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Review article

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Model-based modular hydrogel design

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Abstract

Hydrogels — water-insoluble, three-dimensional networks of polymer chains — are used as biomaterials in various biomedical and clinical applications. Their modularity and versatility have led to the development of increasingly complex hydrogels, which can dynamically respond to their environment, release drugs and regenerate cells and tissues. In this Review, we present a model-based modular hydrogel design framework that is application-driven and considers clinical translation early in the design process. In this approach, every component of the hydrogel formulation is optimized towards multifaceted design criteria of the target application, identifying how multiple properties can be integrated into a single formulation. We highlight the fundamental models of polymer physics that provide the basis of modular hydrogel design and examine how synthetic polymer precursors can be integrated to achieve such modularity. Finally, we discuss clinically approved hydrogel formulations, and investigate how challenges in clinical translation may be addressed by a modular design approach.

Sections

Introduction

The beginning of hydrogels

Adapting fundamental models from polymer physics

Modularity through synthetic precursors

Hydrogel properties as a modular toolbox

Hydrogels in clinical applications

Challenges and solutions for clinical translation

Model-based modular hydrogel design process

Outlook

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Key points

- Hydrogels can be applied as biomaterials for various applications, benefiting from their versatility, their mechanical and structural properties, and their modularity.
- The clinical translation of hydrogels may be accelerated by a model-driven modular design approach, considering how modular changes affect multiple structure–property interactions.
- Modular components can be consistently incorporated into hydrogels using fundamental models to optimize their multiple properties.
- Theoretical models need to be refined to predict relevant properties of hydrogels, and validated with a diverse dataset of well characterized and newly designed hydrogels.

Introduction

Hydrogels can be designed for drug delivery, as tissue-mimicking scaffolds for regeneration and biological modelling, as various biomedical materials, such as contact lenses and wound dressings[1–5], and for adaptable and patient-specific approaches in precision medicine[6]. Each new generation of hydrogels better matches the needs of diverse applications by optimizing physical and chemical properties, introducing dynamic and stimuli-responsive properties, and employing hierarchical, multi-phase structures, as in granular hydrogels[7–11]. These increasingly nuanced hydrogels are highly specialized but remain connected through the fundamental structure–property relationships of hydrogels[12,13].

Opportunities to expand the applications of hydrogels have driven the search for hydrogels with extreme properties (for example, the stiffest possible hydrogel formulation); however, many applications require multiple properties and/or design criteria to be balanced within a single hydrogel formulation. The path to achieving a multifaceted, application-ready hydrogel therefore demands modular design and a fundamental understanding of hydrogels. Modularity, or the ability to exchange components with different properties within a hydrogel formulation, is needed to achieve properties associated with distinct components (for example, matrix-metalloproteinase-degradable crosslinking peptides). Importantly, a fundamental understanding of hydrogels, summarized using mathematical models, allows the adjustment of hydrogel properties into application-ready ranges without losing the effects of the modular components.

Modular hydrogel design has largely focused on incorporating a single new property at a time into a hydrogel, testing the effectiveness of that modification through binary comparison or scaling relationships. However, as hydrogel design becomes more multifaceted, the need for intersectional knowledge increases; that is, an understanding of the properties that emerge from combined modifications, and of how those interactions affect a hydrogel's suitability for a particular biomedical application. Unguided trial-and-error optimization becomes unfeasible with increasingly complex hydrogel formulations; instead, fundamental models need to be applied that coordinate predictions of structure–property relationships in the intersectional design space. Specifically, model-guided hypotheses of how modular changes affect multiple structure–property interactions can support more efficient experimental design for creating hydrogels with multiple properties.

A major bottleneck holding back many biomedical applications of hydrogels is the disconnect between what can be achieved with modular hydrogel components and what can be predictively designed using fundamental hydrogel models. Once modular components can be consistently incorporated into hydrogels, using fundamental models to optimize multiple competing properties, an optimal hydrogel formulation can be designed for a given application. However, modular design and fundamental predictive models are required to bridge the gap between what is possible and what is predictable. Sharing of data and cross-validation of models and modular components will greatly accelerate this approach toward broad applicability and clinical translation of hydrogels.

In this Review, we discuss intersectional, application-driven hydrogel design, emphasizing the importance of fundamental modelling and standardized design. We first present an overview of major advances in fundamental hydrogel modelling and introduce the diverse properties achievable with modular hydrogel design. We then discuss successful clinical translations of hydrogels and examine the current barriers to and limitations of broader clinical translation of hydrogel-based treatments. Finally, we propose a general approach to hydrogel design that can be adapted to address specific clinical needs.

The beginning of hydrogels

By the current definition, hydrogels are three-dimensional, hydrophilic, polymeric networks able to absorb water or biological fluids. However, the earliest published reference to a 'hydrogel', by Thomas Graham in 1864, refers to a gelatinous mixture of silicic acid, alcohol and water[14]. In the early 1940s, Paul Flory and colleagues set the main framework for the analysis of gels, developing the associated thermodynamic theories, statistical mechanics and a first analysis of critical miscibility characteristics, among other properties[15]. Flory and colleagues' seminal work on swollen polymer networks, including the Flory–Rehner equation[16,17], forms the foundation of our current understanding of structure–function relationships in hydrogels.

Biomedical applications of these crosslinked structures have been enabled by the work of Otto Wichterle and Drahoslav Lim in 1960, who were the first to identify the biomedical properties of crosslinked poly(2-hydroxyethyl methacrylate) (PHEMA)[18,19]. PHEMA hydrogels were the basis for the first oxygen-permeable contact lenses and expanded opportunities for biointerfacial materials. The current state of hydrogel research has emerged from the coordination of hydrogel synthesis capabilities, structure–function modelling and a variety of biomedical applications.

Adapting fundamental models from polymer physics

Fundamental models for hydrogels borrow extensively from polymer physics. Rubberlike elasticity theories[15,20] describe the relationship between hydrogel structure and stiffness, and contribute the elastic chemical potential to models of the equilibrium swelling of hydrogels. The Flory–Huggins polymer solution theory[15] provides the mixing chemical potential for equilibrium swelling theory[17]. Introducing the initial or relaxed polymer volume fraction into the equilibrium swelling equation[21,22] facilitates analysis of the swelling of hydrogels formed in aqueous solution. In addition, the constrained junction model defines whether to apply phantom-like or affine deformation to hydrogel swelling and stiffness calculations[23].

Similarly, models for solute transport within hydrogels are based on polymer physics[24], including adopting the assumption from the

Stokes–Einstein model that a polymeric molecule in solution behaves like a hard, non-interacting sphere. Flory's statistical mechanics[25] can be applied to calculate the mesh size of a hydrogel[26], which remains a plausible method for estimating solute transport properties in a hydrogel. Moreover, scaling concepts[27] have contributed to the analysis of solute transport in hydrogels, with the free-volume solute transport model[28] using a scaling relationship. Ogston's obstruction model is more accurate than the free-volume model for larger solutes[29], and a multiscale diffusion model coordinates obstruction and free-volume theories to predict solute transport in hydrogels across a broad range of solute sizes[30].

The theories of equilibrium swelling, rubberlike elasticity and mesh transport were further coordinated into a hydrogel design model that uses synthesis-defined network structure parameters as inputs to predict swelling, stiffness and solute transport[12,13]. This coordinated model standardizes terms across the three source theories and addresses limiting assumptions, such as that all hydrogels have vinyl polymer backbones and tetrafunctional junctions[12]. By rearranging the models from a theoretical 'properties describe structure' format to a practical 'structure predicts properties' format, a model-based hydrogel design approach has been proposed[13], which has been validated and refined by wet-laboratory experiments[31–35]. Specifically, inputting the synthesis-defined structural parameters of a specific hydrogel formulation into the model will yield the hydrogel's expected swelling ratio, stiffness and the diffusion coefficients of solutes within the hydrogel. Importantly, this approach produces structure-based predictions a priori, suggesting how to change a hydrogel's structure to optimize its properties without requiring trial-and-error experimentation. Furthermore, these structure–property relationships are explicit and testable, which means that the accumulation of data that pairs hydrogel formulations with their properties will reliably improve the models, increasing the accuracy of hydrogel design across biomedical applications.

Modularity through synthetic precursors

In addition to theoretical developments and mathematical modelling, breakthroughs in the chemical synthesis and commercial availability of functional precursors of hydrogel network structures have improved efforts toward model-based modular hydrogel design. PHEMA[18], poly(vinyl alcohol) (PVA)[21], poly(ethylene glycol) diacrylate (PEGDA) and end-functionalized multi-arm poly(ethylene glycol) (PEG) are key synthetic precursors of hydrogels. In particular, PEG-based precursors are versatile in their structure (linear or multi-arm) and end-group functionalization, and therefore can be used to investigate and validate fundamental structure–function relationships in biomedically relevant synthetic hydrogels without introducing confounding comparisons of hydrogels made with different polymers. Other precursor polymers also feature modular capabilities for biomedical applications, including natural polymers with modifiable side groups, such as gelatin and hyaluronic acid[36,37]. However, many key developments in modular hydrogel design have been achieved with PEG-based hydrogels, yielding insights that may be extended to other polymers.

Poly(ethylene glycol) diacrylates

PEGDAs are precursor polymers that can form hydrogels through radical polymerization of the acrylate groups as a one-step synthesis in aqueous solution. This end-linking reaction results in two key attributes of PEGDA-based hydrogels: the degree of polymerization between junctions N_j (or the molecular weight between crosslinks M_c) is defined by the length of the precursor polymer[31,38]; and the polymerized acrylate groups form hydrophobic coil-like junctions[39], which can connect many PEG chains[40]. Compared to randomly crosslinked hydrogel systems, such as PVA, the resulting low dispersity and controllability of the degree of polymerization between junctions in PEGDA hydrogels allows the investigation of the relationship between hydrogel structure and properties, despite the variability associated with radically polymerized junctions.

PEGDA hydrogels were first synthesized with a focus on applications. For example, PEGDA hydrogels have been applied to encapsulate islets of Langerhans[41], and to investigate PEGDA hydrogel calcification in a biological environment[42]. The swelling behaviour of PEGDA hydrogels[38] and the relationship between their structure and permeability[43] have been well described. In addition, the network structure of PEGDA hydrogels can be modified to decouple their physical properties. Incorporating PEG monoacrylate into a PEGDA hydrogel increases the frequency of chain-end defects within the networks[40,44]. Combining four-arm PEGs with PEGDA results in networks with two different types of network junctions[45], and the effects of four-arm PEGs and *N*-vinyl pyrrolidone on decoupling stiffness and diffusivity have been described[46]. By including *N*-vinyl pyrrolidone, stiffness and diffusivity can be decoupled, but this changes the chemical and thermodynamic properties of the hydrogel, highlighting the difficulty of structurally decoupling stiffness and diffusivity in hydrogels.

PEGDA-based hydrogels remain relevant as the basis for photopolymerizable hydrogels for tissue-engineering applications and drug delivery applications[47–50].

Multi-arm PEG-based hydrogels

Most current biomedical hydrogels are based on multi-arm PEG, which yields well defined networks, because the junction is at the core of the precursor molecule and, therefore, is not susceptible to reaction-dependent variability in junction functionality, as opposed to PEGDA hydrogels. Additionally, well controlled bifunctional crosslinking reactions at the end of each arm result in precision similar to that of PEGDA hydrogels regarding the degree of polymerization between junctions. Theoretical analysis of multi-arm PEGs suggests that such junction-centred macromers are the basic unit of the network structure[51]. Experimentally, stoichiometrically balanced four-arm PEG networks result in high structural regularity and high strength compared to agarose and acrylamide gels[52] as well as increased toughness and strength compared to photodegradable PEGDA[39]. Thus, multi-arm PEGs enable the design of hydrogels with well defined macromolecular structures.

Four-arm PEG hydrogels were first reported in 1996 (ref. 53), followed by the development of eight-arm PEG hydrogels, which show slower degradation and protein release[54], compared to four-arm PEG hydrogels. In addition, highly branched 'star' PEG hydrogels have been synthesized and characterized[55]. By comparing three-arm, four-arm and eight-arm PEG hydrogels, it has been shown how swelling decreases and stiffness increases with increasing junction functionality[56]. Therefore, junction functionality can serve as a controllable variable in multi-arm PEG hydrogels.

Refinement of the end-group chemistry for efficient reactions in water has further improved the modularity and precision of multi-arm PEG hydrogel design. Norbornene end-groups in multi-arm PEGs facilitate efficient, irreversible and photo-initiated reactions with thiols (and cysteines) to form network structures and for the conjugation of

cell-binding Arg–Gly–Asp (RGD) peptides to hydrogels[57]. The degradable ester linkage in norbornene can also be replaced with a less hydrolytically degradable amide linker, enabling long-term implantation of hydrogels[58]. In addition, spontaneously reacting end-groups, such as maleimide end-groups, can be implemented. We note that maleimide end-groups react more efficiently and are less cytotoxic than triethanolamine (TEA)-dependent acrylate or vinyl sulfone end-groups in four-arm PEG hydrogels[59]. However, the fast reaction between maleimide groups and thiols results in more heterogeneous network structures, compared to norbornene-crosslinked hydrogels[60,61]. Methyl sulfone end-groups provide intermediate gelation times, compared to maleimide and vinyl sulfone end-groups, which is useful for optimizing cell encapsulation[62]. Radical-free gelation chemistries reduce the cytotoxicity associated with photoinitiated crosslinking[63], and thiol-independent reactions make gelation bio-orthogonal[64].

Owing to their modularity, multi-arm PEG hydrogels are often used for tissue engineering and drug delivery applications, for example, to fine-tune protein release and control three-dimensional cellular structures[65,66]. Further modification of the end-groups of four-arm PEG hydrogels enables photoinduced degradation for the spatially controlled expansion of intestinal organoids[67]. Multi-arm PEG hydrogels can further be designed to match the bioactive peptide profiles of the extracellular matrices of the brain and bone marrow[68,69]. The accessibility, homogeneity and modularity of multi-arm PEG hydrogels make them powerful tools for improving the connection between hydrogel modularity and predictive design.

Hydrogel properties as a modular toolbox

Application-ready hydrogels require optimization of multiple properties. For example, a long-term tissue-engineered implant needs to match the stiffness of the target tissue, endure many cycles of applied forces, and minimize a fibrotic response. Modular hydrogel properties enable application-centred hydrogel design.

Stimuli-responsive hydrogels

Stimuli-responsive hydrogels can be externally triggered to change their properties. Response modalities include pH, ionic strength, temperature, light, electric charge, force, magnetism, chemical and biochemical reactions[70–72]. Stimuli-responsive hydrogels, in particular, pH- and temperature-responsive hydrogels, have been explored for a variety of applications[73,74]; however, these hydrogels have yet to be fully incorporated into fundamental hydrogel models[12]. For example, stimuli-responsive properties may be modularly introduced using pendant groups on a simple polymer network; however, responses may require the replacement of all or part of the polymer network with a stimuli-responsive polymer, affecting network properties beyond the targeted stimulus response. Stimulus-specific model development and validation studies, addressing how multiple hydrogel properties change upon stimulation, will help to assimilate stimuli-responsive hydrogels into an overarching modular model.

Dynamic hydrogels

Adhesive, injectable, in-situ-forming, viscoelastic and self-healing hydrogels are dynamic hydrogels that can operate by several mechanisms. These hydrogels may not be explicitly stimuli-responsive, but include important properties for many biomedical applications. Importantly, the dynamic behaviour should occur on a timescale relevant to the application[75]. In-situ-forming and injectable hydrogels are prerequisites for wound-filling and subcutaneous hydrogel drug-delivery reservoirs[76]. Adhesive hydrogels may form permanent bonds, dynamic bonding or physical entrapments owing to the dispersity of chemical groups and network structures, and their chemistry and macroscopic presentation (glues, solid adhesives and bio-inks) must be adapted to the relevant adhesion surface and application[77]. Viscoelastic hydrogels match the viscoelasticity of biological tissues[78] and can relax at varying rates to suit a specific application[79]. Controlling dynamic and adhesive properties requires an integrative understanding of the chemical and physical properties of a hydrogel, which is particularly important for drug delivery and wound-dressing products. Dynamic properties can be introduced modularly by changing the reaction chemistry of all or some of the crosslinks within a network, but these changes may also affect network structure properties, such as the equilibrium swelling, in ways not addressed by fundamental models.

Semi-synthetic biopolymer hydrogels

Semi-synthetic or modified biopolymer hydrogels combine the control features of synthetic hydrogels with the bioactive features of biopolymers. In particular, pendant groups of biopolymers can be functionalized to enable network formation[80]. For example, DNA-based hydrogels, although enzymatically degradable and expensive, compared to gelatin, alginate and synthetic polymers, leverage the structural control of DNA, thereby enabling bonding specificity, targeted bioactivity and structural rigidity, which is difficult to achieve in other polymer networks[81,82]. Unlike DNA-based hydrogels, gelatin and alginate are commercially available with well documented functionalization methods and biological interactions[36,83]. Although biopolymer hydrogels cannot always be modelled using the same assumptions as for synthetic polymer hydrogels[31], their bioactive capabilities are essential for many biomedical applications, warranting further study of their properties and integration into model-based modular hydrogel design.

Tough hydrogels

Hydrogels are often valued as soft and degradable materials; however, toughness and fatigue-resistance are desirable properties for long-term biological implants, and this need can be addressed using tough and fatigue-resistant hydrogels[84,85]. In hydrogel mechanics, stretchability, toughness and fatigue resistance are competing parameters that must be managed alongside other properties desired in the final application. Achieving this balance and simultaneously optimizing for toughness, adhesion, cytocompatibility and degradability remain challenging[86]. Coordinating mechanical models of fracture and toughness, such as the Lake–Thomas model[84], with the swollen polymer network model[12] for swelling, stiffness and solute transport will help us to evaluate the tradeoffs between network structure-dependent properties.

Hydrogel size

The size of a hydrogel is an important control aspect for many applications. Nanoparticle hydrogels require advanced synthesis and characterization strategies, such as emulsion polymerization, dynamic light scattering and quartz crystal microbalance analysis[87–89], but may overcome many challenges in targeted drug and protein delivery, such as the possibility of carrying drugs through cell–cell junctions in the intestines and across the blood–brain barrier[90–92]. Microscale hydrogels can be produced by microfluidic systems or through fragmentation of bulk hydrogels, and can be used in suspension, as aggregate granular hydrogels and in composite hydrogels[93] for various applications, including drug delivery, cell therapy and cell sequencing[94]. The property differences between granular and bulk hydrogels greatly expand the

Table 1 | Hydrogels approved for clinical use

Manufacturer	Product	Hydrogel material	FDA approval date	Clinical application
Allergan (now Abbvie)	Juvéderm	Hyaluronic acid	2020	Age-related dermal-volume-deficit correction
	Voluma XC		2017	Correction of facial wrinkles and folds
	Vollure XC		2010	Correction of facial wrinkles and folds, lip augmentation
	Ultra XC		2016	Treatment of perioral rhytids
	Volbella XC		2021	Correction of infraorbital hollowing
	Vollux XC		2022	Correction of jawline definition
Axonics Modulation Technologies	Bulkamid	Polyacrylamide	2020	Treatment of stress urinary incontinence
ReGelTech	Hydrafil	Poly(*N*-isopropylacrylamide) Poly(ethylene glycol)	2020*	Treatment of degenerative disk disease
Johnson and Johnson	Acuvue Theravision	Poly(2-hydroxyethyl methacrylate) Poly(methacrylic acid)	2022	Antihistamine release for prevention of ocular itch (caused by vision correction or allergic conjunctivitis)
Alcon	Total30	Silicone (Lehfilcon A) with 2-methacryloyloxyethyl phosphorylcholine	2021	Contact lenses for the correction of refractive ametropia and astigmatism (reusable for up to 30 days)
Daré Bioscience	Xaciato	Poloxamer 407 and xanthan gum	2021	Antibacterial vaginal gel for the treatment of bacterial vaginosis

*US Food and Drug Administration breakthrough device designation.

options for modular hydrogel design by introducing the secondary properties of microgel geometry and size, jamming conditions, and void volume fraction and geometry[95–97]. Thus, granular hydrogels may prove necessary to decouple properties that cannot be decoupled within bulk hydrogels.

Composite hydrogels

To overcome the limitations of polymer networks, composite and supramolecular hydrogels have been explored. For example, composite hydrogels can be designed using interpenetrating networks, networks with filler molecules and/or nanoparticles, multicomponent granular hydrogels, and networks with multiple polymer types (for example, synthetic polymers and biopolymers)[98–100]. Supramolecular hydrogels can achieve modular goals by containing several components with distinct functions[101–103]; for example, through crosslinking with a mixture of nanoparticles that respond to different stimuli[104]. However, composite and supramolecular hydrogels are usually too complex for predictive modelling using mean-field-theory assumptions, which may yield unexpected and undesirable interactions.

Each of the abovementioned properties connects back to the fundamental physics and chemistry of swollen polymer networks; however, new or further refined theories and models are needed to fully incorporate these designs into mathematically predictable relationships. Therefore, each feature of hydrogel design should be made as modular and model-defined as possible to allow the rational engineering of hydrogels that meet the multiple criteria of a target application.

Hydrogels in clinical applications

Hydrogels are applied in several clinical fields, including ophthalmology[105], tissue engineering[106], women's health[107,108] and cosmetics (reconstructive surgery and dermal applications)[109,110], which has resulted in a library of clinically approved hydrogel formulations (Table 1).

Contact lenses

Hydrogels have long been clinically used for vision-enhancing contact lenses[105]. In particular, soft and elastic PHEMA hydrogels are transparent and biologically inert, and can thus be used in contact lenses[18]. Their water-rich, biocompatible surfaces do not absorb water from surrounding tissues, and they are soft and oxygen-permeable, providing an advantage over hard corneal and scleral lenses made of poly(methyl methacrylate) (PMMA). However, silicone hydrogels remain the major contact lens material owing to their oxygen permeability, durability and flexibility without compromising their handling[111]. Although the main application of contact lenses has been to correct vision impairments, these hydrophilic materials also allow the delivery of therapeutic agents to treat disease or impart antibacterial properties through diffusion[112,113]. For example, an antihistamine-eluting contact lens has been approved for the treatment of ocular allergy itch (Table 1). In addition, other ophthalmic hydrogels are being explored[114]; for example, lenses that simultaneously provide vision correction, controlled drug delivery and integration with flexible electrical circuits[115].

Injectable hydrogels

Injectable hydrogels have been applied in various applications, including in dermal fillers, spine and intra-articular products[116]. Injectable hydrogels may be injected in the gel state, or they can undergo a transition once they are implanted into the region of interest. The timing and conditions for gelation are major application-specific variables for clinically applied injectable hydrogels[117]. Gelation typically occurs through physical intermolecular interactions or chemical crosslinking using low-molecular-weight crosslinking agents[118].

Context-specific gelation is particularly advantageous as it allows injection into difficult-to-reach physiological regions without requiring invasive surgical procedures. For example, surgical intervention in the spine comes with high risk and may thus benefit from injectable designs. In conditions such as degenerative disc disease, spinal fusion procedures are invasive and may result in neurological injuries or infections[119]. Alternatively, Hydrafil, a poly(*N*-isopropylacrylamide)-based hydrogel, can be applied for nucleus pulposus replacement[120]. Poly(*N*-isopropylacrylamide)-based hydrogels are thermoresponsive and undergo a phase transition at physiological temperatures to form a compact gel[120]. This technology, which received the US Food and

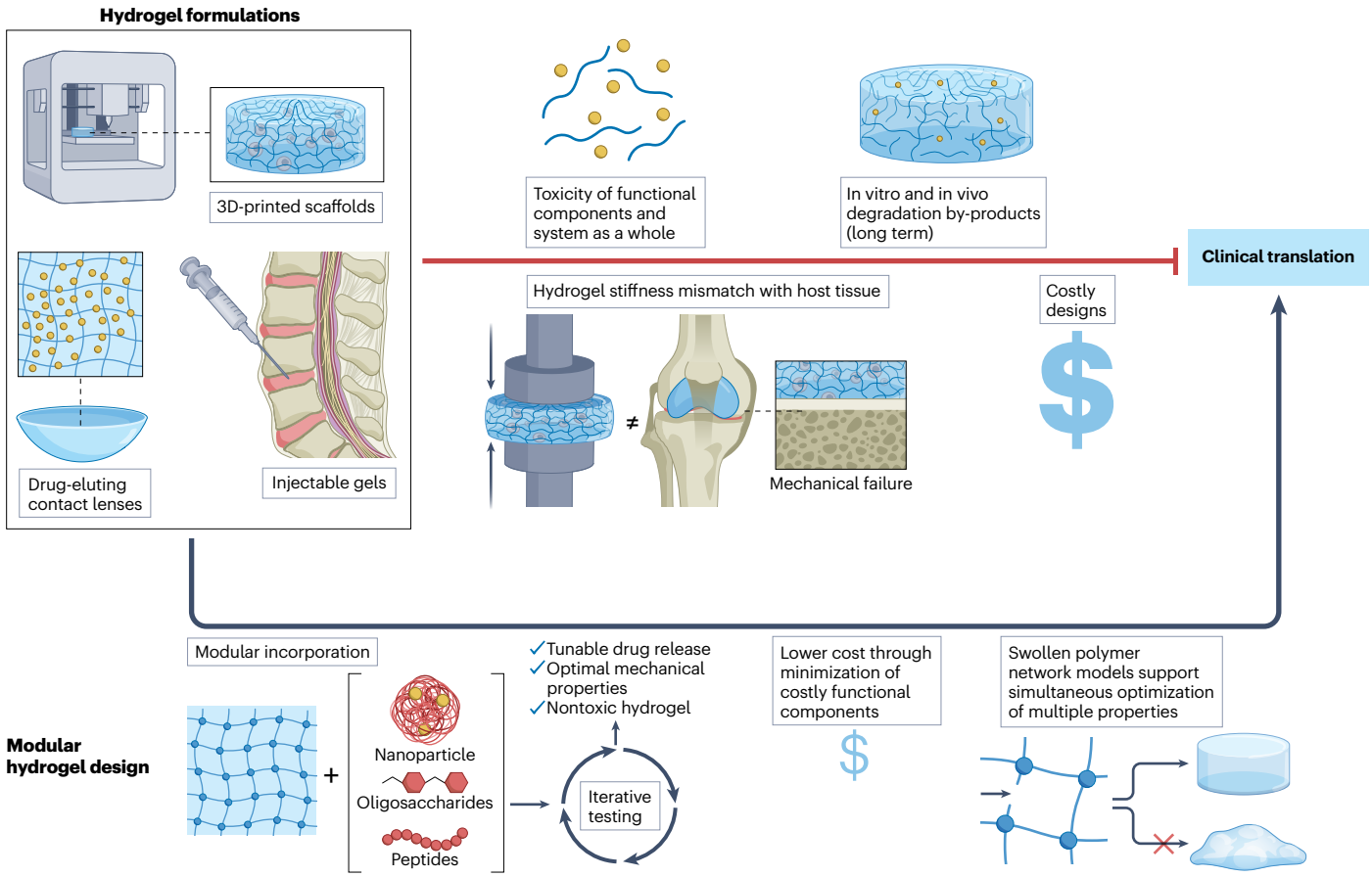

Fig. 1 | Addressing clinical translational challenges of hydrogels. A model-driven modular hydrogel design approach aims to overcome barriers to the clinical translation of hydrogels by simplifying the design process using application-focused design criteria, multi-property modelling, modular hydrogel components and iterative development.

Drug Administration (FDA) breakthrough device designation in 2020, has shown clinical evidence of effectiveness and the premarket review process may be accelerated to obtain FDA approval in the USA[121].

For patients with osteoarthritis, excessive stress on the knee can lead to substantial loss of hyaluronate, causing pain owing to high local friction[122]. Some patients do not respond to the typical treatment of nonsteroidal anti-inflammatory drugs, which leaves surgical intervention as the last resort[122]. Injectable viscosupplementation with hydrogels composed of sodium hyaluronate has emerged as a less invasive and more targeted approach[122,123]; for example, injections of sodium hyaluronate (HYMOVIS and Gel-One) can be applied for the treatment of osteoarthritis of the knee.

Injectable hydrogels can also be administered for facial corrections and cosmetic augmentations, without causing substantial scarring or damage. In particular, hyaluronic-acid-based products are biocompatible and have optimal biodegradation rates in physiological environments[124]. For example, the hyaluronic-acid-based hydrogel Juvéderm[125] is a dermal filler that has been approved by the FDA for perioral enhancements, including facial tissue augmentations, corrections of dermal volume deficits, and infraorbital hollowing in the periorbital complex, with a pre-market approval extension in 2021 (Table 1).

Bulkamid is an injectable periurethral bulking agent for the treatment of stress urinary incontinence and has received European market approval (CE mark) in 2003 and FDA approval in 2021. This polyacrylamide hydrogel can integrate into the surrounding urethral submucosa owing to its similar viscosity and elasticity[126,127]. Furthermore, its high water content and hydrophilicity make it biocompatible and allow minimally invasive administration.

However, many hydrogel-based products have not yet reached the clinic, often because of biocompatibility (and hence safety and efficacy) concerns, lack of feasibility of clinical execution or limited acceptance by the medical community.

Challenges and solutions for clinical translation

Several regulatory and technical challenges that hydrogels face for clinical translation may be addressed by model-based modular hydrogel design (Fig. 1). Safety and efficacy are primary considerations in the clinical approval process of a new drug or device[128–130]. Safety concerns with hydrogel-based devices may be mitigated by using polymers that have previously been used in approved devices. However, the polymer choice should be based on the application; for example, a highly biodegradable polymer should not be used for a long-term implant. Furthermore, crosslinking reagents and functional groups as

well as other modular, functional components of the hydrogel should be tested for toxicity, both independently and as part of the hydrogel, over the expected lifespan and for the use case of the hydrogel device. Component toxicity can be found in the form of unreacted monomers, catalysts, side-products of gelation, active components of the network and degradation by-products[131]. Unintended migration of hydrogel components to other parts of the body must also be addressed, because they may lose their intended effect or contribute to off-target toxicities.

Understanding and designing for the full hydrogel use cycle, including degradation, remains a core challenge of hydrogel design for clinical applications[132–135]. Biomedically relevant hydrogels may degrade by multiple distinct mechanisms, including hydrolysis[136,137], reversible crosslinking reactions[138], enzymatic degradation[139–141] and strain-based fracture[142,143]. Accurate analysis of in vitro and in vivo degradation rates is thus necessary to match hydrogel formulations with their application[144]. Importantly, hydrogels used to scaffold the regrowth of tissue need to be able to degrade and clear from the tissue in accordance with tissue regrowth. Furthermore, degradation changes the hydrogel's properties over time, which must be considered to avoid unintended effects, such as premature release of a drug. Implanted, non-degradable hydrogels may further cause a foreign-body response[145,146]. Finally, degradation by-products must be non-toxic and efficiently cleared by the body, or, otherwise, converted into a safe, bioresorbable form.

Biocompatible degradation may be achieved through model-based modular hydrogel design using biocompatible polymers, such as PEG, for the bulk of the hydrogel to reduce the extent of toxicity testing. In addition, the swollen polymer network model includes the frequency of chain-end defects, which can be manipulated to anticipate how network degradation affects bulk hydrogel properties[12,13]. We note that this approach to modelling hydrogel degradation is broadly applicable, because hydrogel degradation often involves the scission of network chains. Moreover, the modular incorporation of bioactive functional groups into a template hydrogel can be tested iteratively to identify and replace toxic components and manipulate properties, such as enzymatic degradability, independently from other properties; for example, the ratio of enzyme-degradable crosslinks and crosslinks in the base polymer can be modified[68]. Focused degradability studies in combination with model-based modular hydrogel design will enable control of hydrogel longevity in vivo.

Limited cost-effectiveness is a major barrier to the clinical translation of hydrogel devices and should be addressed in design considerations. Cost-effectiveness considerations include scale-up and mass production (Box 1), research and development, the potential and margin for profitability and the likelihood of acceptance by health insurance programmes[116]. However, many hydrogel devices are not cost-effective and this may be improved by model-based modular hydrogel design, for example, by applying cost-efficient polymers and by minimizing the use of costly functional components. In addition, research and development costs associated with trial-and-error hydrogel synthesis may be reduced using model-based modular hydrogel design to achieve multiple target properties simultaneously. Although publicly accessible modular hydrogel design information may ultimately reduce the margin of profitability between competing commercial hydrogel formulations, the margin of profitability for hydrogel-based devices over other forms of treatment may be increased, enabling more therapeutic hydrogel-based devices to enter the healthcare market.

The clinical translation of hydrogels is also limited by the properties of hydrogels. For example, a specific hydrogel device may be able to extend drug release to days or months, but not to years. Therefore, a hydrogel formulation that could substantially extend drug delivery time would hold great promise for clinical translation, a goal that may be achieved by improving the modelling and experimental characterization of solute transport through hydrogels[12,13,32,33]. The quest for more extreme properties, such as high fatigue resistance, may drive hydrogel design away from simpler and more adaptable formulations[84,142,143,147]. Achieving extreme hydrogel properties may initially appear antithetical to modular hydrogel design, which aims to meet several design criteria based on the tools that are already available. However, developing extreme hydrogel properties is already a thriving field of basic research, and clinical translation of these extreme hydrogels will require a framework for integrating those properties into hydrogel formulations that achieve other design criteria as well. Therefore, improving modular hydrogel design capabilities alongside these extreme property studies will greatly reduce the lag between extreme property discovery and clinical translation.

Non-toxic in situ gelation of hydrogels in desirable shapes is complex but is often a prerequisite to clinical applications[76,102], such as to replace and reinforce damaged tissue, to create long-term drug delivery reservoirs or to protect other implantable devices. For each application, the hydrogel must fulfill additional functions beyond the initial in situ gelation. Bioprinted[148], self-healing[101] and granular hydrogels[93,149] may allow in situ gelation and may well be integratable into a model-based modular hydrogel design approach.

Oversimplification of biology in hydrogel design may further lead to designs that do not achieve the desired outcome in clinical testing; for example, the molecular weight of hyaluronic acid determines

Box 1

Modular scale-up and tolerance testing

Hydrogel properties are often characterized at the laboratory scale; however, application-focused hydrogel design must also consider scale-up, property predictability and tolerance, as well as good manufacturing practice. Therefore, minimal hydrogel systems with few modular properties that do not require difficult-to-synthesize components or extensive processing should provide the starting point for new hydrogel designs. Importantly, tolerance and batch variability studies should be conducted in the early stages of hydrogel design to ensure that the material can be produced at scale. Here, tolerance refers to the extent to which structural hydrogel design predictably leads to desirable physical properties. For example, a hydrogel formulation with a 5% initial polymer volume fraction and an identical hydrogel formulation with a 7.5% initial polymer volume fraction may have different properties; the question remains whether those differences are statistically significant after accounting for batch-to-batch variability. Importantly, scale-up processes may affect batch-to-batch variability or in-batch heterogeneity. Model-based modular hydrogel design allows for the assessment of scalability early in and throughout the design process.

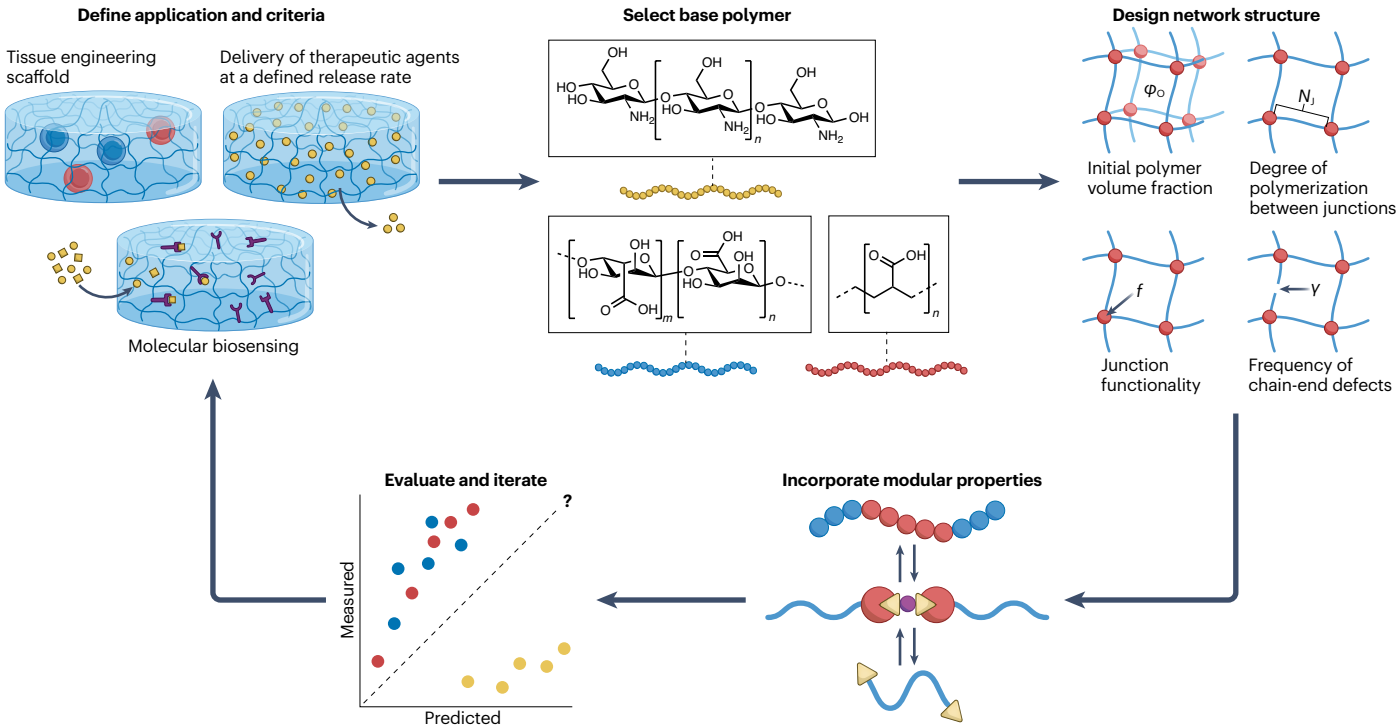

Fig. 2 | Iterative cycle for model-based modular hydrogel design. Application and design criteria should be defined at the start of the design process, followed by selection of the base polymer, which defines many of the properties of the hydrogel, including the network structure parameters that can be manipulated. Model-driven design of the network structure enables optimization of structural properties, such as swelling, stiffness and solute transport within the hydrogel. Modular properties can be integrated into the network by targeted substitutions to produce application-specific hydrogel properties, such as bioactivity or injectability. Finally, characterization of the hydrogel's properties and its suitability for the application inform future iterations and/or validation of the hydrogel's readiness for translation. φ_0, initial polymer volume fraction; N_j, degree of polymerization between junctions; f, junction functionality or the number of chains that converge at each junction; γ, frequency of chain-end defects.

whether this extracellular matrix component has pro-inflammatory or anti-inflammatory properties[150–153], which should be accounted for in hydrogel design. Therefore, multiscale modelling needs to incorporate material properties, cell–environment interactions and intracellular signalling in order to evaluate and address the design in a clinical context.

Ultimately, many of the challenges associated with the clinical translation of hydrogels involve the combination of multiple hydrogel features into a single formulation that meets several design criteria for a targeted application. However, fundamental hydrogel research often aims at developing hydrogels with new properties, whereas applied hydrogel research focuses more on translational considerations. Model-based modular hydrogel design aims to bridge this gap.

Model-based modular hydrogel design process

Model-based modular hydrogel design embraces both fundamental insights that apply to all hydrogels as well as the distinct properties and considerations needed for a specific application. A design process based on modelling, modularity and iteration can thus support clinical translation of hydrogels and provide new insights into hydrogel behaviour and properties (Fig. 2). This approach maximizes the information that can be applied from one hydrogel study to another.

Model-based modular hydrogel design draws from other strategies for translational biomaterials development, including programmable hydrogels[154], precise functional hydrogels[6] and evidence-based biomaterials research[155]. Programmable hydrogels are typically engineered by implementing cells, biochemical groups and a polymer network, followed by the integration of modular crosslinks to manipulate encapsulated cell mobility and organization[154]. Precise functional hydrogels are designed to support multiple distinct biomedical applications by implementing several types of unit operations[6]. Evidence-based biomaterials research incorporates an iterative systemic review into the translation process from basic research to commercialized biomedical products[155]. Model-based modular hydrogel design combines the material-conscious features of programmable hydrogels with the application-driven functionality of precise functional hydrogel design and the iterative progress of evidence-based biomaterials research. Furthermore, modular hydrogel design aims at developing application-ready hydrogels, while feeding back into a robust, comprehensive dataset and model of hydrogel structure–property relationships (Box 2).

Application guides design

The intended application guides model-based modular hydrogel design. For example, drug delivery requires control of drug- or protein-loading efficiency and the release profile[90]; tissue-engineering scaffolds aim to match or modulate the physical and biological properties of tissue-specific extracellular matrices[156]; and hydrogel biosensors often depend on a detectable and reliable response to stimuli[72].

More specific applications may demand more distinct properties; for example, oral drug delivery requires a carrier that can preserve its payload in the acidic stomach, pass through the complex hydrogel-like mucus barrier of the gut lining, and cross the gut epithelium, before entering the bloodstream[73,157]. Long-term tissue culture scaffolds should degrade at a rate that allows cellular motility and extracellular matrix production without creating toxic degradation products or bottlenecks to nutrient and waste transport.

Therefore, application-focused hydrogel design must meet multiple criteria, which must be optimized and balanced, and depend both on the biological question and on materials science: the effects of optimizing a property versus meeting a practical criterion for a target application need to be investigated. Importantly, understanding at what stage further optimization is no longer relevant will free up bandwidth for refining other properties. For example, refining the concentration and timing of drug delivery to a tumour may be more worthwhile than optimizing the loading efficiency of the drug into a nanoparticle[90]. Intersecting criteria should also be identified, which may result in additional challenges to either the materials or the biological aspects; for example, typical structural variations to hydrogels do not decouple stiffness and solute transport, thus confounding the mechanistic study of cell–matrix interactions[31].

The design of a new hydrogel for a specific application should therefore consider one to four main criteria, as, for example, illustrated by the engineering of central nervous system tissues[158]. Although various properties may affect the performance of such hydrogel-based engineered tissues, electrical performance, biocompatibility, durability and versatility are suggested to be the key criteria. Similarly, design priorities for biomaterials intended for the expansion of haematopoietic stem cells should consider ligand presentation, transport of cell-secreted factors, matching niche dynamics and control of hypoxia and reactive oxygen species[159]. A clear goal and milestones toward the final application should guide hydrogel design steps.

Selection of base polymer

After defining the application, a base polymer or precursor for the hydrogel has to be selected. Starting with well characterized and easily modifiable precursor polymers, such as four-arm PEG, allows for subsequent modulation of the resulting hydrogel to achieve more advanced properties (unless there is evidence that such a polymer does not meet the minimum requirements for the given application). The base polymer defines many of the opportunities and limitations of the hydrogel, including the dominant chemical interactions between the polymer, water, cells, solutes and interfaces as well as the available variations to the network structure and therefore physical properties of swelling, stiffness and physical transport[12,31]. Base polymers can also contain bioactive properties (for example, natural polymers) or stimuli-responsive features (for example, pH-responsive polymers); however, such properties can also be separately introduced as modular features. Each natural or synthetic polymer has specific advantages and limitations[160]: for example, self-assembling peptide hydrogels have distinct bioactive properties[161] but are expensive and difficult to translate, validate and scale-up, compared to synthetic polymers. In addition, advantages conferred by unusual base polymers may also be introduced in the modular design phase.

Network structure design

The swollen polymer network model can then be applied to quantitatively predict how the hydrogel's structural parameters should be manipulated to optimize physical properties for the desired application. The model uses four independent, synthesis-controlled structural parameters (initial polymer volume fraction, degree of polymerization between junctions, junction functionality and frequency of chain-end defects) as well as polymer-specific identity parameters to predict the resulting hydrogel formulation's swelling and stiffness and the diffusivity of small solutes within the hydrogel[12,13,31–34]. The model's structure–function predictions correlate with the measured effects of changing structural parameters, and predictions are usually accurate to an order of magnitude.

The swollen polymer network model is particularly useful as a first-pass predictive design model. Furthermore, the model is derived from physical mechanisms without phenomenological fitting parameters[12], and each comparison with real data provides opportunities to test the assumptions used in the model, making it an evolving tool that will improve in breadth and accuracy with more data on the structure and physical properties of diverse hydrogel formulations[31,32]. Thus, an improved model may be able to address additional physical

Box 2

Managing modular hydrogel datasets

Model-driven, modular hydrogel design benefits from large, standardized datasets that relate a hydrogel's structural design to its measured properties. Such datasets provide evidence to identify the limitations of the models, validate assumptions made in the models, and revise the models if measurements deviate from predictions. However, collaboration across laboratories is needed to compare model predictions across a variety of hydrogel systems. For example, by coordinating swelling studies, it was shown that poly(vinyl alcohol) (PVA) and poly(ethylene glycol) diacrylate (PEGDA) hydrogels share structure-swelling trends, whereas the network structure and swelling behaviour of helix-forming gelatin methacrylate hydrogels have a more complex relationship[31].

Moreover, common definitions of structural parameters and swelling properties across hydrogel systems aid in evaluating consistent behaviours despite differences in polymers and network-forming reactions. Although it is possible to retroactively extract consistent properties from non-standardized data, concerted efforts to use standardized properties will accelerate comparison with model predictions, thereby improving hydrogel design models. Thus, reports on hydrogel designs should include the details of hydrogel formulations and physical properties[31,32]. Ideally, these datasets contain data on the formulation and physical properties that are not biased by association with a specific model (for example, reporting mesh size data is less valuable than reporting the diffusion coefficient of a specific solute within a hydrogel formulation, because mesh size is an indirectly measured value dependent on many structural assumptions). Well reported and accessible data will allow for re-evaluation of hydrogel design models to reduce bias and improve designs.

properties, including the fracture energy of a hydrogel and the partition coefficients of solutes into a hydrogel[33].

Incorporation of modular properties

The polymer and network structure establish the foundation of the hydrogel. Modular properties can then be added, removed, replaced or combined to achieve bioactivity, dynamics and responsiveness. For example, tissue culture scaffolds and wound dressings can be engineered using multi-arm PEG hydrogels, in which the same functional groups that form the network can be conjugated to cysteine-containing integrin-binding peptides (for example, RGD)[57,59]. Moreover, any peptide containing two cysteines can serve as the dithiol molecule connecting the PEG precursors, which allows the integration of bioactive features, such as matrix-metalloproteinase-cleavable sequences for cell-driven matrix degradation or sequences degraded by other enzymes for artificially induced degradation[141]. In addition, functional pendant groups can be modularly adapted for a variety of specific interactions with biological solutes or cells, including anti-inflammatory and immunomodulatory effects[4,150,162,163].

Modular dynamic behaviour can be introduced to hydrogels by modifying the functional groups that connect the network. For example, reversible covalent bonds, metal–ligand coordination and host–guest interactions provide dynamic linkages for hydrogels, adaptable to a variety of relaxation times[75]. Furthermore, dynamic covalent chemistries, electrostatic interactions and supramolecular interactions can be leveraged for dynamic adhesive interactions[77]. These diverse binding mechanisms facilitate adhesion between gels, to soft and hard tissues, and to specific binding targets.

Modular responsive properties can be similarly introduced, for example, by copolymerization or grafting of stimuli-responsive polymers, such as pH-responsive acrylic acid and 2-(diethylamino)ethyl methacrylate (DEAEMA), or temperature-responsive *N*-isopropyl acrylamide[70]. Force- and light-responsive hydrogels, achieved by linkage chemistry or photosensitive protein activation[63,64,154,164], provide platforms with which to control the evolving environments of cell culture. In addition to altering core network components, nanoparticles can be incorporated into networks either by tethering or as network junctions. Incorporated nanoparticles can independently drive responsive behaviour of the network[104].

Such modular systems can also be combined, although the complexity of their modelling and prediction may increase. Examples include interpenetrating networks[165], multi-copolymer networks, networks with multiple junction types (for example, a balance of stable and dynamic linkages)[166], multi-phase hydrogels with distinct functional components[167], and the integration of force-revealed cryptic peptides that promote specific bioactive interactions under high strain, reflecting the behaviour of many components of the extracellular matrix[168,169]. Combining modular systems, however, requires a fundamental framework that isolates the effects of individual modular properties and includes intermediate, mechanistic controls. Here, a 'less-is-more' approach may be beneficial, identifying the simplest hydrogel system that achieves the application-driven requirements to maximize translatability and minimize uncertainty about the system. We note that modular changes may also disrupt and invalidate predictions about network physical properties and, therefore, care should be taken to characterize and re-evaluate the physical network properties before and after incorporating modular properties. Ideally, models should account for the independent and composite effects of the modular hydrogel properties, further reducing the uncertainty associated with this stage of hydrogel design.

Evaluation and iteration

Finally, the hydrogel design needs to be evaluated and iterated towards the next version. Following design, synthesis and characterization, application-based criteria should be re-assessed and specific optimization steps and challenges should be identified. In addition, the models and assumptions used in the design process should be re-evaluated. Each new hydrogel formulation, including variations of structural parameters, provides the opportunity to validate or refine the models of hydrogel design, in particular, in conjunction with publicly available data.

Outlook

Model-based modular hydrogel design coordinates fundamental structure–property relationships and modular hydrogel synthesis to address multifaceted biomedical applications. Key challenges for this strategy include refining and connecting theoretical models to predict more of the relevant properties for hydrogels and validating these models with a diverse dataset of well characterized hydrogels. Standardizing terms across the field of hydrogel design, prioritizing broadly applicable structural parameters and consistently measurable properties will help to assemble large datasets and refine the models. Model-based modular hydrogel design has the advantage of using explicit mathematical models accountable to specific structure–property interactions, so that further hypotheses can be derived from those predicted relationships to continuously refine the models.

A current major barrier to predictable bioactive hydrogel design is the non-linear collapse of polyelectrolyte hydrogels, such as alginate, when exposed to increasing concentrations of multivalent ions, such as soluble calcium[170]. More advanced mathematical approaches are needed to integrate the interactions of polyelectrolyte gels and multivalent ions into a comprehensive swollen polymer network model, which is crucial to biomedical applications, because calcium ions are ubiquitous in physiological solutions and many biopolymers include ionized groups. In addition, newly developed hydrogel properties need to be parsed into modular components that can be widely applied, similar to bioactive components of the extracellular matrix that have been isolated as integrin-binding peptides and as matrix-metalloproteinase-degradable peptides, which can be incorporated into synthetic hydrogels. In addition, the effects of degradation and fatigue on network structure and physical properties should be fully model-predictable, because both changes can be structurally defined as increases in the frequency of chain-end defects.

As the field progresses, robust validation of how incorporating individual modular components in a hydrogel affects other properties will lay the groundwork for predictively designing application-ready hydrogels with multiple modifications that may interact with each other. By providing a framework that optimizes insights from fundamental hydrogel research toward meeting multiple biomedical requirements, model-based modular hydrogel design will overcome bottlenecks in the clinical application of hydrogels.

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