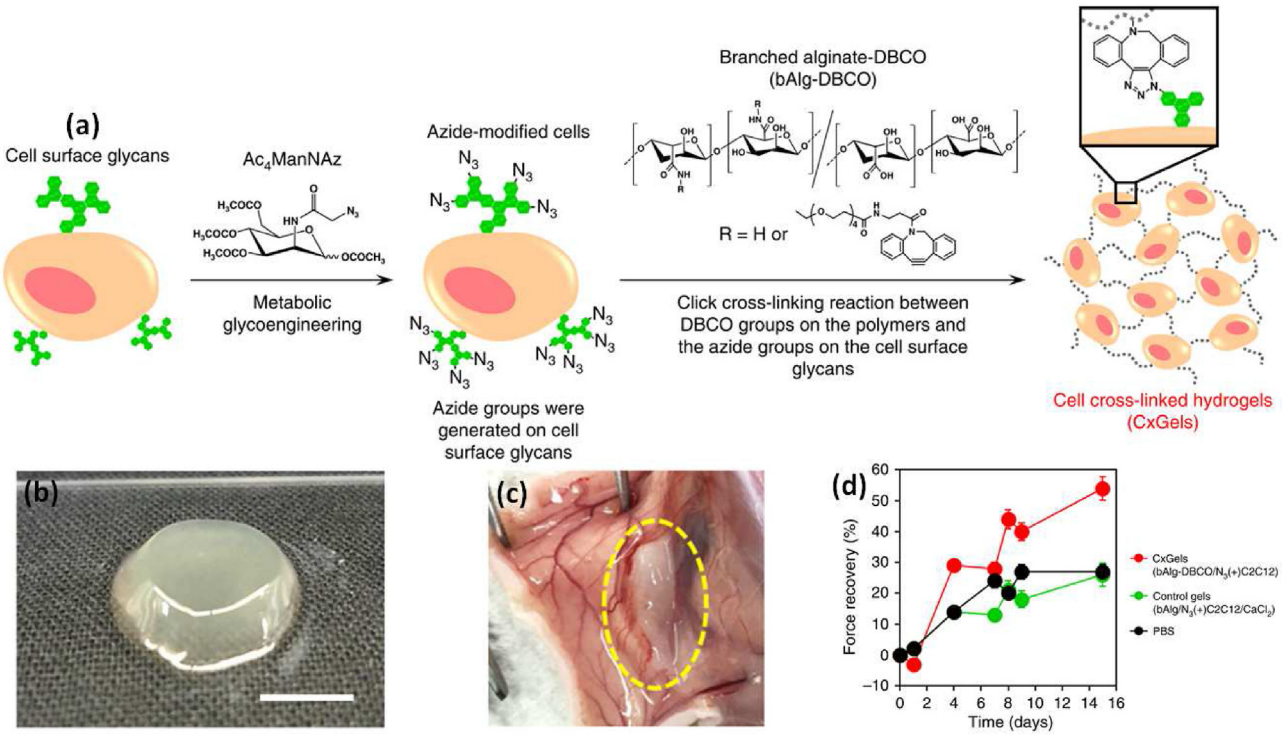


Fig. 5. (a) Schematic illustration of cell-crosslinked hydrogel through "click" chemistry strategy; (b) digital image of CxGel prepared through 'click' reaction between azide-modified C2C12 cells (2.0×10^6 cells) and bAlg-DBCO solution (2%). Scale bar indicates 5 mm; (c) digital image of in vivo-formed CxGels. LifeAct-GFP-expressing azide-modified C2C12 cells (4.0×106) were suspended with 200 μL of bAlg-DBCO solution (2%) and immediately injected subcutaneously into the muscle layer of the back of each mouse; (d) force recovery of injured femoral muscle treated with CxGels prepared through 'click' reaction between LifeAct- GFP-expressing azide-modified C2C12 cells (5.0×10^6) and 250 μL of bAlg-DBCO (2%) or C2C12 cell-encapsulating control physical gels, prepared through non-covalent crosslinking reaction between 250 μL of bAlg solution (2%) and $CaCl_2$ solution (0.5%) in the presence of azide-modified C2C12 cells (5.0×106 cells). Error bars: standard deviation ($n = 3$). Adapted from Ref. [183] with permission, copyright 2018 Nature.

Ada molecules were trapped inside its structure. These positive charges reacted with the negative charges of CMC and generated an electrostatically connected IPN. In addition to the positive Ada, some ibuprofen molecules were trapped in the β-CD network to release these molecules for sustained drug delivery. The strategy consisting of adjusting the ratio of host or guest molecules grafted into the natural skeleton of polymers allowed for tuning the mechanical properties of the hydrogel and therefore the release of drug molecules such as doxorubicin or doxycycline [195]. Ooi et al. [196] highlighted this phenomenon by working with an Alg network modified with CD and crosslinked multibranched PEG modified with Ada. Hydrogel toughness increased with the number of available guest molecules with bi-, quadri-, and octo-branched PEG-Ada.

Regarding host–guest networks based on proteins, Wang et al. [197] studied a mechanically reinforced hydrogel of GelMA mixed with a precursor host/guest solution constituted by 1) a modified β-CD with two vinyl moieties and 2) mono-modified Ada molecules with one vinyl moiety. Despite the host–guest interactions, this precursor solution had no gel property. However, once mixed with GelMA and after photopolymerization, all the vinyl moieties reacted together to form a covalent network of methacrylated gelatin connected with Ada and β-CD, which formed an additional non-covalent network *via* host–guest interactions. This strategy leads to mechanically reinforced DN hydrogels with self-healing properties, injectability for 3D-bioprinting, and biocompatibility imparted by the gelatin network. Silk fibroin (SF) is a natively strong protein widely used when high mechanical properties are targeted. For example, Huang et al. [198] used two networks of different modified silk networks, one with β-CD and another with cholesterol, which is another guest molecule [187]. In this system, mechanical properties depend on the SF itself, creating a strong but brittle network, and the host–guest interactions with β-CD/cholesterol enhance the elastic domain and permit self-healing resulting in a DN system.

Finally, sliding-ring polyrotaxanes [199,200] integrate an original approach in the same frame of host–guest strategies consisting of trapping linear chains grafted to a polymer, weak interactions between several stacked CDs, and linear chains generating a hydrogen bonding network. The CDs inserted along the polyethylene glycol (PEG) chain have the capacity to slide over the polymer chain. Such interesting system allows an equal distribution of the forces along of the 3D matrix, when submitted upon a force loading.

Although synthetic polymers have constituted a good platform to investigate such an approach [201–206], recently, natural polymers [207,208] have been chosen to bring biocompatibility and biodegradability to such systems. Polyrotaxane strategies could also be applied as bioinks, where shear-thinning and long-time maintenance are required [207]. For example, Hu et al. [97] investigated a DC hydrogel constituted by gelatin and PEGylated-CHT (CHT-mPEG). A certain amount of α-CD trapped the side chains and triggered a stacking of several α-CD units to finally establish a non-covalent interaction with other trapped side chains (Fig. 6). Regarding the original pathway to obtain non-covalent interactions with this strategy and the relative lack of research with natural polymers, the polyrotaxane approach constitutes a top field of interest in the association of natural networks in the near future.

3.3.2. *Adhesive phenolic hydrogels*

Wound burns and basically all skin breaches require biomedical devices adhering to skin, adapting to its morphology with no

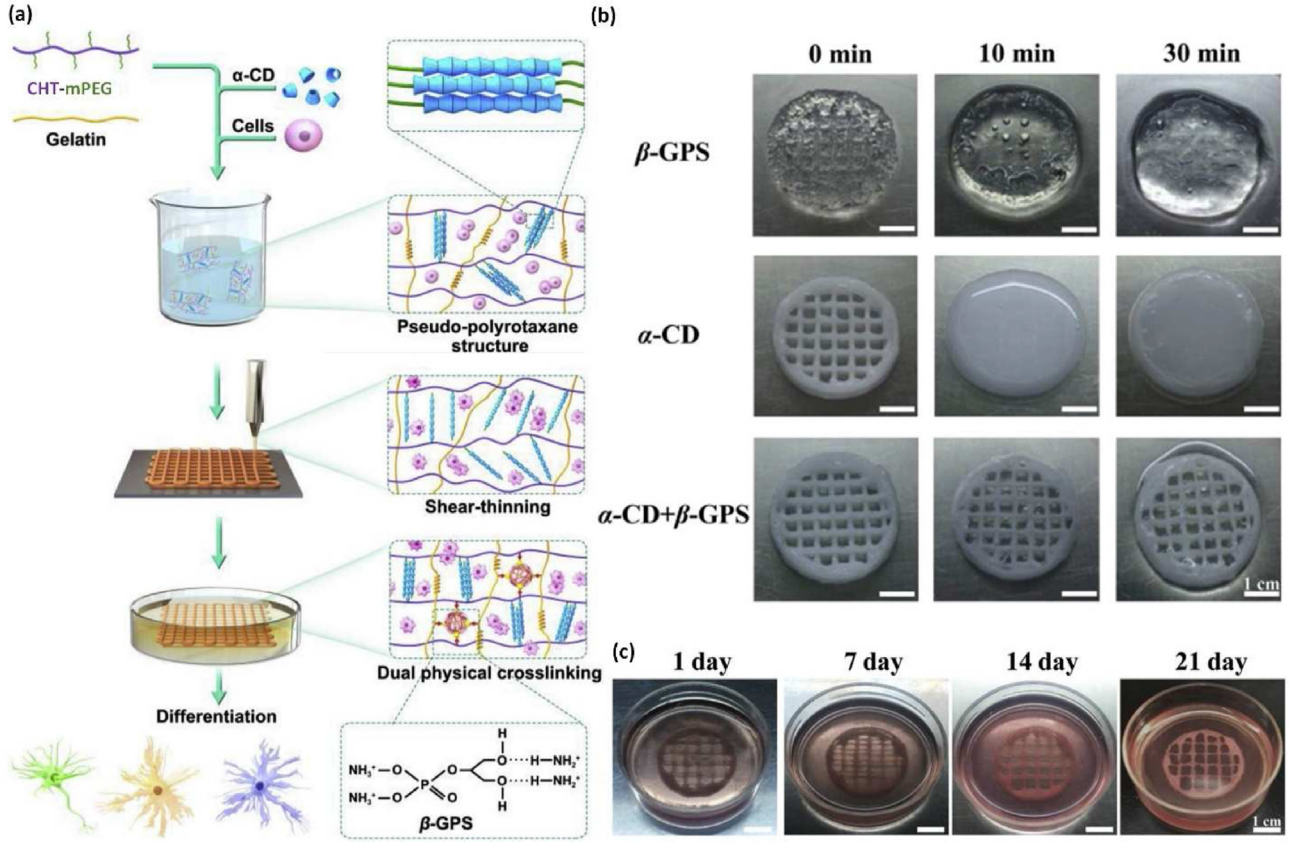


Fig. 6. (a) Schematic illustration and flowchart of CHT-mPEG formulation, bioink preparation, DC system, and 3D bioprinting process; (b) macroscopy image of bioprinted constructs crosslinked by dual physical crosslinking (β-GPS and α-CD) or single crosslinking (only β-GPS or α-CD). α-CD was added to the bioinks; (c) macroscopy image of DC and cell-laden bioprinted constructs cultured in medium under the condition of normal cell culture. Adapted from Ref. [97] with permission, copyright 2020 KeAi.

invasive properties and able to sustain itself on the skin in motion. Also, adhesives are important to treat, for example, postoperative wounds in internal organs, and the hemostatic properties of some of these materials have also been explored in the biomedical field. The chemistry of phenolic compounds [209] and, more specifically, catechol-based systems [210] have been widely used in adhesive [29] hydrogel fabrication for biomedical applications. Thanks to its delocalized structure and its electron donor properties, the phenolic ring has several states of oxidation and could therefore interact through different types of bonding from covalent to non-covalent bonds. Catechol, for example, possesses two oxidation states: *o*-quinone and semiquinone [210–212]; depending on the state, the strategy could lead to non-covalent (for non-oxidated state) or covalent (for oxidated state) bonds. The non-oxidated catechol could be combined with most of the previously presented networks [213]; for example, Wang et al. [98] used a DN system of photocrosslinkable CHT combined with a CHT grafted by Dop moieties. The coordination of the catechol moieties by iron led to an injectable hydrogel with tissue adhesivity and antibacterial activity suiting for wound healing. The mechanical properties exhibited a maximum compression strength of 0.69 MPa at 90% suitable for wound-healing applications. A similar approach was used by Li et al. [99] with the study of a DC hydrogel starting from CHT and grafted with two moieties, furfural, and catechol. The first is covalently crosslinked through a Diels-Alder reaction with dimaleimide PEG, and the second one is non-covalently crosslinked *via* iron complexation of catechol moieties. For both latter cases, the obtained hydrogels were soft and used for injectability purposes. To enhance hydrogel strength in compression and elongation using this phenol-based strategy, it is usually necessary to use the oxidated state to form strong covalent bonds [214–216]. Following an IPN approach, Hu et al. [85] linked an oxidized dextran branched with catechol moieties mixed with a CHT modified with trimethyl ammonium (for antibacterial purposes). The system had two covalent bonds: (1) Schiff bases between CHT amines and dextran aldehydes functions and (2) covalent irreversible bonds from two oxidated catechols. Cyclic compression study at 60% strain (~25 kPa) of such hydrogels showed good and fast recoverability after all the cycles, meaning that these systems presented good anti-fatigue behavior. DNs could also be considered; for example, Guo et al. [217] proposed a catechol-based hydrogel starting with the coupling of HA by Dop moieties. After mixing with Alg, $NaIO_4$ was added to initiate the gelation process involving the oxidation of the catechol moieties and the formation of covalent bonds between catechol phenyl rings. Ionic crosslinking of Alg was then triggered by Ca^{2+} to form a highly stretchable, tough (461 kJ/m^3) and adhesive DN hydrogel, compatible with human umbilical vein endothelial cells (HUVECs) 3D culture.

Many other natural compounds could be a source of catechols or other phenolic moieties to develop adhesive hydrogels. TA, already mentioned in this review, could be used as a crosslinking agent for many proteins [209,218–220], or included in natural structures to build adhesive hydrogels [221,222], thin films [223–225] or nanoparticle emulsions [226]. Moreover, TA presents antioxidant activity due to its phenolic groups and is recognized as safe by the Food and Drug Administration (FDA) [227]. Wang et al. [228] studied a hydrogel from γ-PGA covalently linked with ethylene glycol diglycidyl ether, in which TA was added to establish an

efficient hydrogen bonding network, reaching a robust skin-integration, anti-UV, and self-recovery hydrogel for wound healing. As previously presented in section 3.2, TA could also be modified; in fact, Chen et al. [221] proposed an original hydrogel fabrication with TA and thioctic acid through a ring-opening polymerization. Thioctic acid, a small biocompatible molecule, was first polymerized resulting in a linear polymer with sulfide tails and then reacting with the phenolic ring of TA to form a robust covalent network. Several subsequent cycles of freezing/thawing induced the formation of a hydrogen bonding network, which led to a highly adhesive, injectable, and self-healing hydrogel. Galloyl is a substructure of TA, which could be easily grafted by peptide coupling using EDC/NHS [229,230], and can also be used as a crosslinking agent [231].

3.3.3. Nucleobase self-assembly

Recently, the fast propagation of SARS-CoV-2 forced scientists to find ways to diagnose, evaluate, and localize infected people to take health measures such as quarantines or confinements. In that aim, DNA hydrogels [232] found applications in the biosensor field for detecting the virus using DNA's ability for hybridization [233,234], resting on the supramolecular pairing of nucleobases. Better known as Watson-Crick or Hoogsteen interactions, such interactions were described as hydrogen bonding and π-π stacking networks between nucleobases: adenine/thymine or cytosine/guanine [235]. Recently, guanine has attracted a lot of attention for its ability to form stable 3D complexes called G-quadruplexes, formed by the stacking of several plans composed of four guanines chelated by a cation [236]. Such interactions are an inspiration to biomaterials researchers to develop advanced biomedical hydrogels [237] due to the native biocompatibility of nucleobases and the possibility of modifying their structures.

Natural polymers crosslinked through nuclear base pairing have been investigated [238]. An HA-based hydrogel grafted independently with guanosine and cytosine [239] formed soft hydrogels with self-healing properties. This base-pairing effect could be more efficient and lead to high mechanical properties with the involvement of nucleotide sequences. Liu [240,241] and co-workers investigated DN systems involving a DNA sequence as a network itself. This network was composed of DNA linear sequences, so-called 'linkers', and a branched complementary DNA sequence called a 'Y-scaffold'. These two sequences interacted by hybridization to form a full DNA hydrogel [242,243]. The linkers are composed of 44 nucleotides, and the Y-scaffold is composed of 40 nucleotides; their association produced a precursor hydrogel at ~4% w/v in PBS of pure DNA hydrogel. DNA sequences can be added onto biocompatible polypeptides [244,245], yielding an efficient association with DNA linkers. As described in section 3.2, TA can covalently link several natural macromolecules. Haeshin Lee and collaborators [220,246] proved that TA is also capable of crosslinking DNA sequences [247], leading to a mechanically tough hydrogel termed TNA hydrogel (TA + DNA). Here, TA plays the role of molecular glue by hydrogen bonding with the phosphodiester linker connecting nucleotides from the salmon DNA sequence. Additionally, the salmon DNA sequence promotes an efficient base-pairing interaction using an alternation of guanosine and cytosine nucleotides, leading to a double non-covalent hydrogel with full biocompatibility and high adhesive properties. DNA sequences are interesting biological macromolecules because of their reactivity with targeted biological cancer cells to inhibit their activity, such as prostate cancer cells [248], making the delivery of a DNA sequence a promising goal for biomedical DNA hydrogels. Taking advantage of the benefit of HA water solubility, Fujita et al. [249] grafted two short and complementary sequences of nine oligonucleotides into HA backbones and fabricated a stiff hydrogel exhibiting an elastic modulus of 100 Pa. Willner and co-workers [250–252] explored two supramolecular assemblies: (1) base pairing of oligonucleotides and (2) G-quadruplexes using cellulose. In an initial DC approach, cellulose was grafted with catechol moieties and an oligonucleotide with mainly guanosine moieties able to promote G-quadruplex self-assembly (Fig. 7). Adding a strong species acceptor, bipyridinium dithienylethene, formed the first reversible crosslinking with oxidized catechol moieties. On the other hand, the potassium cation triggered the guanosine unit DNA sequences through self-assembled G-quadruplex interactions. A second similar DC strategy was also studied using complementary sequences of a specific oligonucleotide inducing the formation of base pairing using about 10 nucleobases connected by hydrogen bonding. Their results showed the possibility of utilizing parameters such as oxidation or spectroscopy to switch from soft to stiff hydrogel with self-healing and shape memory features.

4. Natural hydrogels supported by synthetic networks

Synthetized from monomers of low molecular-weight, the structure and size of synthetic polymers are easily controllable *via* classical organic chemistry reactions, which has facilitated exploring a larger spectrum of mechanical behaviors of hydrogels prepared from these molecules, with reported soft to tough features [253]. Furthermore, improving the characterization of such materials allows for better controlling their reactivity to design enhanced systems with, for example, switching ability, drug delivery, or self-healing properties. The combination of synthetic polymers with natural macromolecules constitutes a strategy that aims at conserving the versatile and increased mechanical properties enabled by synthetic materials and, at the same time, permitting biofunctionality (e.g., improved biocompatibility and biodegradability) achieved from the intrinsic properties of several natural counterparts.

Combinations of synthetic and natural networks constitute one of the easiest ways to produce hydrogel devices with high stretchability and no breaking at high compression (Table 2). For example, Guo et al. [254] used agarose sol-gel transition properties associated with a strong covalent PA network to obtain a robust hydrogel with extremely high stretchability features exhibiting a maximum strength of 0.85 MPa at 1767%. The obtained hydrogel also showed switching mechanical properties depending on agarose self-assembly from random coils into ordered fibers by cooling/heating cycles switching from a storage modulus of 0–0.4 MPa, respectively. Guo et al. [255] investigated an ionically linked Alg combined with a covalent PAA hardened using acrylic linkers, polyethyleneglycoldialdehyde (PEGDA). This hydrogel exhibited toughness with no breaking even at high strain and under a compressive stress superior to 40 MPa, combined with a satisfactory biocompatibility and biodegradability suitable for bone repair. The strategy that combines the electrostatic behavior of natural polymers and covalent synthetic networks can be applied to almost all the other polysaccharides available and capable of establishing electrostatic interactions [256,257]. For instance, Zhang et al. [258] used a low molecular-weight CHT electrostatically connected to citrate [259] or sulfate [260] anionic species associated with poly (*N*-(2-hydroxyethyl)acrylamide) reinforced by an organic linker. Synthetic networks could also be used for electrostatic interactions such as PAA, which is negatively charged, used as a co-network to set up rigid domains with a positive charge. Cao et al. [261] showed that a PAA/CHT hydrogel could behave differently when a cationic or anionic specie is used. Here, the strategy was to play on the ability of both networks to be attracted and therefore generate rigid domains to sustain up to 2.80 MPa of strain at 541% elongation or repulsed by the negative PAA charges.

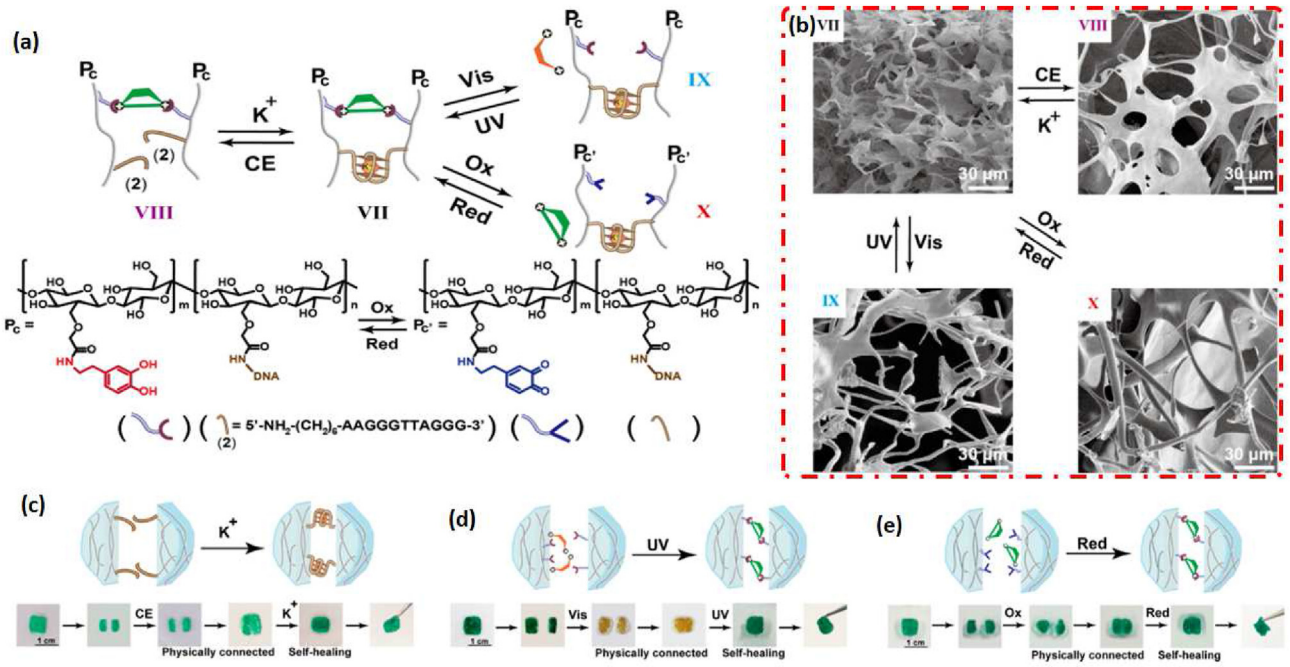


Fig. 7. (a) Synthesis of a triple-trigger stimuli-responsive hydrogel responding to light, redox agents or chemical agents; (b) SEM images corresponding to the cyclic and reversible interconversion between the high-stiffness hydrogel (state VII) and low-stiffness hydrogels are triggered *via* three different stimuli: K+/CE (state VII → state VIII), UV/vis (state VII → state IX) and redox (state VII → state X); (c–e) triple-triggered self-healing of the stiff hydrogel in state VII crosslinked by the G-quadruplexes and Dop/DTEc interactions using (c) chemical triggers, (d) photochemical triggers, and (e) redox triggers. Adapted from Ref. [250] with permission, copyright 2018 ACS.

Synthetic polymers are also of high interest when conductive biomaterials are targeted. Generally, conductivity is set up using a delocalized π-π network such as polyaniline [123], graphene oxide [262] or other inorganic materials such as carbon nanotubes [263] or polythiophene [44]. Gan et al. [264] used the ability of polypyrrole to bring conductivity to DN hydrogels involving CHT and PA. Using a single $FeCl_3$ soaking, CHT and pyrrole monomers were electrostatically crosslinked and polymerized, respectively, leading to a tough and conductive hydrogel. Polypyrrole has doped and no-doped states, enabling the loading/releasing of drugs such as dexamethasone through an electrostatic process. Zhao et al. [265] used proteins to develop a DN hydrogel from PA, micelles, and silk fibers in an IPN approach with fast gelation under mild conditions. With the presence of sodium dodecyl sulfate micelles, strong hydrophobic and electrostatic interactions were set up and induced the sol-gel transition of the silk fibers to form the hydrogel able to support an elongation strength of 0.44 MPa until 900% deformation. To solve the adhesion problems of tough hydrogels, Karami

Table 2
Examples of synthetic/natural hydrogel formulations.

Constituent macromolecule(s)	Strategies and main chemical routes	Main properties – applications	Ref.
PA/agarose	DN photocrosslinking + thermal rearrangement	Thermal reversibility, high stretchability, high fracture strain – biochip fabrication, stem cell differentiation, bone defect repair	[254]
CHT/PAA/PA/halloysite nanotubes	Hybrid DN/DC co-radical polymerization + hydrogen bonding or electrostatic interactions	Self-recoverability, high tensile stress, stretchability, and toughness – load-bearing structural materials	[257]
CHT/PEGDA	DN photopolymerization + hydrogen bonding or electrostatic interactions	High compressive strength, high elongation at break – wound healing, antibacterial, anti-inflammatory vascularization-promoting, skin repair	[260]
CHT/PAA	DN radical polymerization + hydrogen-bonding or electrostatic interactions	High compressive strength, high elongation at break – antifreeze sensors, conductive hydrogels, biosensors, wearable devices	[261]
CM-CHT/NIPAm/GO	DN radical polymerization + hydrogen bonding or electrostatic interactions	High compressive strength, high elongation at break – remote actuators, healthcare biosensors, wound repair, conductive devices, biocompatibility	[262]
CHT/PAM/PPy	IPN photo and radical polymerization + hydrogen bonding or electrostatic interactions	Tough hydrogel – wound repair, biocompatibility, conductive devices	[264]
PAM/silk/SDS micelle	DN photo + thermal polymerization	High stretchability, toughness – biocompatibility, low cytotoxicity	[265]
CNC@TA/PVA borax	DN boronate ester bond + hydrogen bonding or electrostatic interactions	High stretchability, self-healing – flexible/wearable electronic devices, biocompatibility	[267]
PVA/PAA + PEGDA/cellulose	Multi-network radical polymerization + hydrogen bonding or electrostatic interactions	High strength, self-healing – shape memory device, antibacterial properties	[268]
CHT/PA/PAA/SiO_2	Composite DN sol-gel process + hydrogen bonding or electrostatic interactions	High strength – conductive hydrogels, sensors, electric skin, wearable devices, motion detection	[269]

et al. [266] worked on a system of three components with the inclusion of cellulose nanofibers in an Alg and a dimethacrylate PEG matrix. Cellulose fibers contributed to reinforcing adhesion by hydrogen bonding and fiber penetration into the skin.

When more than two components are involved in the fabrication of hydrogels, DC, DN, and IPN approaches can be combined, which impacts the viability and increases the complexity or the cost of such a process. Lin et al. [267] proposed a strategy that combined many approaches: (1) cellulose nano crystals were used as a main network covered by TA, so-called TA@CNC, coordinated by silver, and (2) the latter was mixed with PVA and crosslinked *via* boronate ester using sodium borate, leading to a highly stretchable hydrogel until ~4000% elongation suitable for artificial skin-like biomaterials. Wang et al. [268] used three systems where quaternized cellulose/PVA/PAA were put together to form a multifunctional hydrogel. Quaternized cellulose was responsible for the antibacterial properties; meanwhile, synthetic polymers carried the toughness and self-healing properties. In the same vein, Li et al. [269] used a combination of neat CHT, PA, and PAA. First, PA and PAA were co-polymerized through a sol-gel process at 37 °C, forming the covalent network. Then, the hydrogel was soaked in iron oxide solution, inducing the coordination of all the available functions (amine, carboxylate, hydroxyl) in a large network of ionic and hydrogen bonding to form a tough hydrogel able to support an elongation strength of 1.13 MPa. Zhao et al. [270] investigated a conductive self-healing hydrogel from three biocompatible materials: PVA/agarose/carboxyethyl CHT (CEC) with silver nanowires trapped in the matrix for the conductivity. Using the large number of 1,3-diol functions of the PVA, borax, and glycerine were used to covalently link PVA diols, whereas agarose and CEC contributed to the hydrogel cohesion by hydrogen bonding.

5. Critical discussion, future trends and conclusions

The chemical modification of natural polymers and proteins has enabled the fabrication of a variety of hydrogels for biomedical applications. In specific, the manufacturing of natural-based hydrogels with tailorable mechanical properties — namely with high toughness and the ability to withstand cyclic deformation — has been challenging, with the adaptation of standard DN, DC or IPN strategies, with the main concepts and applications primarily developed for synthetic polymers, to circumvent difficulties associated to these processes.

Networks modified to show chemical responsivity to light are well-explored approaches to confer on-demand crosslinking ability to natural molecules. Therefore, this approach is a well-established way to produce biomedical hydrogels, as well as, to prepare precursors amenable to integrate a plethora of combinatorial strategies, mostly comprising photocrosslinking and non-covalent network reinforcement. Photopolymerization reactions are relatively fast and mostly easy to apply. Despite the generation of free radicals during exposure to irradiation, well-controlled reactions are often compatible with high cell viability, low tissue damage, and overall clinical requirements. One important impairment associated with photocrosslinking strategies concerns the effective penetration of light through biological matter. Indeed, photopolymerization processes could be limited when precursor solutions are opaque and tend to absorb the used irradiation at the relevant photoinitiator absorption wavelength, or when injured tissues are not at superficial locations amenable to be homogeneously and effectively irradiated, which is often the case for intracorporeal applications. Electrostatically reacted biomacromolecules are often associated with methacrylated networks to reach high mechanical performance. Those have allowed achieving cohesive hydrogels with use as, for example, pH-dependent soft devices. Facing the relative weakness and instability of such interactions and, importantly, their usual dependency on conditions that diverge from the physiological range (e.g. the dependency on acidic pHs to achieve charged amine groups) the use of dynamic covalent networks based on reversible bonding through Schiff base and boronic ester may be useful to create multistimuli-responsive (e.g., to pH, temperature, ionic strength, glucose) devices capable of being stimulated within cytocompatible conditions [271].

Additionally, the pursuit of a better control of the rate of such interactions or more complex associations involving DN could lead to development of materials with higher resistance. Systems based on irreversible bonds formed after enzymatic and 'click' reactions have been very valuable to enable tough protein-based hydrogels with high stretchability and biocompatibility. However, the reactivity of enzymes with biological molecules makes the effects of their combination with cells or other living organisms uncertain. The adaptation of combined chemical routes to achieve mechanically versatile hydrogels to biorthogonal chemistries, i.e., highly selective chemical reactions that occur independently from endogenous cellular groups, may be an interesting manner to avoid unspecific interactions of crosslinkers with surrounding tissues and cells [272]. Also, chemical strategies involving the usage of small molecules widely discussed in this review, often involving PEG derivatives, used as linkers or crosslink agents may also elicit toxicity and biological unpredictability issues. In fact, the use of such small molecules to enhance the mechanical properties of biomedical hydrogels is still an open debate. There is an idea that the postelimination of these small molecules avoids any toxicity, against the counter idea arguing that even traces could affect the biocompatibility and bring new problems, including antigen-specific reactivity [273]. Therefore, the development of 'eco-friendly' chemical routes to modify natural components is fundamental to enhance all the physical and chemical properties of biomedical hydrogels. Hydrogels composed of natural components represent a higher challenge for researchers but also constitute a way for medical devices production to align with sustainable economic and ecological politics.

Several works presented in this review and elsewhere in the recent scientific literature use the term 'green chemistry' to define a sustainable way to produce chemicals or materials [274] involving hydrogel manufacturing. The 12 principles of green chemistry, such as prevention, less hazardous chemical syntheses, atom economy, and catalysis processes, were created to support the development of a 'good sense' reflexion to reactions and materials fabrication. Using a full base of natural components for advanced hydrogel production respects the principles of 'green chemistry' in terms of renewable resources and encourages the cyclic usage of biomass, highly beneficial to the environment and local economy. From Tables 1 and 2 of this review, it is possible to distinguish the link between the used approaches, mechanical properties, and applications to finally establish the limitations of the currently available medical hydrogels. Using synthetic polymers in a hydrogel formulation generally allows for achieving high mechanical properties (i.e., high elongation and compression features, high percentage of recovery), and there is evidence that synthetic polymers do not obtrude biocompatibility or cell viability. Self-healing ability has been widely reported for fully natural formulations, where the mechanical properties are often lower than for synthetic counterparts, possibly permitting a better recovery of molecular interactions after structural damage. Furthermore, for a plethora of proteins and some polysaccharides, biodegradability issues are also manageable due to higher assimilation by the body. DC approaches, mainly explored for modified biomacromolecules, enable development of multifunctional hydrogels using fewer materials with a

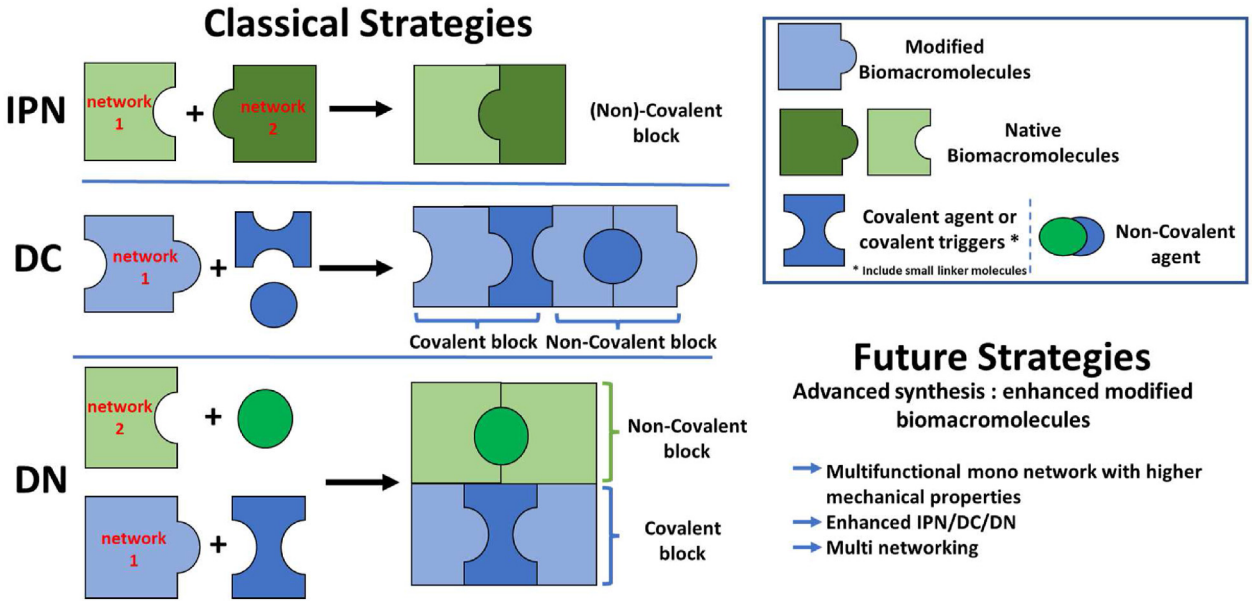


Fig. 8. General schematic outline of the classic and future strategies for hydrogel fabrication.

lower degree of complexity. It is interesting to discern the ability of fully natural associations to achieve high mechanical properties, which are lesser than with synthetic ones but still enable the study of all the spectra of medical applications.

Considering the plethora of chemical pathways discussed in this review, it is interesting to highlight which ones are the most promising regarding the development of TE systems. The usage of natural linker molecules, such as TA, to harden a system is a common strategy [275] to avoid synthetic crosslinking agents. Due to its ability to crosslink proteins and polysaccharides, using either electrostatic interactions or hydrogen bonding, TA can also be grafted to a natural polymer backbone by chemical functionalization. Strategies involving supramolecular self-assembly constitute interesting approaches because of the large range of 'smart' applications and the inherent TA adhesive capacity. Host–guest approaches seem to be promising in leveraging natural molecules for precise drug delivery and responsive hydrogels, especially because the main molecules involved, CDs, already come from natural sources. The possibility to adjust the diameter of CDs allows envisioning a number of ways to trap functional groups and investigate new types of interactions between natural compounds. The switching process triggered by external stimuli such as electrochemical variations, light exposure, and so on, constitutes a clean way to work on the internal variation entropy of the hydrogel and therefore its stability from soft to tough states. In 2016, Sir J. Fraser Stoddart, Bernard L. Feringa and Jean-Pierre Sauvage received the Nobel Prize in Chemistry for their research on 'molecular machine straitly'. They showed the possibility to play with the conformation and space of molecules to switch from one specific shape to another with a variation of the system entropy. Such a system might be applied to DN, DC, and IPN hydrogels and more specifically to stimuli-responsive biomaterials involving natural components. Currently, such systems are mainly based on synthetic molecules/polymers, which is why transposing such an approach to natural polymers and proteins constitutes a high and ambitious challenge for the coming years.

In summary, classical IPN, DC, and DN can be conceptualized using a graphic concept close to 'puzzle pieces' representing combinations of blocks (networks/biomacromolecules), which may be chemically modified or not (Fig. 8). By convention, blue blocks represent modified biomacromolecules *(i.e.* using a synthesis pathway) and green blocs correspond to native biomacromolecules able to react even without chemical modifications (such as the ability of CHT to stablish ionic interactions or a Schiff base generated by native free amine). For Blue blocks, modification(s) are symbolized by an external or internal extension (an extra half-circle). These blocks can be connected by crosslink agents into a covalent or non-covalent system. In a future perspective, we believe that the insertions of more modifications into 'puzzle pieces' may enable more possibilities of interactions for one single block. Classical concepts could also be joined/mixed with, for example, an association of IPN and DC forming DN-like structures. Also, multi-modified biomacromolecules integrated into classical or advanced strategies may be explored as future targets in which the classical concepts – IPN, DC or DN – will be used as 'basic tools' to create innovative and high-performing combinations. The development of new materials (or upgrade the functionalization of existing ones), new synthesis pathways with higher yields and more efficient purification technics may allow to develop new and more mechanically versatile hydrogels.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to acknowledge the support of the European Union (EU) Horizon 2020 for the project InterLynk, grant agreement: H2020-NMBP-TR-IND-2020, project ID: 953169. This work was supported by the project 'A Bioactivated Nano-layered Hydrogel for Dermal Regeneration in Hard-to-Heal Ulcers' (BioNaNOR) financed by Research Council of Norway (RCN) Nano2021: grant number 287991. This work was also developed within the

scope of the project CICECO-Aveiro Institute of Materials, UIDB/50011/2020, UIDP/50011/2020 and LA/P/0006/2020, financed by national funds through the FCT/MEC (PIDDAC) This work was also supported by the Programa Operacional Competitividade e Internacionalização (POCI), in the component FEDER, and by national funds (OE) through FCT/MCTES in the scope of the project MARGEL (PTDC/BTM-MAT/31498/2017). The MARGEL project is acknowledged for the individual Junior Researcher contract of Dora C. S. Costa, and M. B. Oliveira knowledges the individual Assistant Researcher contract 2021.03588. CEECIND.

Abbreviations

N	double network
DC	dual-crosslinked
IPN	interpenetrating network
ECM	extracellular matrix
CHT	chitosan
HA	hyaluronic acid
Alg	sodium alginate
BSA	bovine serum albumin
GelMA	methacryloyl gelatin
TA	tannic acid
CD	cyclodextrin
SF	silk fibroin
CMC	carboxymethyl chitosan
CNC	cellulose nano crystals
EGCG	epigallocatechin
PA	polyamide
PAA	polyacrylic acid
TPP	tripolyphosphate
TG	transglutaminase
PBS	phosphate-buffered saline
PVA	polyvinylalcohol
PEG	polyethyleneglycol
PEO	poly(ethyleneoxyde)
PEGDA	polyethyleneglycoldialdehyde
Ada	adamantane
EDTA	ethylenediaminetetraacetic acid
DTT	dithiothreitol
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
NHS	*N*-hydroxysuccinimide
DMAP	4-dimethylaminopyridine
GO	graphite oxide
DDA	degree of deacetylation

References

[1] H. Fan, J.P. Gong, Fabrication of bioinspired hydrogels: challenges and opportunities, Macromolecules 53 (2020) 2769–2782, https://doi.org/10.1021/acs.macromol.0c00238.
[2] J.P. Gong, Y. Katsuyama, T. Kurokawa, Y. Osada, Double-network hydrogels with extremely high mechanical strength, Adv. Mater. 15 (2003) 1155–1158, https://doi.org/10.1002/adma.200304907.
[3] J.A. Stammen, S. Williams, D.N. Ku, R.E. Guldberg, Mechanical properties of a novel PVA hydrogel in shear and unconfined compression, Biomaterials 22 (2001) 799–806, https://doi.org/10.1016/S0142-9612(00)00242-8.
[4] A.M.S. Costa, J.F. Mano, Extremely strong and tough hydrogels as prospective candidates for tissue repair - a review, Eur. Polym. J. 72 (2015) 344–364, https://doi.org/10.1016/j.eurpolymj.2015.07.053.
[5] L.S. Nair, C.T. Laurencin, Biodegradable polymers as biomaterials, Prog. Polym. Sci. 32 (2007) 762–798, https://doi.org/10.1016/j.progpolymsci.2007.05.017.
[6] A. Banerjee, K. Chatterjee, G. Madras, Enzymatic degradation of polymers : a brief review, Mater. Sci. Technol. 30 (2014) 567–573, https://doi.org/10.1179/1743284713Y.0000000503.
[7] X. Du, L. Wu, H. Yan, L. Qu, L. Wang, X. Wang, S. Ren, D. Kong, L. Wang, Multifunctional hydrogel patch with toughness, tissue adhesiveness, and antibacterial activity for sutureless wound closure, ACS Biomater. Sci. Eng. 5 (2019) 2610–2620, https://doi.org/10.1021/acsbiomaterials.9b00130.
[8] S. Talebian, M. Mehrali, N. Taebnia, C.P. Pennisi, F.B. Kadumudi, J. Foroughi, M. Hasany, M. Nikkhah, M. Akbari, G. Orive, A. Dolatshahi-Pirouz, Self-healing hydrogels: the next paradigm shift in tissue engineering? Adv. Sci. 6 (2019), 1801664 https://doi.org/10.1002/advs.201801664.
[9] N.K. Simha, C.S. Carlson, J.L. Lewis, Evaluation of fracture toughness of cartilage by micropenetration, J. Mater. Sci. Mater. Med. 15 (2004) 631–639, https://doi.org/10.1023/B:JMSM.0000026104.30607.c7.
[10] P. Fratzl, Biomimetic materials research: what can we really learn from nature's structural materials? J. R. Soc. Interface 4 (2007) 637–642, https://doi.org/10.1098/rsif.2007.0218.
[11] Y. Sun, D. Nan, H. Jin, X. Qu, Recent advances of injectable hydrogels for drug delivery and tissue engineering applications, Polym. Test. 81 (2020), 106283, https://doi.org/10.1016/j.polymertesting.2019.106283.
[12] Y. Li, J. Rodrigues, H. Tomás, Injectable and biodegradable hydrogels: gelation, biodegradation and biomedical applications, Chem. Soc. Rev. 41 (2012) 2193–2221, https://doi.org/10.1039/c1cs15203c.
[13] P.D.C. Costa, D.C.S. Costa, T.R. Correia, V.M. Gaspar, J.F. Mano, Natural origin biomaterials for 4D bioprinting tissue-like constructs, Adv. Mater. Technol. 6 (2021), 2100168, https://doi.org/10.1002/admt.202100168.
[14] S. Supper, N. Anton, N. Seidel, M. Riemenschnitter, C. Schoch, T. Vandamme, Rheological study of chitosan/polyol-phosphate systems: influence of the polyol part on the thermo-induced gelation mechanism, Langmuir 29 (2013) 10229–10237, https://doi.org/10.1021/la401993q.
[15] Y. Bu, A. Pandit, Cohesion mechanisms for bioadhesives, Bioact. Mater. 13 (2022) 105–118, https://doi.org/10.1016/j.bioactmat.2021.11.008.
[16] J.P. Gong, Why are double network hydrogels so tough? Soft Matter 6 (2010) 2583–2590, https://doi.org/10.1039/b924290b.
[17] Jian Ping Gong, T. Kurokawa, T. Narita, G. Kagata, Y. Osada, G. Nishimura, M. Kinjo, Synthesis of hydrogels with extremely low surface friction, J. Am. Chem. Soc. 123 (2001) 5582–5583, https://doi.org/10.1021/ja003794q.
[18] V.N. Khiêm, T.T. Mai, K. Urayama, J.P. Gong, M. Itskov, A Multiaxial theory of double network hydrogels, Macromolecules 52 (2019) 5937–5947, https://doi.org/10.1021/acs.macromol.9b01044.
[19] Z. Zou, B. Zhang, X. Nie, Y. Cheng, Z. Hu, M. Liao, S. Li, A sodium alginate-based sustained-release IPN hydrogel and its applications, RSC Adv. 10 (2020) 39722–39730, https://doi.org/10.1039/d0ra04316h.
[20] W. Chu, M. Nie, X. Ke, J. Luo, J. Li, Recent advances in injectable dual cross-linking hydrogels for biomedical applications, Macromol. Biosci. 21 (2021), 2100109, https://doi.org/10.1002/mabi.202100109.
[21] R. Dimatteo, N.J. Darling, T. Segura, In situ forming injectable hydrogels for drug delivery and wound repair, Adv. Drug Deliv. Rev. 127 (2018) 167–184, https://doi.org/10.1016/j.addr.2018.03.007.
[22] N. Boucard, C. Viton, D. Agay, E. Mari, T. Roger, Y. Chancerelle, A. Domard, The use of physical hydrogels of chitosan for skin regeneration following third-degree burns, Biomaterials 28 (2007) 3478–3488, https://doi.org/10.1016/j.biomaterials.2007.04.021.
[23] J. Chen, Y. Wan, Y. Lin, H. Jiang, Platelet-rich fibrin and concentrated growth factors as novel platelet concentrates for chronic hard-to-heal skin ulcers: a systematic review and Meta-analysis of randomized controlled trials, J. Dermatol. Treat. 33 (2020) 613–621, https://doi.org/10.1080/09546634.2020.1773386.
[24] V. Falanga, M. Sabolinski, A bilayered living skin construct (APLIGRAF®) accelerates complete closure of hard-to-heal venous ulcers, Wound Repair Regen. 7 (1999) 201–207, https://doi.org/10.1046/j.1524-475X.1999.00201.x.
[25] M. Romanelli, V. Dini, P. Vowden, M.S. Ågren, Amelogenin, an extracellular matrix protein, in the treatment of venous leg ulcers and other hard-to-heal wounds: experimental and clinical evidence, Clin. Interv. Aging 3 (2008) 263–272, https://doi.org/10.2147/cia.s1846.
[26] X. Bai, M. Gao, S. Syed, J. Zhuang, X. Xu, X.Q. Zhang, Bioactive hydrogels for bone regeneration, Bioact. Mater. 3 (2018) 401–417, https://doi.org/10.1016/j.bioactmat.2018.05.006.
[27] M. Rahmati, J.J. Blaker, S.P. Lyngstadaas, J.F. Mano, H.J. Haugen, Designing multigradient biomaterials for skin regeneration, Mater, Today Adv 5 (2020), 100051, https://doi.org/10.1016/j.mtadv.2019.100051.
[28] T. Weng, P. Wu, W. Zhang, Y. Zheng, Q. Li, R. Jin, H. Chen, C. You, S. Guo, C. Han, X. Wang, Regeneration of skin appendages and nerves: current status and further challenges, J. Transl. Med. 18 (2020) 83, https://doi.org/10.1186/s12967-020-02248-5.
[29] J. Saiz-Poseu, J. Mancebo-Aracil, F. Nador, F. Busqué, D. Ruiz-Molina, The chemistry behind catechol-based adhesion, Angew. Chemie - Int. Ed. 58 (2019) 696–714, https://doi.org/10.1002/anie.201801063.
[30] H.M.C. Azeredo, K.W. Waldron, Crosslinking in polysaccharide and protein films and coatings for food contact - a review, Trends Food Sci. Technol. 52 (2016) 109–122, https://doi.org/10.1016/j.tifs.2016.04.008.
[31] A. Gaspar-Pintiliescu, A.M. Stanciuc, O. Craciunescu, Natural composite dressings based on collagen, gelatin and plant bioactive compounds for wound healing: a review, Int. J. Biol. Macromol. 138 (2019) 854–865, https://doi.org/10.1016/j.ijbiomac.2019.07.155.
[32] M.R. Singh, S. Patel, D. Singh, Natural polymer-based hydrogels as scaffolds for tissue engineering, in: A.M. Grumezescu (Ed.), Nanobiomaterials Soft Tissue Eng. Appl. Nanobiomaterials, Elsevier, 2016, pp. 231–260, https://doi.org/10.1016/B978-0-323-42865-1.00009-X.
[33] F. Raza, H. Zafar, Y. Zhu, Y. Ren, A. Ullah, A.U. Khan, X. He, H. Han, M. Aquib, K.O. Boakye-Yiadom, L. Ge, A review on recent advances in stabilizing peptides/proteins upon fabrication in hydrogels from biodegradable polymers,

Pharmaceutics 10 (2018) 16, https://doi.org/10.3390/pharmaceutics10010016.
[34] A. Blanco, G. Blanco, in: A. Blanco, G. Blanco (Eds.), Chapter 3. Proteins, Med. Biochem., Elsevier, 2017, pp. 21–71, https://doi.org/10.1016/B978-0-12-803550-4/00003-3.
[35] D. Sheehan, Introduction to proteins : structure , function and motion methods in molecular biology , vol . 695 : 3D cell culture : methods and protocols, Chembiochem 12 (2011) 1603–1604, https://doi.org/10.1002/cbic.201100254.
[36] K. Baler, R. Michael, I. Szleifer, G.A. Ameer, Albumin hydrogels formed by electrostatically triggered self- assembly and their drug delivery capability, Biomacromolecules 15 (2014) 3625–3633, https://doi.org/10.1021/bm500883h.
[37] J. Ong, J. Zhao, A.W. Justin, A.E. Markaki, Albumin-based hydrogels for regenerative engineering and cell transplantation, Biotechnol. Bioeng. 116 (2019) 3457–3468, https://doi.org/10.1002/bit.27167.
[38] N. Amdursky, M.M. Mazo, M.R. Thomas, E.J. Humphrey, J.L. Puetzer, J.P. St-Pierre, S.C. Skaalure, R.M. Richardson, C.M. Terracciano, M.M. Stevens, Elastic serum-albumin based hydrogels: mechanism of formation and application in cardiac tissue engineering, J. Mater. Chem. B. 6 (2018) 5604–5612, https://doi.org/10.1039/c8tb01014e.
[39] D.R. Grisham, V. Nanda, Zeta potential prediction from protein structure in general aqueous electrolyte solutions, Langmuir 36 (2020) 13799–13803, https://doi.org/10.1021/acs.langmuir.0c02031.
[40] S. Ravindran, M.A.K. Williams, R.L. Ward, G. Gillies, Understanding how the properties of whey protein stabilized emulsions depend on pH, ionic strength and calcium concentration, by mapping environmental conditions to zeta potential, Food Hydrocoll 79 (2018) 572–578, https://doi.org/10.1016/j.foodhyd.2017.12.003.
[41] Y. Zhang, P.S. Cremer, Interactions between macromolecules and ions: the Hofmeister series, Curr. Opin. Chem. Biol. 10 (2006) 658–663, https://doi.org/10.1016/j.cbpa.2006.09.020.
[42] Q. He, Y. Huang, S. Wang, Hofmeister effect-assisted one step fabrication of ductile and strong gelatin hydrogels, Adv. Funct. Mater. 28 (2018), 1705069, https://doi.org/10.1002/adfm.201705069.
[43] W.L. Ng, W.Y. Yeong, M.W. Naing, Development of polyelectrolyte chitosan-gelatin hydrogels for skin bioprinting, Procedia CIRP 49 (2016) 105–112, https://doi.org/10.1016/j.procir.2015.09.002.
[44] H. Sun, Y. Zhao, C. Wang, K. Zhou, C. Yan, G. Zheng, J. Huang, K. Dai, C. Liu, C. Shen, Ultra-Stretchable, durable and conductive hydrogel with hybrid double network as high performance strain sensor and stretchable triboelectric nanogenerator, Nano Energy 76 (2020), 105035, https://doi.org/10.1016/j.nanoen.2020.105035.
[45] Y. Yang, X. Wang, F. Yang, H. Shen, D. Wu, A universal soaking strategy to convert composite hydrogels into extremely tough and rapidly recoverable double-network hydrogels, Adv. Mater. 28 (2016) 7178–7184, https://doi.org/10.1002/adma.201601742.
[46] M.M. Islam, M. Shahruzzaman, S. Biswas, M. Nurus Sakib, T.U. Rashid, Chitosan based bioactive materials in tissue engineering applications-A review, Bioact. Mater. 5 (2020) 164–183, https://doi.org/10.1016/j.bioactmat.2020.01.012.
[47] Z. Shariatinia, A.M. Jalali, Chitosan-based hydrogels: preparation, properties and applications, Int. J. Biol. Macromol. 115 (2018) 194–220, https://doi.org/10.1016/j.ijbiomac.2018.04.034.
[48] J.M.M. Rodrigues, E.J. Castanheira, D.C.S. Costa, D.H.A. Rocha, J. Borges, J.F. Mano, Chapter 8: extending the functionality of marine-origin polysaccharides through chemical modification for biomedical applications, in: J.F. Mano, H.S. Azevedo, J. Borges (Eds.), Soft Matter Biomed. Appl., Royal Society of Chemistry, 2021, pp. 180–204, https://doi.org/10.1039/9781839161124-00180.
[49] T. Marmier, C.R. Szczepanski, C. Candet, A. Zenerino, R.P. Godeau, G. Godeau, Investigation on Mecynorhina torquata Drury, 1782 (Coleoptera, Cetoniidae, Goliathini) cuticle: surface properties, chitin and chitosan extraction, Int. J. Biol. Macromol. 164 (2020) 1164–1173, https://doi.org/10.1016/j.ijbiomac.2020.07.155.
[50] M. Sukul, P. Sahariah, H.L. Lauzon, J. Borges, M. Másson, J.F. Mano, H.J. Haugen, J.E. Reseland, In vitro biological response of human osteoblasts in 3D chitosan sponges with controlled degree of deacetylation and molecular weight, Carbohydr. Polym. 254 (2021), 117434, https://doi.org/10.1016/j.carbpol.2020.117434.
[51] L. Xu, C. Wang, Y. Cui, A. Li, Y. Qiao, D. Qiu, Conjoined-network rendered stiff and tough hydrogels from biogenic molecules, Sci. Adv. 5 (2019), https://doi.org/10.1126/sciadv.aau3442 eaau3442.
[52] A.M.S. Costa, J.F. Mano, Highly robust hydrogels via a fast, simple and cytocompatible dual crosslinking-based process, Chem. Commun. 51 (2015) 15673–15676, https://doi.org/10.1039/c5cc05564d.
[53] S. Samani, S. Bonakdar, A. Farzin, J. Hadjati, M. Azami, A facile way to synthesize a photocrosslinkable methacrylated chitosan hydrogel for biomedical applications, Int. J. Polym. Mater. Polym. Biomater. 70 (2020) 730–741, https://doi.org/10.1080/00914037.2020.1760274.
[54] M. Diolosà, I. Donati, G. Turco, M. Cadenaro, R. Di Lenarda, L. Breschi, S. Paoletti, Use of methacrylate-modified chitosan to increase the durability of dentine bonding systems, Biomacromolecules 15 (2014) 4606–4613, https://doi.org/10.1021/bm5014124.
[55] D.R. Sahoo, T. Biswal, Alginate and its application to tissue engineering, SN Appl. Sci. 3 (2021) 30, https://doi.org/10.1007/s42452-020-04096-w.
[56] K.Y. Lee, D.J. Mooney, Alginate: properties and biomedical applications, Prog. Polym. Sci. 37 (2012) 106–126, https://doi.org/10.1016/j.progpolymsci.2011.06.003.
[57] K. Varaprasad, T. Jayaramudu, V. Kanikireddy, C. Toro, E.R. Sadiku, Alginate-based composite materials for wound dressing application:A mini review, Carbohydr. Polym. 236 (2020), 116025, https://doi.org/10.1016/j.carbpol.2020.116025.
[58] Y. Gao, X. Jin, Dual crosslinked methacrylated alginate hydrogel micron fibers and tissue constructs for cell biology, Mar. Drugs 17 (2019) 557, https://doi.org/10.3390/md17100557.
[59] M. Dai, B. Sui, Y. Hua, Y. Zhang, B. Bao, Q. Lin, X. Liu, L. Zhu, J. Sun, A well defect-suitable and high-strength biomimetic squid type II gelatin hydrogel promoted in situ costal cartilage regeneration via dynamic immunomodulation and direct induction manners, Biomaterials 240 (2020), 119841, https://doi.org/10.1016/j.biomaterials.2020.119841.
[60] A. Mora-Boza, E. López-Ruiz, M.L. López-Donaire, G. Jiménez, M.R. Aguilar, J.A. Marchal, J.L. Pedraz, B. Vázquez-Lasa, J.S. Román, P. Gálvez-Martín, Evaluation of glycerylphytate crosslinked semi-and interpenetrated polymer membranes of hyaluronic acid and chitosan for tissue engineering, Polymers (Basel) 12 (2020) 2661, https://doi.org/10.3390/polym12112661.
[61] A. Ronca, U. D'Amora, M.G. Raucci, H. Lin, Y. Fan, X. Zhang, L. Ambrosio, A combined approach of double network hydrogel and nanocomposites based on hyaluronic acid and poly(ethylene glycol) diacrylate blend, Materials 11 (2018) 2454, https://doi.org/10.3390/ma11122454.
[62] W. Xiao, X. Qu, J. Li, L. Chen, Y. Tan, K. Li, B. Li, X. Liao, Synthesis and characterization of cell-laden double-network hydrogels based on silk fibroin and methacrylated hyaluronic acid, Eur. Polym. J. 118 (2019) 382–392, https://doi.org/10.1016/j.eurpolymj.2019.05.040.
[63] L. Yuan, Y. Wu, Q. sheng Gu, H. El-Hamshary, M. El-Newehy, X. Mo, Injectable photo crosslinked enhanced double-network hydrogels from modified sodium alginate and gelatin, Int. J. Biol. Macromol. 96 (2017) 569–577, https://doi.org/10.1016/j.ijbiomac.2016.12.058.
[64] I. Hussain, S.M. Sayed, S. Liu, O. Oderinde, M. Kang, F. Yao, G. Fu, Enhancing the mechanical properties and self-healing efficiency of hydroxyethyl cellulose-based conductive hydrogels via supramolecular interactions, Eur. Polym. J. 105 (2018) 85–94, https://doi.org/10.1016/j.eurpolymj.2018.05.025.
[65] H. Zhang, X. Wu, Z. Qin, X. Sun, H. Zhang, Q. Yu, M. Yao, S. He, X. Dong, F. Yao, J. Li, Dual physically cross-linked carboxymethyl cellulose-based hydrogel with high stretchability and toughness as sensitive strain sensors, Cellulose 5 (2020) 9975–9989, https://doi.org/10.1007/s10570-020-03463-5.
[66] T. Ni, M. Liu, Y. Zhang, Y. Cao, R. Pei, 3D bioprinting of bone marrow mesenchymal stem cell-laden silk fibroin double network scaffolds for cartilage tissue repair, Bioconjug. Chem. 31 (2020), https://doi.org/10.1021/acs.bioconjchem.0c00298, 1938–1947.
[67] M. Zargarzadeh, A.J.R. Amaral, C.A. Custódio, J.F. Mano, Biomedical applications of laminarin, Carbohydr. Polym. 232 (2020), 115774, https://doi.org/10.1016/j.carbpol.2019.115774.
[68] C.A. Custódio, R.L. Reis, J.F. Mano, Photo-Cross-linked laminarin-based hydrogels for biomedical applications, Biomacromolecules 17 (2016) 1602–1609, https://doi.org/10.1021/acs.biomac.5b01736.
[69] W. Ahn, J.-H. Lee, S.R. Kim, J. Lee, E.J. Lee, Designed protein- and peptide-based hydrogels for biomedical sciences, J. Mater. Chem. B. 9 (2021) 1919–1940, https://doi.org/10.1039/d0tb02604b.
[70] A. Schloss, D.M. Williams, L.J. Regan, Protein-based hydrogels for tissue engineering, Adv. Exp. Med. Biol. 940 (2016) 167–177, https://doi.org/10.1007/978-3-319-39196-0.
[71] S. Pacelli, K. Rampetsreiter, S. Modaresi, S. Subham, A.R. Chakravarti, S. Lohfeld, M.S. Detamore, A. Paul, Fabrication of a double crosslinked interpenetrating polymeric modified network with (IPN) hydrogel to surface modulate polydopamine osteogenic differentiation of adipose-derived stem cells, ACS Appl. Mater. Interfaces 10 (2018) 24955–24962, https://doi.org/10.1021/acsami.8b05200.
[72] X. Huang, Y. Zhang, F. Li, J. Zhang, Y. Dai, M. Shi, Y. Zhao, Highly efficient alginate-based macromolecular photoinitiator for crosslinking and toughening gelatin hydrogels, J. Polym. Sci. 58 (2020) 1439–1449, https://doi.org/10.1002/pol.20200138.
[73] B. Liu, Y. Wang, Y. Miao, X. Zhang, Z. Fan, G. Singh, X. Zhang, K. Xu, B. Li, Z. Hu, M. Xing, Hydrogen bonds autonomously powered gelatin methacrylate hydrogels with super-elasticity , self-heal and underwater self- adhesion for sutureless skin and stomach surgery and E-skin, Biomaterials 171 (2018) 83–96, https://doi.org/10.1016/j.biomaterials.2018.04.023.
[74] J. Antunes, V.M. Gaspar, L. Ferreira, M. Monteiro, R. Henrique, C. Jerónimo, J.F. Mano, In-air production of 3D co-culture tumor spheroid hydrogels for expedited drug screening, Acta Biomater. 94 (2019) 392–409, https://doi.org/10.1016/j.actbio.2019.06.012.
[75] X.Y. He, A. Sun, T. Li, Y.J. Qian, H. Qian, Y.F. Ling, L.H. Zhang, Q.Y. Liu, T. Peng, Z. Qian, Mussel-inspired antimicrobial gelatin/chitosan tissue adhesive rapidly activated in situ by H2O2/ascorbic acid for infected wound closure, Carbohydr, Polym 247 (2020), 116692, https://doi.org/10.1016/j.carbpol.2020.116692.
[76] X. He, X. Liu, J. Yang, H. Du, N. Chai, Z. Sha, M. Geng, X. Zhou, C. He, Tannic acid-reinforced methacrylated chitosan/methacrylated silk fibroin hydrogels

with multifunctionality for accelerating wound healing, Carbohydr. Polym. 247 (2020), 116689, https://doi.org/10.1016/j.carbpol.2020.116689.
[77] Y. Zhang, M. Chen, J. Tian, P. Gu, H. Cao, X. Fan, W. Zhang, In situ bone regeneration enabled by a biodegradable hybrid double-network hydrogel, Biomater. Sci. 7 (2019) 3266–3276, https://doi.org/10.1039/c9bm00561g.
[78] T. Burnouf, H.A. Goubran, T.M. Chen, K.L. Ou, M. El-Ekiaby, M. Radosevic, Blood-derived biomaterials and platelet growth factors in regenerative medicine, Blood Rev. 27 (2013) 77–89, https://doi.org/10.1016/j.blre.2013.02.001.
[79] S.C. Santos, C.A. Custódio, J.F. Mano, Photopolymerizable platelet lysate hydrogels for customizable 3D cell culture platforms, Adv. Healthc. Mater. 7 (2018), 1800849, https://doi.org/10.1002/adhm.201800849.
[80] J.A. Yang, J. Yeom, B.W. Hwang, A.S. Hoffman, S.K. Hahn, In situ-forming injectable hydrogels for regenerative medicine, Prog. Polym. Sci. 39 (2014) 1973–1986, https://doi.org/10.1016/j.progpolymsci.2014.07.006.
[81] S. Tang, J. Yang, L. Lin, K. Peng, Y. Chen, S. Jin, W. Yao, Construction of physically crosslinked chitosan/sodium alginate/calcium ion double-network hydrogel and its application to heavy metal ions removal, Chem. Eng. J. 393 (2020), 124728, https://doi.org/10.1016/j.cej.2020.124728.
[82] S. Azevedo, A.M.S. Costa, A. Andersen, I.S. Choi, H. Birkedal, J.F. Mano, Bio-inspired ultratough hydrogel with fast recovery, self-healing, injectability and cytocompatibility, Adv. Mater. 29 (2017), 1700759, https://doi.org/10.1002/adma.201700759.
[83] J. Guo, W. Sun, J. Peter, X. Lu, Q. Li, M. Lin, O. Mrowczynski, E.B. Rizk, J. Cheng, G. Qian, J. Yang, Development of tannin-inspired antimicrobial bioadhesives, Acta Biomater. 72 (2018) 35–44, https://doi.org/10.1016/j.actbio.2018.03.008.
[84] X. Xu, L. Che, L. Xu, D. Huang, J. Wu, Z. Du, Y. Lin, X. Hu, Q. Zhao, Z. Lin, L. Xu, Green preparation of anti-inflammation an injectable 3D porous hydrogel for speeding up deep second-degree scald wound healing, RSC Adv. 10 (2020) 36101–36110, https://doi.org/10.1039/d0ra04990e.
[85] C. Hu, L. Long, J. Cao, S. Zhang, Y. Wang, Dual-crosslinked mussel-inspired smart hydrogels with enhanced antibacterial and angiogenic properties for chronic infected diabetic wound treatment via pH-responsive quick cargo release, Chem. Eng. J. 411 (2021), 128564, https://doi.org/10.1016/j.cej.2021.128564.
[86] Y.H. Yeo, W.H. Park, Dual-crosslinked, self-healing and thermo-responsive methylcellulose/chitosan oligomer copolymer hydrogels, Carbohydr. Polym. 258 (2021), 117705.
[87] B. Yang, J. Song, Y. Jiang, M. Li, J. Wei, J. Qin, W. Peng, F.L. Lasaosa, Y. He, H. Mao, J. Yang, Z. Gu, Injectable Adhesive self-healing multicross-linked double-network hydrogel facilitates full-thickness skin wound healing, ACS Appl. Mater. Interfaces 12 (2020) 57782–57797, https://doi.org/10.1021/acsami.0c18948.
[88] T. Figueiredo, J. Jing, I. Jeacomine, J. Olsson, T. Gerfaud, J.G. Boiteau, C. Rome, C. Harris, R. Auzély-Velty, Injectable self-healing hydrogels based on boronate ester formation between hyaluronic acid partners modified with benzoxaborin derivatives and saccharides, Biomacromolecules 21 (2020) 230–239, https://doi.org/10.1021/acs.biomac.9b01128.
[89] Y. Choi, K. Park, H. Choi, D. Son, M. Shin, Self-healing, stretchable, biocompatible, and conductive alginate hydrogels through dynamic covalent bonds for implantable electronics, Polymers (Basel) 13 (2021) 1133, https://doi.org/10.3390/polym13071133.
[90] L. Jiang, D. Su, S. Ding, Q. Zhang, Z. Li, F. Chen, Salt-assisted toughening of protein hydrogel with controlled degradation for bone regeneration, Adv. Funct. Mater. 29 (2019), 1901314, https://doi.org/10.1002/adfm.201901314.
[91] Q. Chen, X. Tian, J. Fan, H. Tong, Q. Ao, An interpenetrating alginate/gelatin network for three-dimensional (3D) cell cultures and organ bioprinting, Molecules 25 (2020) 756.
[92] M.H. Ghanian, H. Mirzadeh, H. Baharvand, In situ forming, cytocompatible, and self-recoverable tough hydrogels based on dual ionic and click cross-linked alginate, Biomacromolecules 19 (2018) 1646–1662, https://doi.org/10.1021/acs.biomac.8b00140.
[93] R. Debone Piazza, J.V. Brandt, C. Carvalho dos Santos, R. Fernando Costa Marques, M. Jafelicci Junior, Gelatin/dextran-based hydrogel cross-linked by Diels–Alder click chemistry: the swelling and potassium diclofenac releasing, Med. Devices Sensors 4 (2021), e10151, https://doi.org/10.1002/mds3.10151.
[94] Y. Yao, P. Wang, X. Li, Y. Xu, G. Lu, Q. Jiang, Y. Sun, Y. Fan, X. Zhang, A di-self-crosslinking hyaluronan-based hydrogel combined with type I collagen to construct a biomimetic injectable cartilage-filling scaffold, Acta Biomater. 111 (2020) 197–207, https://doi.org/10.1016/j.actbio.2020.05.007.
[95] C.B. Rodell, N.N. Dusaj, C.B. Highley, J.A. Burdick, Injectable and cytocompatible tough double-network hydrogels through tandem supramolecular and covalent crosslinking, Adv. Mater. 28 (2016) 8419–8424, https://doi.org/10.1002/adma.201602268.
[96] Y. Kim, D. Jeong, V.V. Shinde, Y. Hu, C. Kim, S. Jung, Azobenzene-grafted carboxymethyl cellulose hydrogels with photo-switchable, reduction-responsive and self-healing properties for a controlled drug release system, Int. J. Biol. Macromol. 163 (2020) 824–832, https://doi.org/10.1016/j.ijbiomac.2020.07.071.
[97] T. Hu, X. Cui, M. Zhu, M. Wu, Y. Tian, B. Yao, W. Song, Z. Niu, S. Huang, X. Fu, 3D-printable supramolecular hydrogels with shear-thinning property: fabricating strength tunable bioink via dual crosslinking, Bioact. Mater. 5 (2020) 808–818, https://doi.org/10.1016/j.bioactmat.2020.06.001.
[98] L. Wang, X. Zhang, K. Yang, Y.V. Fu, T. Xu, S. Li, D. Zhang, L.N. Wang, C.S. Lee, A novel double-crosslinking-double-network design for injectable hydrogels with enhanced tissue adhesion and antibacterial capability for wound treatment, Adv. Funct. Mater. 30 (2019), 1904156, https://doi.org/10.1002/adfm.201904156.
[99] S. Li, L. Wang, X. Yu, C. Wang, Z. Wang, Synthesis and characterization of a novel double cross-linked hydrogel based on Diels-Alder click reaction and coordination bonding, Mater. Sci. Eng. C. 82 (2018) 299–309, https://doi.org/10.1016/j.msec.2017.08.031.
[100] M. Ishihara, S. Kishimoto, S. Nakamura, Y. Sato, H. Hattori, Polyelectrolyte complexes of natural polymers and their biomedical applications, Polymers (Basel) 11 (2019) 672, https://doi.org/10.3390/polym11040672.
[101] Y. Hu, Z. Zhang, Y. Li, X. Ding, D. Li, C. Shen, F.J. Xu, Dual-crosslinked amorphous polysaccharide hydrogels based on chitosan/alginate for wound healing applications, Macromol. Rapid Commun. 39 (2018), 1800069, https://doi.org/10.1002/marc.201800069.
[102] M. Gierszewska, J. Ostrowska-Czubenko, E. Chrzanowska, pH-responsive chitosan/alginate polyelectrolyte complex membranes reinforced by tripolyphosphate, Eur. Polym. J. 101 (2018) 282–290, https://doi.org/10.1016/j.eurpolymj.2018.02.031.
[103] Z. Li, L. Chen, M. Xu, Y. Ma, L. Chen, F. Dai, Double crosslinking hydrogel with tunable properties for potential biomedical application, J. Polym. Res. 27 (2020) 262, https://doi.org/10.1007/s10965-020-02242-x.
[104] X. Lv, W. Zhang, Y. Liu, Y. Zhao, J. Zhang, M. Hou, Hygroscopicity modulation of hydrogels based on carboxymethyl chitosan/Alginate polyelectrolyte complexes and its application as pH-sensitive delivery system, Carbohydr. Polym. 198 (2018) 86–93, https://doi.org/10.1016/j.carbpol.2018.06.058.
[105] X. Lv, Y. Liu, S. Song, C. Tong, X. Shi, Y. Zhao, J. Zhang, M. Hou, Influence of chitosan oligosaccharide on the gelling and wound healing properties of injectable hydrogels based on carboxymethyl chitosan/alginate polyelectrolyte complexes, Carbohydr. Polym. 205 (2019) 312–321, https://doi.org/10.1016/j.carbpol.2018.10.067.
[106] K. Yan, F. Xu, C. Wang, Y. Li, Y. Chen, X. Li, Z. Lu, D. Wang, A multifunctional metal-biopolymer coordinated double network hydrogel combined with multi-stimulus responsiveness, self-healing, shape memory and antibacterial properties, Biomater. Sci. 8 (2020) 3193–3201, https://doi.org/10.1039/d0bm00425a.
[107] X. Shen, J.L. Shamshina, P. Berton, G. Gurau, R.D. Rogers, Hydrogels based on cellulose and chitin: fabrication, properties, and applications, Green Chem. 18 (2015) 53–75, https://doi.org/10.1039/c5gc02396c.
[108] Z. Wang, W. Hu, Y. Du, Y. Xiao, X. Wang, S. Zhang, J. Wang, C. Mao, Green gas-mediated cross-linking generates biomolecular hydrogels with enhanced strength and excellent hemostasis for wound healing, ACS Appl. Mater. Interfaces 12 (2020) 13622–13633, https://doi.org/10.1021/acsami.9b21325.
[109] P. Sacco, F. Furlani, A. Marfoglia, M. Cok, C. Pizzolitto, E. Marsich, I. Donati, Temporary/permanent dual cross-link gels formed of a bioactive lactose-modified chitosan, Macromol. Biosci. 20 (2020), 2000236, https://doi.org/10.1002/mabi.202000236.
[110] F. Furlani, P. Sacco, M. Cok, G. De Marzo, E. Marsich, S. Paoletti, I. Donati, Biomimetic, multiresponsive, and self-healing lactose-modified chitosan (CTL)-Based gels formed via competitor-assisted mechanism, ACS Biomater. Sci. Eng. 5 (2019) 5539–5547, https://doi.org/10.1021/acsbiomaterials.9b01256.
[111] P. Sacco, F. Furlani, S. Paoletti, I. Donati, PH-assisted gelation of lactose-modified chitosan, Biomacromolecules 20 (2019) 3070–3075, https://doi.org/10.1021/acs.biomac.9b00636.
[112] N. Naseri, B. Deepa, A.P. Mathew, K. Oksman, L. Girandon, Nanocellulose-based interpenetrating polymer network (IPN) hydrogels for cartilage applications, Biomacromolecules 17 (2016) 3714–3723, https://doi.org/10.1021/acs.biomac.6b01243.
[113] X. Zhu, T. Chen, B. Feng, J. Weng, K. Duan, J. Wang, X. Lu, A biomimetic bacterial cellulose-enhanced double- network hydrogel with excellent mechanical properties applied for the osteochondral defect repair, ACS Biomater. Sci. Eng. 4 (2018) 3534–3544, https://doi.org/10.1021/acsbiomaterials.8b00682.
[114] J. Xu, Y. Liu, S. Hsu, Hydrogels based on Schiff base linkages for biomedical applications, Molecules 24 (2019) 3005.
[115] P. Lavrador, V.M. Gaspar, J.F. Mano, Mechanochemical patternable ECM-mimetic hydrogels for programmed cell orientation, Adv. Healthc. Mater. 9 (2020) 1–15, https://doi.org/10.1002/adhm.201901860.
[116] L. Zhang, Q. Zhang, Y. Zheng, Z. He, P. Guan, X. He, L. Hui, Y. Dai, Study of Schiff base formation between dialdehyde cellulose and proteins, and its application for the deproteinization of crude polysaccharide extracts, Ind. Crops Prod. 112 (2018) 532–540, https://doi.org/10.1016/j.indcrop.2017.12.056.
[117] K. Lei, Z. Li, D. Zhu, C. Sun, Y. Sun, C. Yang, Z. Zheng, X. Wang, Polysaccharide-based recoverable double-network hydrogel with high strength and self-healing properties, J. Mater. Chem. B. 8 (2020) 794–802, https://doi.org/10.1039/c9tb01679a.
[118] J. Liu, J. Li, F. Yu, Y. xin Zhao, X. mei Mo, J. feng Pan, In situ forming hydrogel of natural polysaccharides through Schiff base reaction for soft tissue adhesive and hemostasis, Int. J. Biol. Macromol. 147 (2020) 653–666, https://doi.org/10.1016/j.ijbiomac.2020.01.005.
[119] X. Zheng, Q. Zhang, J. Liu, Y. Pei, K. Tang, A unique high mechanical strength dialdehyde microfibrillated cellulose/gelatin composite hydrogel with a giant network structure, RSC Adv. 6 (2016) 71999–72007, https://doi.org/10.1039/c6ra12517d.

[120] Y. Yan, M. Li, D. Yang, Q. Wang, F. Liang, X. Qu, D. Qiu, Z. Yang, Construction of injectable double-network hydrogels for cell delivery, Biomacromolecules 18 (2017) 2128–2138, https://doi.org/10.1021/acs.biomac.7b00452.
[121] L.L. Wang, C.B. Highley, Y.C. Yeh, J.H. Galarraga, S. Uman, J.A. Burdick, Three-dimensional extrusion bioprinting of single- and double-network hydrogels containing dynamic covalent crosslinks, J. Biomed. Mater. Res., Part A 106 (2018) 865–875, https://doi.org/10.1002/jbm.a.36323.
[122] F. Huang, T. Chen, J. Chang, C. Zhang, F. Liao, L. Wu, W. Wang, Z. Yin, A conductive dual-network hydrogel composed of oxidized dextran and hyaluronic-hydrazide as BDNF delivery systems for potential spinal cord injury repair, Int. J. Biol. Macromol. 167 (2021) 434–445, https://doi.org/10.1016/j.ijbiomac.2020.11.206.
[123] J. Qu, X. Zhao, P.X. Ma, B. Guo, Injectable antibacterial conductive hydrogels with dual response to an electric field and pH for localized "smart" drug release, Acta Biomater. 72 (2018) 55–69, https://doi.org/10.1016/j.actbio.2018.03.018.
[124] S. Cho, S.Y. Hwang, D.X. Oh, J. Park, Recent progress in self-healing polymers and hydrogels based on reversible dynamic B–O bonds: boronic/boronate esters, borax, and benzoxaborole, J. Mater. Chem. A. 9 (2021) 14630–14655, https://doi.org/10.1039/d1ta02308j.
[125] G. Springsteen, B. Wang, A detailed examination of boronic acid-diol complexation, Tetrahedron 58 (2002) 5291–5300, https://doi.org/10.1016/S0040-4020(02)00489-1.
[126] J.N. Cambre, B.S. Sumerlin, Biomedical applications of boronic acid polymers, Polymer (Guildf) 52 (2011) 4631–4643, https://doi.org/10.1016/j.polymer.2011.07.057.
[127] B.M. Dufort, M.W. Tibbitt, Design of moldable hydrogels for biomedical applications using dynamic covalent boronic esters, Mater. Today Chem. 12 (2019) 16–33, https://doi.org/10.1016/j.mtchem.2018.12.001.
[128] H. An, Y. Bo, D. Chen, Y. Wang, H. Wang, Y. He, J. Qin, Cellulose-based self-healing hydrogel through boronic ester bonds with excellent biocompatibility and conductivity, RSC Adv. 10 (2020) 11300–11310, https://doi.org/10.1039/c9ra10736c.
[129] A.J.R. Amaral, V.M. Gaspar, J.F. Mano, Responsive laminarin-boronic acid self-healing hydrogels for biomedical applications, Polym. J. 52 (2020) 997–1006, https://doi.org/10.1038/s41428-020-0348-3.
[130] A. Pettignano, S. Grijalvo, M. Häring, R. Eritja, N. Tanchoux, F. Quignard, D. Díaz Díaz, Boronic acid-modified alginate enables direct formation of injectable, self-healing and multistimuli-responsive hydrogels, Chem. Commun. 53 (2017) 3350–3353, https://doi.org/10.1039/c7cc00765e.
[131] S.H. Hong, S. Kim, J.P. Park, M. Shin, K. Kim, J.H. Ryu, H. Lee, Dynamic bonds between boronic acid and alginate: hydrogels with stretchable, self-healing, stimuli-responsive, remoldable, and adhesive properties, Biomacromolecules 19 (2018) 2053–2061, https://doi.org/10.1021/acs.biomac.8b00144.
[132] S.H. Hong, M. Shin, E. Park, J.H. Ryu, J.A. Burdick, H. Lee, Alginate-boronic acid: pH-triggered bioinspired glue for hydrogel assembly, Adv. Funct. Mater. 30 (2020), 1908497, https://doi.org/10.1002/adfm.201908497.
[133] T. Figueiredo, V. Cosenza, Y. Ogawa, I. Jeacomine, A. Vallet, S. Ortega, R. Michel, J.D.M. Olsson, T. Gerfaud, J.G. Boiteau, J. Jing, C. Harris, R. Auzély-Velty, Boronic acid and diol-containing polymers: how to choose the correct couple to form "strong" hydrogels at physiological pH, Soft Matter 16 (2020) 3628–3641, https://doi.org/10.1039/d0sm00178c.
[134] Z. Huang, P. Delparastan, P. Burch, J. Cheng, Y. Cao, P.B. Messersmith, Injectable dynamic covalent hydrogels of boronic acid polymers cross-linked by bioactive plant-derived polyphenols, Trans. Annu. Meet. Soc. Biomater. Annu. Int. Biomater. Symp. 40 (2019) 61, https://doi.org/10.1039/C8BM00453F.
[135] A.J.R. Amaral, V.M. Gaspar, P. Lavrador, J.F. Mano, Double network laminarin-boronic/alginate dynamic bioink for 3D bioprinting cell-laden constructs, Biofabrication 13 (2021), 035045, https://doi.org/10.1088/1758-5090/abfd79.
[136] L.S. Moreira Teixeira, J. Feijen, C.A. van Blitterswijk, P.J. Dijkstra, M. Karperien, Enzyme-catalyzed crosslinkable hydrogels: emerging strategies for tissue engineering, Biomaterials 33 (2012) 1281–1290, https://doi.org/10.1016/j.biomaterials.2011.10.067.
[137] M. Kurisawa, F. Lee, L.S. Wang, J.E. Chung, Injectable enzymatically cross-linked hydrogel system with independent tuning of mechanical strength and gelation rate for drug delivery and tissue engineering, J. Mater. Chem. 20 (2010) 5371–5375, https://doi.org/10.1039/b926456f.
[138] W. Song, J. Ko, Y.H. Choi, N.S. Hwang, Recent advancements in enzyme-mediated crosslinkable hydrogels: in vivo-mimicking strategies, APL Bioeng 5 (2021), 021502, https://doi.org/10.1063/5.0037793.
[139] G. Yang, Z. Xiao, X. Ren, H. Long, H. Qian, K. Ma, Y. Guo, Enzymatically crosslinked gelatin hydrogel promotes the proliferation of adipose tissue-derived stromal cells, PeerJ 4 (2016) 2497, https://doi.org/10.7717/peerj.2497.
[140] O. Hasturk, K.E. Jordan, J. Choi, D.L. Kaplan, Enzymatically crosslinked silk and silk-gelatin hydrogels with tunable gelation kinetics, mechanical properties and bioactivity for cell culture and encapsulation, Biomaterials 232 (2020), 119720, https://doi.org/10.1016/j.biomaterials.2019.119720.
[141] J.W. Bae, J.H. Choi, Y. Lee, K.D. Park, Horseradish peroxidase-catalysed in situ-forming hydrogels for tissue-engineering applications, J. Tissue Eng. Regen. Med. 9 (2015) 1225–1232, https://doi.org/10.1002/term.
[142] L. Wang, B. Xu, Y. Nong, P. Wang, Y. Yu, C. Deng, J. Yuan, Q. Wang, Laccase-mediated construction of fl exible double-network hydrogels based on silk fi broin and tyramine-modi fi ed hyaluronic acid, Int. J. Biol. Macromol. 160 (2020) 795–805, https://doi.org/10.1016/j.ijbiomac.2020.05.258.
[143] E. Lih, J.S. Lee, K.M. Park, K.D. Park, Rapidly curable chitosan-PEG hydrogels as tissue adhesives for hemostasis and wound healing, Acta Biomater. 8 (2012) 3261–3269, https://doi.org/10.1016/j.actbio.2012.05.001.
[144] E. Jooybar, M.J. Abdekhodaie, M. Alvi, A. Mousavi, M. Karperien, P.J. Dijkstra, An injectable platelet lysate-hyaluronic acid hydrogel supports cellular activities and induces chondrogenesis of encapsulated mesenchymal stem cells, Acta Biomater. 83 (2019) 233–244, https://doi.org/10.1016/j.actbio.2018.10.031.
[145] J.A. Shadish, C.A. DeForest, Site-selective protein modification: from functionalized proteins to functional biomaterials, Matter 2 (2020) 50–77, https://doi.org/10.1016/j.matt.2019.11.011.
[146] L. Duarte, C.R. Matte, C.V. Bizarro, M.A.Z. Ayub, Review transglutaminases: part II—industrial applications in food, biotechnology, textiles and leather products, World J. Microbiol. Biotechnol. 36 (2020) 11, https://doi.org/10.1007/s11274-019-2792-9.
[147] I. Stachel, U. Schwarzenbolz, T. Henle, M. Meyer, Cross-linking of type I collagen with microbial transglutaminase: identification of cross-linking sites, Biomacromolecules 11 (2010) 698–705, https://doi.org/10.1021/bm901284x.
[148] N.R. Raia, B.P. Partlow, M. McGill, E.P. Kimmerling, C.E. Ghezzi, D.L. Kaplan, Enzymatically crosslinked silk-hyaluronic acid hydrogels, Biomaterials 131 (2017) 58–67, https://doi.org/10.1016/j.biomaterials.2017.03.046.
[149] M.R. Arkenberg, H.D. Nguyen, C.C. Lin, Recent advances in bio-orthogonal and dynamic crosslinking of biomimetic hydrogels, J. Mater. Chem. B. 8 (2020) 7835–7855, https://doi.org/10.1039/d0tb01429j.
[150] J. Gopinathan, I. Noh, Click chemistry-based injectable hydrogels and bioprinting inks for tissue engineering applications, Tissue Eng. Regen, Med. 15 (2018) 531–546, https://doi.org/10.1007/s13770-018-0152-8.
[151] A. Uliniuc, M. Popa, T. Hamaide, M. Dobromir, New approaches in hydrogel synthesis - click chemistry: a review, Cellul. Chem. Technol. 46 (2012) 1–11.
[152] X. Hu, Z. Gao, H. Tan, H. Wang, X. Mao, J. Pang, An injectable hyaluronic acid-based composite hydrogel by DA click chemistry with pH sensitive nanoparticle for biomedical application, Front. Chem. 7 (2019) 477, https://doi.org/10.3389/fchem.2019.00477.
[153] C. García-Astrain, A. Gandini, C. Peña, I. Algar, A. Eceiza, M. Corcuera, N. Gabilondo, Diels-Alder "click" chemistry for the cross-linking of furfuryl-gelatin-polyetheramine hydrogels, RSC Adv. 4 (2014) 35578–35587, https://doi.org/10.1039/c4ra06122e.
[154] M. Montiel-Herrera, A. Gandini, F.M. Goycoolea, N.E. Jacobsen, J. Lizardi-Mendoza, M.T. Recillas-Mota, W.M. Argüelles-Monal, Furan–chitosan hydrogels based on click chemistry, Iran, Polym. J 24 (2015) 349–357, https://doi.org/10.1007/s13726-015-0325-4. English Ed.
[155] S. Magli, G.B. Rossi, G. Risi, S. Bertini, C. Cosentino, L. Crippa, E. Ballarini, G. Cavaletti, L. Piazza, E. Masseroni, F. Nicotra, L. Russo, Design and synthesis of chitosan—gelatin hybrid hydrogels for 3D printable in vitro models, Front. Chem. 8 (2020) 524, https://doi.org/10.3389/fchem.2020.00524.
[156] A.B. Lowe, Thiol-ene "click" reactions and recent applications in polymer and materials synthesis: a first update, Polym. Chem. 5 (2014) 4820–4870, https://doi.org/10.1039/c4py00339j.
[157] H. Ding, B. Li, Y. Jiang, G. Liu, S. Pu, Y. Feng, D. Jia, Y. Zhou, pH-responsive UV crosslinkable chitosan hydrogel via "thiol-ene" click chemistry for active modulating opposite drug release behaviors, Carbohydr. Polym. 251 (2021), 117101, https://doi.org/10.1016/j.carbpol.2020.117101.
[158] A.C. Madl, C.M. Madl, D. Myung, Injectable cucurbit[8]uril-based supramolecular gelatin hydrogels for cell encapsulation, ACS Macro Lett. 9 (2020) 619–626, https://doi.org/10.1021/acsmacrolett.0c00184.
[159] R.M. Desai, S.T. Koshy, S.A. Hilderbrand, D.J. Mooney, N.S. Joshi, Versatile click alginate hydrogels crosslinked via tetrazine-norbornene chemistry, Biomaterials 50 (2015) 30–37, https://doi.org/10.1016/j.biomaterials.2015.01.048.
[160] A. Famili, K. Rajagopal, Bio-Orthogonal cross-linking chemistry enables in situ protein encapsulation and provides sustained release from hyaluronic acid based hydrogels, Mol. Pharm. 14 (2017) 1961–1968, https://doi.org/10.1021/acs.molpharmaceut.7b00067.
[161] C.F. Hansell, P. Espeel, M.M. Stamenović, I.A. Barker, A.P. Dove, F.E. Du Prez, R.K. Oreilly, Additive-free clicking for polymer functionalization and coupling by tetrazine-norbornene chemistry, J. Am. Chem. Soc. 133 (2011) 13828–13831, https://doi.org/10.1021/ja203957h.
[162] S.T. Koshy, R.M. Desai, P. Joly, D.J. Mooney, Click-crosslinked injectable gelatin hydrogels, Adv. Healthc. Mater. 5 (2016) 541–547, https://doi.org/10.1002/adhm.201500757.Click-Crosslinked.
[163] M.M. Pérez-Madrigal, J.E. Shaw, M.C. Arno, J.A. Hoyland, S.M. Richardson, A.P. Dove, Robust alginate/hyaluronic acid thiol-yne click-hydrogel scaffolds with superior mechanical performance and stability for load-bearing soft tissue engineering, Biomater. Sci. 8 (2020) 405–412, https://doi.org/10.1039/c9bm01494b.
[164] H. Hu, B. Ye, Y. Lv, Q. Zhang, Preparing antibacterial and in-situ formable double crosslinking chitosan/hyaluronan composite hydrogels, Mater. Lett. 254 (2019) 17–20, https://doi.org/10.1016/j.matlet.2019.06.102.
[165] Y. Zhang, P. Heher, J. Hilborn, H. Redl, D.A. Ossipov, Hyaluronic acid-fibrin interpenetrating double network hydrogel prepared in situ by orthogonal

disulfide cross-linking reaction for biomedical applications, Acta Biomater. 38 (2016) 23–32, https://doi.org/10.1016/j.actbio.2016.04.041.
[166] R. Li, Z. Cai, Z. Li, Q. Zhang, S. Zhang, L. Deng, L. Lu, L. Li, C. Zhou, Synthesis of in-situ formable hydrogels with collagen and hyaluronan through facile Michael addition, Mater. Sci. Eng. C. 77 (2017) 1035–1043, https://doi.org/10.1016/j.msec.2017.04.046.
[167] J. Pupkaite, J. Rosenquist, J. Hilborn, A. Samanta, Injectable shape-holding collagen hydrogel for cell encapsulation and delivery cross-linked using thiol-michael addition click reaction, Biomacromolecules 20 (2019) 3475–3484, https://doi.org/10.1021/acs.biomac.9b00769.
[168] S. Trujillo, M. Seow, A. Lueckgen, M. Salmeron-Sanchez, A. Cipitria, Dynamic mechanical control of alginate-fibronectin hydrogels with dual crosslinking: covalent and ionic, Polymers (Basel) 13 (2021) 433, https://doi.org/10.3390/polym13030433.
[169] H.W. Ooi, C. Mota, A. Tessa Ten Cate, A. Calore, L. Moroni, M.B. Baker, Thiol-ene alginate hydrogels as versatile bioinks for bioprinting, Biomacromolecules 19 (2018) 3390–3400, https://doi.org/10.1021/acs.biomac.8b00696.
[170] S. Xu, W. Liang, G. Xu, C. Huang, J. Zhang, M. Lang, A fast and dual cross-linking hydrogel based on vinyl ether sodium alginate, Appl. Surf. Sci. 515 (2020), 145811, https://doi.org/10.1016/j.apsusc.2020.145811.
[171] E. Hui, K.I. Gimeno, G. Guan, S.R. Caliari, Spatiotemporal control of viscoelasticity in phototunable hyaluronic acid hydrogels, Biomacromolecules 20 (2019) 4126–4134, https://doi.org/10.1021/acs.biomac.9b00965.
[172] P.H. Elchinger, P.A. Faugeras, B. Boëns, F. Brouillette, D. Montplaisir, R. Zerrouki, R. Lucas, Polysaccharides: the “click” chemistry impact, Polymers (Basel) 3 (2011) 1607–1651, https://doi.org/10.3390/polym3041607.
[173] V. Engkagul, A. Sereemaspun, S. Chirachanchai, One pot preparation of chitosan/hyaluronic acid-based triple network hydrogel via in situ click reaction, metal coordination and polyion complexation in water, Carbohydr. Polym. 200 (2018) 616–623, https://doi.org/10.1016/j.carbpol.2018.07.090.
[174] S.A. McNelles, J.L. Pantaleo, E. Meichsner, A. Adronov, Strain-promoted azide-alkyne cycloaddition-mediated step-growth polymerization, Macromolecules 52 (2019) 7183–7187, https://doi.org/10.1021/acs.macromol.9b01609.
[175] N.J. Agard, J.A. Prescher, C.R. Bertozzi, A strain-promoted [3 + 2] azide-alkyne cycloaddition for covalent modification of biomolecules in living systems, J. Am. Chem. Soc. 126 (2004) 15046–15047, https://doi.org/10.1021/ja044996f.
[176] X. Wang, Z. Li, T. Shi, P. Zhao, K. An, C. Lin, H. Liu, Injectable dextran hydrogels fabricated by metal-free click chemistry for cartilage tissue engineering, Mater. Sci. Eng. C. 73 (2017) 21–30, https://doi.org/10.1016/j.msec.2016.12.053.
[177] S. Fu, H. Dong, X. Deng, R. Zhuo, Z. Zhong, Injectable hyaluronic acid/poly(-ethylene glycol) hydrogels crosslinked via strain-promoted azide-alkyne cycloaddition click reaction, Carbohydr. Polym. 169 (2017) 332–340, https://doi.org/10.1016/j.carbpol.2017.04.028.
[178] V.X. Truong, M.P. Ablett, H.T.J. Gilbert, J. Bowen, S.M. Richardson, J.A. Hoyland, A.P. Dove, In situ-forming robust chitosan-poly(ethylene glycol) hydrogels prepared by copper-free azide-alkyne click reaction for tissue engineering, Biomater. Sci. 2 (2014) 167–175, https://doi.org/10.1039/c3bm60159e.
[179] S.Y. Wang, H. Kim, G. Kwak, H.Y. Yoon, S.D. Jo, J.E. Lee, D. Cho, I.C. Kwon, S.H. Kim, Development of biocompatible HA hydrogels embedded with a new synthetic peptide promoting cellular migration for advanced wound care management, Adv. Sci. 5 (2018), 1800852, https://doi.org/10.1002/advs.201800852.
[180] S.S. Han, H.Y. Yoon, J.Y. Yhee, M.O. Cho, H.E. Shim, J.E. Jeong, D.E. Lee, K. Kim, H. Guim, J.H. Lee, K.M. Huh, S.W. Kang, In situ cross-linkable hyaluronic acid hydrogels using copper free click chemistry for cartilage tissue engineering, Polym. Chem. 9 (2018) 20–27, https://doi.org/10.1039/c7py01654a.
[181] A. Takahashi, Y. Suzuki, T. Suhara, K. Omichi, A. Shimizu, K. Hasegawa, N. Kokudo, S. Ohta, T. Ito, In situ cross-linkable hydrogel of hyaluronan produced via copper-free click chemistry, Biomacromolecules 14 (2013) 3581–3588, https://doi.org/10.1021/bm4009606.
[182] M. Fan, Y. Ma, J. Mao, Z. Zhang, H. Tan, Cytocompatible in situ forming chitosan/hyaluronan hydrogels via a metal-free click chemistry for soft tissue engineering, Acta Biomater. 20 (2015) 60–68, https://doi.org/10.1016/j.actbio.2015.03.033.
[183] K. Nagahama, Y. Kimura, A. Takemoto, Living functional hydrogels generated by bioorthogonal cross-linking reactions of azide-modified cells with alkyne-modified polymers, Nat. Commun. 9 (2018) 2195, https://doi.org/10.1038/s41467-018-04699-3.
[184] V.M. Gaspar, P. Lavrador, J. Borges, M.B. Oliveira, J.F. Mano, Advanced bottom-up engineering of living architectures, Adv. Mater. 32 (2020), 1903975, https://doi.org/10.1002/adma.201903975.
[185] J.Y.C. Lim, Q. Lin, K. Xue, X.J. Loh, Recent advances in supramolecular hydrogels for biomedical applications, Mater, Today Adv 3 (2019), 100021, https://doi.org/10.1016/j.mtadv.2019.100021.
[186] M.A. Ramin, L. Latxague, K.R. Sindhu, O. Chassande, P. Barthélémy, Low molecular weight hydrogels derived from urea based-bolaamphiphiles as new injectable biomaterials, Biomaterials 145 (2017) 72–80, https://doi.org/10.1016/j.biomaterials.2017.08.034.
[187] S.M. Mantooth, B.G. Munoz-Robles, M.J. Webber, Dynamic hydrogels from host–guest supramolecular interactions, Macromol. Biosci. 19 (2019), 1800281, https://doi.org/10.1002/mabi.201800281.
[188] J. Jin, L. Cai, Y.G. Jia, S. Liu, Y. Chen, L. Ren, Progress in self-healing hydrogels assembled by host-guest interactions: preparation and biomedical applications, J. Mater. Chem. B. 7 (2019) 1637–1651, https://doi.org/10.1039/c8tb02547a.
[189] Y. Zhou, Y. Zhang, Z. Dai, F. Jiang, J. Tian, W. Zhang, A super-stretchable, self-healing and injectable supramolecular hydrogel constructed by a host-guest crosslinker, Biomater. Sci. 8 (2020) 3359–3369, https://doi.org/10.1039/d0bm00290a.
[190] X. Zhang, Y. Liu, J. Wen, Z. Zhao, H. Chen, X. Liu, S. Liu, Host-guest interaction-mediated fabrication of a hybrid microsphere-structured supramolecular hydrogel showing high mechanical strength, Soft Matter 16 (2020) 3416–3424, https://doi.org/10.1039/d0sm00271b.
[191] G. Liu, Q. Yuan, G. Hollett, W. Zhao, Y. Kang, J. Wu, Cyclodextrin-based host-guest supramolecular hydrogel and its application in biomedical fields, Polym. Chem. 9 (2018) 3436–3449, https://doi.org/10.1039/c8py00730f.
[192] A.M. Rosales, C.B. Rodell, M.H. Chen, M.G. Morrow, K.S. Anseth, J.A. Burdick, Reversible control of network properties in azobenzene-containing hyaluronic acid-based hydrogels, Bioconjug. Chem. 29 (2018) 905–913, https://doi.org/10.1021/acs.bioconjchem.7b00802.
[193] L. Ouyang, C.B. Highley, C.B. Rodell, W. Sun, J.A. Burdick, 3D printing of shear-thinning hyaluronic acid hydrogels with secondary cross-linking, ACS Biomater. Sci. Eng. 2 (2016) 1743–1751, https://doi.org/10.1021/acsbiomaterials.6b00158.
[194] X. Fan, T. Wang, W. Miao, The preparation of pH-sensitive hydrogel based on host-guest and electrostatic interactions and its drug release studies in vitro, J. Polym. Res. 25 (2018) 215, https://doi.org/10.1007/s10965-018-1608-1.
[195] J.E. Mealy, C.B. Rodell, J.A. Burdick, Sustained small molecule delivery from injectable hyaluronic acid hydrogels through host-guest mediated retention, J. Mater. Chem. B. 3 (2015) 8010–8019, https://doi.org/10.1039/c5tb00981b.
[196] H.W. Ooi, J.M.M. Kocken, F.L.C. Morgan, A. Malheiro, B. Zoetebier, M. Karperien, P.A. Wieringa, P.J. Dijkstra, L. Moroni, M.B. Baker, Multivalency enables dynamic supramolecular host-guest hydrogel formation, Biomacromolecules 21 (2020) 2208–2217, https://doi.org/10.1021/acs.biomac.0c00148.
[197] Z. Wang, G. An, Y. Zhu, X. Liu, Y. Chen, H. Wu, Y. Wang, X. Shi, C. Mao, 3D-printable self-healing and mechanically reinforced hydrogels with host-guest non-covalent interactions integrated into covalently linked networks, Mater. Horizons. 6 (2019) 733–742, https://doi.org/10.1039/c8mh01208c.
[198] X. Huang, M. Zhang, J. Ming, X. Ning, S. Bai, High-strength and high-toughness silk fibroin hydrogels: a strategy using dynamic host-guest interactions, ACS Appl. Bio Mater. 3 (2020) 7103–7112, https://doi.org/10.1021/acsabm.0c00933.
[199] A.K. Rajendan, Y. Arisaka, N. Yui, S. Iseki, Polyrotaxanes as emerging biomaterials for tissue engineering applications: a brief review, Inflamm. Regen. 40 (2020) 27, https://doi.org/10.1186/s41232-020-00136-5.
[200] T. Ooya, H.S. Choi, A. Yamashita, N. Yui, Y. Sugaya, A. Kano, A. Maruyama, H. Akita, R. Ito, K. Kogure, H. Harashima, Biocleavable polyrotaxane-plasmid DNA polyplex for enhanced gene delivery, J. Am. Chem. Soc. 128 (2006) 3852–3853, https://doi.org/10.1021/ja055868+.
[201] A. Bin Imran, K. Esaki, H. Gotoh, T. Seki, K. Ito, Y. Sakai, Y. Takeoka, Extremely stretchable thermosensitive hydrogels by introducing slide-ring polyrotaxane cross-linkers and ionic groups into the polymer network, Nat. Commun. 5 (2014) 5124, https://doi.org/10.1038/ncomms6124.
[202] H. Wei, A.Y. Zhang, L. Qian, H. Yu, D. Hou, R. Qiu, Z.G. Feng, Supramolecular structured hydrogel preparation based on self-assemblies of photocurable star-shaped macromers with α-cyclodextrins, J. Polym. Sci. Part A Polym. Chem. 43 (2005) 2941–2949, https://doi.org/10.1002/pola.20773.
[203] R. Ardeleanu, A.I. Dascalu, A. Neamtu, D. Peptanariu, C.M. Uritu, S.S. Maier, A. Nicolescu, B.C. Simionescu, M. Barboiu, M. Pinteala, Multivalent polyrotaxane vectors as adaptive cargo complexes for gene therapy, Polym. Chem. 9 (2018) 845–859, https://doi.org/10.1039/c7py01256j.
[204] G. Yu, Z. Yang, X. Fu, B.C. Yung, J. Yang, Z. Mao, L. Shao, B. Hua, Y. Liu, F. Zhang, Q. Fan, S. Wang, O. Jacobson, A. Jin, C. Gao, X. Tang, F. Huang, X. Chen, Polyrotaxane-based supramolecular theranostics, Nat. Commun. 9 (2018) 766, https://doi.org/10.1038/s41467-018-03119-w.
[205] T. Cai, S. Huo, T. Wang, W. Sun, Z. Tong, Self-healable tough supramolecular hydrogels crosslinked by poly-cyclodextrin through host-guest interaction, Carbohydr. Polym. 193 (2018) 54–61, https://doi.org/10.1016/j.carbpol.2018.03.039.
[206] Y. Sakai, R. Gomi, K. Kato, H. Yokoyama, K. Ito, Structure and dynamics of polyrotaxane-based sliding graft copolymers with alkyl side chains, Soft Matter 9 (2013) 1895–1901, https://doi.org/10.1039/c2sm27047a.
[207] S.Y. Zheng, C. Liu, L. Jiang, J. Lin, J. Qian, K. Mayumi, Z.L. Wu, K. Ito, Q. Zheng, Slide-ring cross-links mediated tough metallosupramolecular hydrogels with superior self-recoverability, Macromolecules 52 (2019) 6748–6755, https://doi.org/10.1021/acs.macromol.9b01281.
[208] I.S. Cho, T. Ooya, Cell-encapsulating hydrogel puzzle: polyrotaxane-based self-healing hydrogels, Chem. Eur J. 26 (2020) 913–920, https://doi.org/10.1002/chem.201904446.
[209] G. Schmidt, B.R. Hamaker, J.J. Wilker, High strength adhesives from catechol cross-linking of zein protein and plant phenolics, Adv. Sustain. Syst. 2 (2018), 1700159, https://doi.org/10.1002/adsu.201700159.

[210] G.P. Maier, C.M. Bernt, A. Butler, Catechol oxidation: considerations in the design of wet adhesive materials, Biomater. Sci. 6 (2018) 332–339, https://doi.org/10.1039/c7bm00884h.
[211] X. Zhao, Y. Liang, Y. Huang, J. He, Y. Han, B. Guo, Physical double-network hydrogel adhesives with rapid shape adaptability, fast self-healing, antioxidant and NIR/pH stimulus-responsiveness for multidrug-resistant bacterial infection and removable wound dressing, Adv. Funct. Mater. 30 (2020), 1910748, https://doi.org/10.1002/adfm.201910748.
[212] L. Han, L. Yan, K. Wang, L. Fang, H. Zhang, Y. Tang, Y. Ding, L.T. Weng, J. Xu, J. Weng, Y. Liu, F. Ren, X. Lu, Tough, self-healable and tissue-adhesive hydrogel with tunable multifunctionality, NPG Asia Mater. 9 (2017) e372, https://doi.org/10.1038/am.2017.33.
[213] L. Koivusalo, M. Kauppila, S. Samanta, V.S. Parihar, T. Ilmarinen, S. Miettinen, O.P. Oommen, H. Skottman, Tissue adhesive hyaluronic acid hydrogels for sutureless stem cell delivery and regeneration of corneal epithelium and stroma, Biomaterials 225 (2019), 119516, https://doi.org/10.1016/j.biomaterials.2019.119516.
[214] Y. Zhou, Z. Yue, Z. Chen, G. Wallace, 3D coaxial printing tough and elastic hydrogels for tissue engineering using a catechol functionalized ink system, Adv. Healthc. Mater. 9 (2020), 2001342, https://doi.org/10.1002/adhm.202001342.
[215] M.J. Hossen, S.D. Sarkar, M.M. Uddin, C.K. Roy, M.S. Azam, Mussel-inspired adhesive nano-filler for strengthening polyacrylamide hydrogel, ChemistrySelect 5 (2020) 8906–8914, https://doi.org/10.1002/slct.202001632.
[216] R. Wang, J. Li, W. Chen, T. Xu, S. Yun, Z. Xu, Z. Xu, T. Sato, B. Chi, H. Xu, A biomimetic mussel-inspired ε-Poly-l-lysine hydrogel with robust tissue-anchor and anti-infection capacity, Adv. Funct. Mater. 27 (2017), 1604894, https://doi.org/10.1002/adfm.201604894.
[217] Z. Guo, J. Xia, S. Mi, W. Sun, Mussel-inspired naturally derived double-network hydrogels and their application in 3D printing: from soft, injectable bioadhesives to mechanically strong hydrogels, ACS Biomater. Sci. Eng. 6 (2020) 1798–1808, https://doi.org/10.1021/acsbiomaterials.9b01864.
[218] G. Schmidt, J.T. Woods, L.X.B. Fung, C.J. Gilpin, B.R. Hamaker, J.J. Wilker, Strong adhesives from corn protein and tannic acid, Adv. Sustain. Syst. 3 (2019), 1900077, https://doi.org/10.1002/adsu.201900077.
[219] L. Xie, R.L. Wehling, O. Ciftci, Y. Zhang, Formation of complexes between tannic acid with bovine serum albumin, egg ovalbumin and bovine beta-lactoglobulin, Food Res. Int. 102 (2017) 195–202, https://doi.org/10.1016/j.foodres.2017.10.007.
[220] M. Shin, H.A. Lee, M. Lee, Y. Shin, J.J. Song, S.W. Kang, D.H. Nam, E.J. Jeon, M. Cho, M. Do, S. Park, M.S. Lee, J.H. Jang, S.W. Cho, K.S. Kim, H. Lee, Targeting protein and peptide therapeutics to the heart via tannic acid modification, Nat. Biomed. Eng. 2 (2018) 304–317, https://doi.org/10.1038/s41551-018-0227-9.
[221] C. Chen, X. Yang, S. Li, C. Zhang, Y. Ma, Y. Ma, P. Gao, S. Gao, X. Huang, Tannic acid–thioctic acid hydrogel: a novel injectable supramolecular adhesive gel for wound healing, Green Chem. 24 (2021) 1794–1804, https://doi.org/10.1039/d0gc02909b.
[222] S. Yu, Y. Ji, C. Guo, D. Lu, Z. Geng, D. Pei, Q. Liu, A dual-cross-linked hydrogel based on hyaluronic acid/gelatin tethered via tannic acid: mechanical properties' enhancement and stability control, Iran, Polym. J. 30 (2021) 307–317, https://doi.org/10.1007/s13726-020-00891-9.
[223] P. Taheri, R. Jahanmardi, M. Koosha, S. Abdi, Physical, mechanical and wound healing properties of chitosan/gelatin blend films containing tannic acid and/or bacterial nanocellulose, Int. J. Biol. Macromol. 154 (2020) 421–432, https://doi.org/10.1016/j.ijbiomac.2020.03.114.
[224] B. Kaczmarek, K. Nadolna, A. Owczarek, M. Michalska-Sionkowska, A. Sionkowska, The characterization of thin films based on chitosan and tannic acid mixture for potential applications as wound dressings, Polym. Test. 78 (2019), 106007, https://doi.org/10.1016/j.polymertesting.2019.106007.
[225] R. Shah, P. Stodulka, K. Skopalova, P. Saha, Dual crosslinked collagen/chitosan film for potential biomedical applications, Polymers (Basel) 11 (2019) 2094.
[226] C. Jia, D. Cao, S. Ji, X. Zhang, B. Muhoza, Tannic acid-assisted cross-linked nanoparticles as a delivery system of eugenol: the characterization, thermal degradation and antioxidant properties, Food Hydrocoll 104 (2020), 105717, https://doi.org/10.1016/j.foodhyd.2020.105717.
[227] T. Aewsiri, S. Benjakul, W. Visessanguan, P.A. Wierenga, H. Gruppen, Antioxidative activity and emulsifying properties of cuttlefish skin gelatin-tannic acid complex as influenced by types of interaction, Innov. Food Sci. Emerg. Technol. 11 (2010) 712–720, https://doi.org/10.1016/j.ifset.2010.04.001.
[228] R. Wang, X. Wang, Y. Zhan, Z. Xu, Z. Xu, X. Feng, S. Li, H. Xu, A dual network hydrogel sunscreen based on poly-γ-glutamic acid/tannic acid demonstrates excellent anti-UV, self-recovery, and skin-integration capacities, ACS Appl. Mater. Interfaces 11 (2019) 37502–37512, https://doi.org/10.1021/acsami.9b14538.
[229] B. Kang, T.P. Vales, Development of gallic acid-modified hydrogels using interpenetrating chitosan network and evaluation of their antioxidant activity, Molecules 22 (2017), https://doi.org/10.3390/molecules22111976, 1976.
[230] N.D. Sanandiya, S. Lee, S. Rho, H. Lee, I.S. Kim, D.S. Hwang, Tunichrome-inspired pyrogallol functionalized chitosan for tissue adhesion and hemostasis, Carbohydr. Polym. 208 (2019) 77–85, https://doi.org/10.1016/j.carbpol.2018.12.017.
[231] M. Zhao, Z. Tang, X. Zhang, Z. Li, H. Xiao, M. Zhang, K. Liu, Y. Ni, L. Huang, L. Chen, H. Wu, A self-healing, stretchable, and conductive Poly(N-vinylpyrrolidone)/gallic acid composite hydrogel formed via hydrogen bonding for wearable electronic sensors, Compos. Sci. Technol. 198 (2020), 108294, https://doi.org/10.1016/j.compscitech.2020.108294.
[232] R.A. Barclay, I. Akhrymuk, A. Patnaik, V. Callahan, C. Lehman, P. Andersen, R. Barbero, S. Barksdale, R. Dunlap, D. Goldfarb, T. Jones-Roe, R. Kelly, B. Kim, S. Miao, A. Munns, D. Munns, S. Patel, E. Porter, R. Ramsey, S. Sahoo, O. Swahn, J. Warsh, K. Kehn-Hall, B. Lepene, Hydrogel particles improve detection of SARS-CoV-2 RNA from multiple sample types, Sci. Rep. 10 (2020), 22425, https://doi.org/10.1038/s41598-020-78771-8.
[233] H. soo Kim, N. Abbas, S. Shin, A rapid diagnosis of SARS-CoV-2 using DNA hydrogel formation on microfluidic pores, Biosens. Bioelectron. 177 (2021), 113005, https://doi.org/10.1016/j.bios.2021.113005.
[234] Y. Shao, H. Jia, T. Cao, D. Liu, Supramolecular hydrogels based on DNA self-assembly, Acc. Chem. Res. 50 (2017) 659–668, https://doi.org/10.1021/acs.accounts.6b00524.
[235] F. Li, J. Tang, J. Geng, D. Luo, D. Yang, Polymeric DNA hydrogel: design, synthesis and applications, Prog. Polym. Sci. 98 (2019), 101163, https://doi.org/10.1016/j.progpolymsci.2019.101163.
[236] G.M. Peters, J.T. Davis, Supramolecular gels made from nucleobase, nucleoside and nucleotide analogs, Chem. Soc. Rev. 45 (2016) 3188–3206, https://doi.org/10.1039/c6cs00183a.
[237] M. Rahmati, E.A. Silva, J.E. Reseland, C.A. Heyward, H.J. Haugen, Biological responses to physicochemical properties of biomaterial surface, Chem. Soc. Rev. 49 (2020) 5178–5224, https://doi.org/10.1039/d0cs00103a.
[238] X. Ye, X. Li, Y. Shen, G. Chang, J. Yang, Z. Gu, Self-healing pH-sensitive cytosine- and guanosine-modified hyaluronic acid hydrogels via hydrogen bonding, Polymer (Guildf) 108 (2017) 348–360, https://doi.org/10.1016/j.polymer.2016.11.063.
[239] W. Wang, S. Liu, B. Chen, X. Yan, S. Li, X. Ma, X. Yu, DNA-inspired adhesive hydrogels based on the biodegradable polyphosphoesters tackified by a nucleobase, Biomacromolecules 20 (2019) 3672–3683, https://doi.org/10.1021/acs.biomac.9b00642.
[240] E. Cheng, Y. Xing, P. Chen, Yang, Y. Sun, D. Zhou, T. Xu, Q. Fan, D. Liu, A pH-triggered, fast-responding DNA hydrogel, Angew. Chemie - Int. Ed. 48 (2009) 7660–7663, https://doi.org/10.1002/anie.200902538.
[241] Y. Wu, C. Li, F. Boldt, Y. Wang, S.L. Kuan, T.T. Tran, V. Mikhalevich, C. Förtsch, H. Barth, Z. Yang, D. Liu, T. Weil, Programmable protein–DNA hybrid hydrogels for the immobilization and release of functional proteins, Chem. Commun. 50 (2014) 14620–14622, https://doi.org/10.1039/c4cc07144a.
[242] T. Cao, H. Jia, Y. Dong, S. Gui, D. Liu, In situ formation of covalent second network in a DNA supramolecular hydrogel and its application for 3D cell imaging, ACS Appl. Mater. Interfaces 12 (2020) 4185–4192, https://doi.org/10.1021/acsami.9b11534.
[243] C. Li, M.J. Rowland, Y. Shao, T. Cao, C. Chen, H. Jia, X. Zhou, Z. Yang, O.A. Scherman, D. Liu, Responsive double network hydrogels of interpenetrating DNA and CB[8] host-guest supramolecular systems, Adv. Mater. 27 (2015) 3298–3304, https://doi.org/10.1002/adma.201501102.
[244] C. Li, X. Zhou, Y. Shao, P. Chen, Y. Xing, Z. Yang, Z. Li, D. Liu, A supramolecular hydrogel with identical cross-linking point density but distinctive rheological properties, Mater. Chem. Front. 1 (2017) 654–659, https://doi.org/10.1039/c6qm00176a.
[245] C. Li, A. Faulkner-Jones, A.R. Dun, J. Jin, P. Chen, Y. Xing, Z. Yang, Z. Li, W. Shu, D. Liu, R.R. Duncan, Rapid formation of a supramolecular polypeptide-DNA Hydrogel for in situ three-dimensional multilayer bioprinting, Angew. Chemie - Int. Ed. 54 (2015) 3957–3961, https://doi.org/10.1002/anie.201411383.
[246] M. Shin, E. Park, H. Lee, Plant-inspired pyrogallol-containing functional materials, Adv. Funct. Mater. 29 (2019), 1903022, https://doi.org/10.1002/adfm.201903022.
[247] M. Shin, J.H. Ryu, J.P. Park, K. Kim, J.W. Yang, H. Lee, DNA/tannic acid hybrid gel exhibiting biodegradability, extensibility, tissue adhesiveness, and hemostatic ability, Adv. Funct. Mater. 25 (2015) 1270–1278, https://doi.org/10.1002/adfm.201403992.
[248] S. Karaki, S. Benizri, R. Mejías, V. Baylot, N. Branger, T. Nguyen, B. Vialet, K. Oumzil, P. Barthélémy, P. Rocchi, Lipid-oligonucleotide conjugates improve cellular uptake and efficiency of TCTP-antisense in castration-resistant prostate cancer, J. Control. Release. 258 (2017) 1–9, https://doi.org/10.1016/j.jconrel.2017.04.042.
[249] S. Fujita, S. Hara, A. Hosono, S. Sugihara, H. Uematsu, S.I. Suye, Hyaluronic acid hydrogel crosslinked with complementary DNAs, Adv. Polym. Technol. 2020 (2020) 1–7, https://doi.org/10.1155/2020/1470819.
[250] Z. Li, G. Davidson-Rozenfeld, M. Vázquez-González, M. Fadeev, J. Zhang, H. Tian, I. Willner, Multi-triggered supramolecular DNA/bipyridinium dithienylethene hydrogels driven by light, redox, and chemical stimuli for shape-memory and self-healing applications, J. Am. Chem. Soc. 140 (2018) 17691–17701, https://doi.org/10.1021/jacs.8b10481.
[251] C. Wang, M. Fadeev, M. Vázquez-González, I. Willner, Stimuli-responsive donor–acceptor and DNA-crosslinked hydrogels: application as shape-memory and self-healing materials, Adv. Funct. Mater. 28 (2018), 1803111, https://doi.org/10.1002/adfm.201803111.
[252] C. Wang, M. Fadeev, J. Zhang, M. Vázquez-González, G. Davidson-Rozenfeld, H. Tian, I. Willner, Shape-memory and self-healing functions of DNA-based

carboxymethyl cellulose hydrogels driven by chemical or light triggers, Chem. Sci. 9 (2018) 7145–7152, https://doi.org/10.1039/c8sc02411a.
[253] M.A. Haque, T. Kurokawa, J.P. Gong, Super tough double network hydrogels and their application as biomaterials, Polymer (Guildf) 53 (2012) 1805–1822, https://doi.org/10.1016/j.polymer.2012.03.013.
[254] J. Guo, J. Duan, S. Wu, J. Guo, C. Huang, L. Zhang, Robust and thermoplastic hydrogels with surface micro-patterns for highly oriented growth of osteoblasts, J. Mater. Chem. B. 5 (2017) 8446–8450, https://doi.org/10.1039/c7tb02412f.
[255] F. Guo, K. Huang, J. Niu, T. Kuang, Y. Zheng, Z. Gu, J. Zou, Enhanced osseointegration of double network hydrogels via calcium polyphosphate incorporation for bone regeneration, Int. J. Biol. Macromol. 151 (2020) 1126–1132, https://doi.org/10.1016/j.ijbiomac.2019.10.155.
[256] A. Shi, X. Dai, Z. Jing, Tough and self-healing chitosan/poly(acrylamide-co-acrylic acid) double network hydrogels, Polym. Sci. - Ser. A. 62 (2020) 228–239, https://doi.org/10.1134/S0965545X20030128.
[257] S.N. Li, B. Li, Z.R. Yu, Y. Li, K.Y. Guo, L.X. Gong, Y. Feng, D. Jia, Y. Zhou, L.C. Tang, Constructing dual ionically cross-linked poly(acrylamide-co-acrylic acid)/chitosan hydrogel materials embedded with chitosan decorated halloysite nanotubes for exceptional mechanical performance, Compos. Part B Eng. 194 (2020), 108046, https://doi.org/10.1016/j.compositesb.2020.108046.
[258] J. Zhang, L. Chen, B. Shen, L. Chen, J. Feng, Ultra-high strength poly(N-(2-hydroxyethyl)acrylamide)/chitosan hydrogel with “repelling and killing” bacteria property, Carbohydr. Polym. 225 (2019), 115160, https://doi.org/10.1016/j.carbpol.2019.115160.
[259] J. Zhang, L. Chen, B. Shen, Y. Wang, P. Peng, F. Tang, J. Feng, Highly transparent, self-healing, injectable and self-adhesive chitosan/polyzwitterion-based double network hydrogel for potential 3D printing wearable strain sensor, Mater. Sci. Eng. C. 117 (2020), 111298, https://doi.org/10.1016/j.msec.2020.111298.
[260] L. Huang, Z. Zhu, D. Wu, W. Gan, S. Zhu, W. Li, J. Tian, L. Li, C. Zhou, L. Lu, Antibacterial poly (ethylene glycol) diacrylate/chitosan hydrogels enhance mechanical adhesiveness and promote skin regeneration, Carbohydr. Polym. 225 (2019), 115110, https://doi.org/10.1016/j.carbpol.2019.115110.
[261] J. Cao, Y. Wang, C. He, Y. Kang, J. Zhou, Ionically crosslinked chitosan/poly (acrylic acid) hydrogels with high strength , toughness and antifreezing capability, Carbohydr. Polym. 242 (2020), 116420, https://doi.org/10.1016/j.carbpol.2020.116420.
[262] Y. Chen, W. Wu, J. Yu, Y. Wang, J. Zhu, Z. Hu, Mechanical strong stretchable conductive multi-stimuli-responsive nanocomposite double network hydrogel as biosensor and actuator, J. Biomater. Sci. Polym. Ed. 31 (2020) 1770–1792, https://doi.org/10.1080/09205063.2020.1775760.
[263] L. Wu, L. Li, L. Pan, H. Wang, Y. Bin, MWCNTs reinforced conductive, self-healing polyvinyl alcohol/carboxymethyl chitosan/oxidized sodium alginate hydrogel as the strain sensor, J. Appl. Polym. Sci. 138 (2021), 49800, https://doi.org/10.1002/app.49800.
[264] D. Gan, L. Han, M. Wang, W. Xing, T. Xu, H. Zhang, K. Wang, L. Fang, X. Lu, Conductive and tough hydrogels based on biopolymer molecular templates for controlling in situ formation of polypyrrole nanorods, ACS Appl. Mater. Interfaces 10 (2018) 36218–36228, https://doi.org/10.1021/acsami.8b10280.
[265] Y. Zhao, J. Guan, S.J. Wu, Highly stretchable and tough physical silk fibroin–based double network hydrogels, Macromol. Rapid Commun. 40 (2019), 1900389, https://doi.org/10.1002/marc.201900389.
[266] P. Karami, C.S. Wyss, A. Khoushabi, A. Schmocker, M. Broome, C. Moser, P.E. Bourban, D.P. Pioletti, Composite double-network hydrogels to improve adhesion on biological surfaces, ACS Appl. Mater. Interfaces 10 (2018) 38692–38699, https://doi.org/10.1021/acsami.8b10735.
[267] F. Lin, Z. Wang, Y. Shen, L. Tang, P. Zhang, Y. Wang, Y. Chen, B. Huang, B. Lu, Natural skin-inspired versatile cellulose biomimetic hydrogels, J. Mater. Chem. A. 7 (2019) 26442–26455, https://doi.org/10.1039/c9ta10502f.
[268] Y. Wang, Z. Wang, K. Wu, J. Wu, G. Meng, Z. Liu, X. Guo, Synthesis of cellulose-based double-network hydrogels demonstrating high strength, self-healing, and antibacterial properties, Carbohydr, Polym 168 (2017) 112–120, https://doi.org/10.1016/j.carbpol.2017.03.070.
[269] S.N. Li, B. Li, Z.R. Yu, L.X. Gong, Q.Q. Xia, Y. Feng, D. Jia, Y. Zhou, L.C. Tang, Chitosan in-situ grafted magnetite nanoparticles toward mechanically robust and electrically conductive ionic-covalent nanocomposite hydrogels with sensitive strain-responsive resistance, Compos. Sci. Technol. 195 (2020), 108173, https://doi.org/10.1016/j.compscitech.2020.108173.
[270] Y. Zhao, Z. Li, Q. Li, L. Yang, H. Liu, R. Yan, L. Xiao, H. Liu, J. Wang, B. Yang, Q. Lin, Transparent conductive supramolecular hydrogels with stimuli-responsive properties for on-demand dissolvable diabetic foot wound dressings, Macromol. Rapid Commun. (2020), 2000441, https://doi.org/10.1002/marc.202000441, 1–11.
[271] P. Lavrador, M.R. Esteves, V.M. Gaspar, J.F. Mano, Stimuli-responsive nanocomposite hydrogels for biomedical applications, Adv. Funct. Mater. (2020), 2005941, https://doi.org/10.1002/adfm.202005941, 1–30.
[272] S.L. Scinto, D.A. Bilodeau, R. Hincapie, W. Lee, S.S. Nguyen, M. Xu, C.W. am Ende, M.G. Finn, K. Lang, Q. Lin, J.P. Pezacki, J.A. Prescher, M.S. Robillard, J.M. Fox, Bioorthogonal chemistry, Nat. Rev. Methods Prim. 1 (2021) 30, https://doi.org/10.1038/s43586-021-00028-z.
[273] C.C. Lee, Y.C. Su, T.P. Ko, L.L. Lin, C.Y. Yang, S.S.C. Chang, S.R. Roffler, A.H.J. Wang, Structural basis of polyethylene glycol recognition by antibody, J. Biomed. Sci. 27 (2020) 12, https://doi.org/10.1186/s12929-019-0589-7.
[274] K. Crouvisier-Urion, F. Regina da Silva Farias, S. Arunatat, D. Griffin, M. Gerometta, J.R. Rocca-Smith, G. Weber, N. Sok, T. Karbowiak, Functionalization of chitosan with lignin to produce active materials by waste valorization, Green Chem. 21 (2019) 4633–4641, https://doi.org/10.1039/c9gc01372e.
[275] R. Lu, X. Zhang, X. Cheng, Y. Zhang, X. Zan, L. Zhang, Medical applications based on supramolecular self-assembled materials from tannic acid, Front. Chem. 8 (2020), 583484, https://doi.org/10.3389/fchem.2020.583484.