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Biological Hydrogels as Selective Diffusion Barriers

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Abstract

The controlled exchange of molecules between organelles, cells, or organisms and their environment is critical for life. Biological gels such as mucus, the extracellular matrix or the biopolymer barrier within the nuclear pore are well suited to achieve such a selective exchange, allowing for the passage of certain molecules while rejecting many others. Although hydrogel-based filters are integral parts of biology, clear concepts of how their barrier function is controlled on a microscopic level are still missing. Here, we summarize our current understanding of how selective filtering is established by different biopolymer-based hydrogels. We ask if the modulation of microscopic particle transport in biological hydrogels might be based on a generic filtering principle, which employs biochemical/biophysical interactions with the filtered molecules rather than size exclusion effects.

Keywords

biological hydrogels; microscopic filtering; mucus; nuclear pores; extracellular matrix; biofilms

Biological hydrogels

Biological hydrogels are networks of protein-polysaccharide chains that typically contain 90-99% water. They surround biological functional entities such as cellular compartments, distinct cells, tissues or organs. Past research has mostly focused on the mechanical characteristics of biological gels. These gels can cover a wide spectrum of material properties, ranging from relatively soft and viscous-like to highly elastic. Indeed, biological hydrogels establish and regulate the mechanical properties of cells and tissues[1, 2] and serve as lubricants in joints or on epithelial surfaces[3-5].

However, the physiological role of biological gels is not limited to their mechanical performance. They can also form selective barriers, which control the exchange of molecules between different compartments. In environments where biological hydrogels serve as diffusion barriers, they are often associated with a lipid bilayer (Fig. 1). The selective permeability properties of lipid bilayers have been extensively studied in the last century[6, 7]. However, little is known about the structure and dynamics of the associated hydrogels and how their properties allow them to act as selective barriers that permit passage of certain objects but reject others.

The extracellular matrix in the connective tissue of mammalians mediates cell adhesion and proliferation[8] and regulates the distribution of proteins, growth factors, ions and drugs[9, 10], which is necessary for successful communication between distinct cells (Fig. 2A). Similarly,

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the basal lamina creates an envelope around blood vessels, controls the exchange of material between the bloodstream and the tissue and governs angiogenesis[11].

The mucus layer of wet epithelia (Fig. 2B) not only serves as a lubricant, but also acts as our body's first line of defense against pathogens, aids in the adsorption of nutrients to facilitate their uptake by the epithelium, and and changes its properties to enable sperm migration through the gel during ovulation[12, 13]. The selective permeability properties of mucus have a critical role in health and disease. Alterations in mucus permeability can result in severe problems ranging from viral and parasitic infections, and cystic fibrosis[14, 15], to some forms of infertility due to a failure of the sperm to migrate through the female genital tract.

The nuclear membrane in eukaryotic cells constitutes a major barrier that regulates the exchange of macromolecules between the nucleus and cytoplasmic compartments[16]. The exchange of material occurs through nuclear pore complexes[17], large macromolecular assemblies that are filled with polymers and permit passage of specific nuclear transport receptors, but reject the majority of cytoplasmic proteins (Fig. 2C).

Extracellular matrix, mucus and nuclear pore complexes may seem very different with respect to their composition and function. Yet, all three systems are based on hydrogels that act as diffusion barriers by allowing the passage of some types of macromolecules, while rejecting many others. Here, we highlight the mechanisms that govern selective filtering in these three hydrogel-based filters. We point out similarities and differences in their filtering mechanisms, and relate them to structural key components of these biological hydrogels. Our intention is not to provide a detailed review of each gel system, for this we refer the reader to excellent reviews of the respective subjects. Instead, we will discuss selected gel features that contribute to our understanding of the mechanisms governing selective filtering.

Design strategies for a biopolymer-based permeability filter

A permeability barrier could discriminate molecules either by size or by surface properties. In the first case, the mesh size of the hydrogel (Box 1) defines a molecular size cut-off: objects with dimensions larger than the mesh size will be rejected, while smaller objects are allowed to pass (Box 2, Figure IIA). One drawback of size exclusion is its relatively low flexibility, since it cannot further distinguish between small particles below the cut-off. A second and independent principle of microscopic filtering might be necessary to overcome this limitation.

Interactions of molecules with the biopolymers of the hydrogel could serve as such an additional filtering mechanism. In this scenario, the surface properties of molecules would constitute the relevant selection criteria. Particles with certain surface properties might engage in strong interactions with the hydrogel polymers and thereby get trapped, whereas molecules with different properties might be able to escape retention and thus efficiently diffuse within the hydrogel. Such an interaction filter would select particles more or less independently of their size: it could trap even particles that are much smaller than the mesh size, while allowing larger ones to pass (Box 2, Figure IIB), provided that their size is still smaller than the size cut-off of the hydrogel.

In biological systems, size and interaction filtering are probably not mutually exclusive, as size exclusion is a mechanism that cannot be avoided. In the following, we discuss the extent to which biological hydrogels harness either size and/or interaction filtering strategies to regulate their microscopic permeability.

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Regulation of diffusion in the extracellular matrix

The extracellular matrix in the connective tissue or the basal lamina (ECM, Fig. 2A) is a hydrogel, which consists of a collection of different protein and proteoglycan polymers, including tenascin, laminin, vitronectin, fibronectin and collagens[18]. The exact composition of the ECM varies, depending on the physiological context. The ECM polymers can interact with each other to form a cross-linked gel, and sometimes cross-linking is performed by additional molecules such as nidogen/entactin[19].

Several studies suggest that the ECM traps particles mostly by size exclusion. For instance, the composition of the ECM in tumor tissue is altered, and at the same time, small test molecules show reduced diffusivity. It was suggested that this reduction in permeability arises from the increased biopolymer content in the extracellular space[18]. Size filtering as a key strategy for permeability regulation for the ECM has also been proposed on the basis of experiments obtained from reconstituted ECM gels[20, 21].

Numerous other studies, however, challenge the concept of size filtering for the ECM and suggest interaction filtering as an additional, if not primary, mechanism. For example, studies in brain extracellular space show that the microscopic mobility of small and large molecules is comparable, while selected molecules in the same size range sometimes show stronger impediment in their diffusive behaviour[22, 23]. Moreover, enzymatic degradation of the ECM proteoglycan decorin[23], or the glycosaminoglycan heparan sulfate[24, 25], can alter the diffusion behaviour of microscopic particles. Decorin and heparan sulfate represent only a few percent of the total biopolymer content in the respective hydrogels; therefore, their enzymatic degradation should only have a minor effect on the size cut-off of the hydrogel. If a significant change in the hydrogel mesh size is unlikely to occur, which other mechanism could explain the changes in hydrogel permeability after enzymatic removal of decorin and heparan sulfate?

One possibility is that decorin and heparan sulfate can delay the passage of diffusing molecules by directly interacting with them. Both decorin and heparan sulfate carry a negative net charge, and growth factors such as Fibroblast Growth Factor (FGF) can bind to decorin and heparan sulfate, as well as to other components of the ECM[26]. The binding interaction of FGF with the ECM components becomes stronger with increasing charge density on the heparan sulfate chains[27, 28], which, in turn, is set by the degree of sulfation of the heparan sulfate. Moreover, the mobility of a molecule within the ECM correlates with its interaction strength with heparan sulfate chains[29, 30]. High salt concentrations as well as the formation of electrostatically neutral complexes with other molecules such as heparin or protamine sulfate can rescue the mobility of otherwise trapped particles[25, 29]. Together, these findings suggest that the permeability of the ECM can be modulated by electrostatic interactions between the ECM biopolymers and diffusing particles/molecules.

Control of translocation through mucus hydrogels

Mucus is a glycopeptide gel that coats all wet epithelial surfaces in our body (Fig. 2B) including the oral cavity, the airway, and the gastrointestinal and urogenital tracts. Depending on the epithelia that mucus covers, its thickness can vary between 10-700 μm[13], which might be linked to the different functions mucus can assume, ranging from a mechanical lubricant to a protective diffusion barrier. “Old” mucus that has trapped molecules and pathogens is excreted via the gastrointestinal tract. At the same time, our body continuously replenishes the mucus barrier by secreting fresh mucus on the epithelial surfaces.

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The gel-like properties of mucus are brought about by the mucins, macromolecular glycoproteins which form by oligomerization[3, 31] and can have molecular weights up to several hundreds of kDa. Mucins consist of a protein backbone, which in some regions is densely glycosylated with complex oligosaccharide structures[31, 32]. As a consequence of their dense glycosylation, mucins acquire a brush-like structure. At least 16 members of the mucin polymer family have been identified so far, which can be categorized as either secreted or membrane-bound mucins[3, 33].

It might be tempting to assume that size filtering is an appropriate framework for the description of mucus permeability. Indeed, experiments on sputum mucus support the idea of size filtering as they report a decrease of particle mobility with increasing particle size[34]. Yet, the opposite effect is observed in cervicovaginal mucus, in which small, strongly negatively charged particles (100 nm) are less mobile than larger, neutral particles (200 nm and 500 nm)[35], suggesting alternative mechanisms to size filtering. Considering that one main task of mucus is the formation of a barrier towards infectious agents, it is noteworthy that the average mesh size in cervicovaginal mucus is on the order of 300-400 nm, and thereby significantly larger than the typical size of mucosotropic viruses[36]. Thus, also inside mucus, other filtering principles besides size exclusion appear to govern the permeability of the barrier.

In cervical mucus, the mobility of charged microspheres can be enhanced by coating the particles with the inert polymer poly(ethylene glycol) (PEG)[37-39], thus avoiding ‘mucoadhesion’. One might speculate that the sugar chains of the mucin glycoprotein are critical for this mucoadhesive effect, and that a loss of these sugars might compromise the barrier function of mucus hydrogels. However, experimental data on this particular problem are still missing.

Experiments with both native and reconstituted mucus hydrogels have shown that the strength of selectivity of a mucin hydrogel can be modulated by pH. For example, negatively charged HIV viruses are trapped in acidic cervicovaginal mucus, but not at neutral pH[40]. Similarly, at low pH, the mobility of charged, but not neutral particles[41] is suppressed in reconstituted mucin gels. In contrast, at neutral pH, both charged and neutral micron-sized particles behave similarly and diffuse almost freely within reconstituted mucus. Trapped particles can regain mobility in mucus if heparin[42] or high salt concentrations[41] are added to the hydrogel. Together, these experiments suggest that the filtering principles of mucus may in part be governed by electrostatic interactions between the mucin polymers and diffusing particles. It appears that the strength of this interaction, and thus the filtering specificity, is regulated by the charge states of the polymer or the particle surface. These charge states, in turn, are sensitive to pH, as they depend on the protonation levels of the amino acids, and the linked sugar moieties can add additional charges.

The sensitivity of the mucus barrier to pH is exploited by the body, for example, during ovulation, when the pH level of cervical mucus is temporarily raised to neutral conditions[43], or when the acidic pH of cervical mucus is neutralized by seminal fluid during intercourse[44], allowing for the effective penetration of sperm cells through mucus. This temporary increase in permeability may come with a price, as it could present a window of opportunity for pathogens to penetrate the mucus barrier. Also, certain pathogens take advantage of the possibility to change the permeability properties of mucus by altering the pH. For instance, *Helicobacter pylori* locally perturbs the physiological pH conditions of gastric mucus, thus compromising its barrier function and enabling the bacteria to navigate in the stomach mucosa[45].

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Exchange of material through the nuclear pore

Nuclear pores are filled with a hydrogel that is highly selective and allows rapid translocation only for a certain subset of molecules known as nuclear transport receptors, whereas efficiently hindering free passage of the majority of other cellular molecules[46-48]. The permeability barrier within the nuclear pore is constituted by a subset of nucleoporins (Fig. 2C), which typically contain a series of phenylalanine-rich repeats (FG-repeats) separated by largely unfolded and hydrophilic spacer sequences. Minimal model systems reconstituted from peptides containing FG-repeats were able to reproduce the specific permeability properties of native nuclear pores[49, 50].

The permeability properties of the nuclear pore complex are puzzling: some relatively small proteins such as histones or ribosomal proteins with sizes in the range of 15 – 21 kDa are unable to pass the nuclear pore efficiently by themselves[51, 52], whereas much larger nuclear transport receptors (90 – 200 kDa) can rapidly enter the nucleus[46, 53]. This paradox already indicates that a size filtering mechanism[54] cannot fully explain the selectivity of the nuclear pore complex, and suggests that other molecule properties serve as criteria for selective translocation.

Indeed, by directly comparing the nuclear uptake of two proteins with equal hydrodynamic dimensions, it has been visualized that selection for transport through the nuclear pore can occur independently of size. Whereas the transport receptor NTF2 (30 kDa) fully equilibrates between nucleus and cytoplasm within a few seconds, GFP (28 kDa) enters the nucleus ~100fold slower than NTF2[55].

One hallmark of translocation competent molecules is their high degree of hydrophobicity[55-60]. Indeed, current mechanistic models of nuclear translocation mainly describe the contribution of hydrophobic forces and entropic effects to the translocation process[61]. However, a closer inspection of translocation competent proteins reveals that also electrostatic interactions may contribute to the pore selectivity. Whereas translocation-competent molecules are characterized by a negative net charge, the polymers constituting the nuclear pore barrier carry positively charged groups[60], which are present in unfolded hydrophilic domains that separate FG-repeats. This positive portion of the polymers is conserved across multiple species and has been postulated to contribute to the filtering process by sieving proteins of opposite charge by means of electrostatic interactions.

Electrostatic sieving may help the NPC to control the entry of particles according to their surface charge, independently of their size. This is illustrated with the example of histones, relatively small proteins that cannot diffuse efficiently through the pore channel by themselves. Owing to their positive charge, those proteins encounter a high energy barrier when entering the nuclear pore. However, by binding to their transport receptors, importinb and importin7, histones can acquire a negative net charge and become translocation competent[51]. A future challenge will be to implement electrostatic interactions into the current picture of nuclear transport.

Regulation of diffusion in other biological hydrogels

One further example of a biological, polymer-based filter is found in bacterial biofilms. Many bacteria secrete and surround themselves with extracellular polymeric substances, a mix of polysaccharides, proteins, lipids, and nucleic acids[62]. A community of bacteria embedded in extracellular polymers is referred to as a biofilm (Fig. 2D). Biofilms can form on many types of surfaces including teeth, ship hulls, and pipes, and they can also contaminate foreign body materials such as contact lenses, catheters, and implants[63]. Biofilms appear to efficiently shield the bacteria from antibiotics[63, 64], detergents and

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disinfectants[65], but still allow for the penetration of nutrients and their accumulation in the biofilm matrix[62].

In general, the diffusive motion of molecules is delayed by the biofilm polymers compared to free diffusion in water[66]. This delay is more pronounced with increasing biofilm biomass. However, within the biofilm matrix, small charged molecules are sometimes less mobile than larger neutral solutes[67]. This effect is mainly attributed to bacterial exopolysaccharides such as alginate or gellan gum[68], and is thought to originate from electrostatic interactions between positively charged diffusing molecules and negatively charged biofilm biopolymers. Similarly, the penetration of antibiotics into biofilms is hindered for positively charged aminoglycosides whereas other antibiotics of similar size can efficiently enter the biofilm matrix[69, 70]. Together, these studies indicate that electrostatic binding interactions with the matrix biopolymers also contribute to the permeability control in bacterial biofilms, and that this mechanism may play an important role for the resistance of many biofilm forming bacterial strains toward certain antibiotics.

Interaction filtering strategies might also apply to the vitreous humour, the hydrogel in the mammalian eye, which molecules have to penetrate to reach the retinal cells (Fig. 2E). The main components of vitreous humour are collagens and anionic glycosaminoglycans such as hyaluronic acid, chondroitin sulfate and heparan sulfate[71]. Also the permeability properties of the vitreous humour are selective; some antibiotics can penetrate the vitreous humour while others are blocked[72]. Similarly, the diffusion of certain small dyes is delayed in the hydrogel, whereas others, although similar in size, are able to diffuse freely[73]. This suggests that, also in the ocular hydrogel, interaction filtering strategies contribute to the microscopic regulation of diffusion. However, systematic studies on the permeability properties of the vitreous humour are still missing.

Concluding remarks

We have discussed how biological hydrogels such as the extracellular matrix, mucus, the nuclear pore hydrogel, bacterial biofilms, and the vitreous humour harness interaction filtering principles in order to regulate their microscopic permeability. In all these gels, size filtering effects as imposed by the microarchitecture of the hydrogel need to be considered as well. However, given the relatively large mesh sizes of the hydrogel systems discussed here, geometrical hindrance effects will be less important for the diffusion behaviour of molecules or particles smaller than the hydrogel size cut-off.

It appears that the detailed microscopic forces responsible for controlling the diffusion of molecules or particles in biological hydrogels depend on the particular hydrogel system (Box 2). In principle, one can imagine that electrostatic forces, hydrophobic forces, hydrogen bonds and specific binding interactions might be equally suited to achieve a selective accumulation of molecules in a hydrogel matrix. Such a selective accumulation of molecules might not only serve the purpose of regulating the translocation of particles through hydrogel barriers, but could also be a key mechanism for creating and maintaining gradients, and localizing signalling molecules (Box 3).

Both size and interaction filtering possess their own intrinsic advantages and disadvantages. A size filter is relatively easy to construct as the only parameter cells need to control is the density of the hydrogel polymers. On the other hand, size filtering may not be selective enough since all particles below a certain cut-off size will be allowed to pass the hydrogel. In contrast, biopolymers offer the possibility to tune their interaction with diffusing particles by adjusting the biochemical substructure of the individual biopolymers. One might imagine that this could be realized more or less independently of the mechanical properties of the biopolymer and thus the hydrogel. Conversely, the surface properties of proteins can be

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transiently altered by post-translational modifications, or by the formation of complexes with transport mediators. Surface modifications might be a fast and efficient way to reversibly tune the interaction strength of the molecule with the hydrogel and could thus provide a key mechanism for regulating molecular transport inside the gel.

Even though the biochemical composition and physiological roles of distinct biopolymer based hydrogel filters may differ from each other, the microscopic principles, which govern their selectivity, seem to follow a generic principle. Employing biophysical interactions with the filtered objects offers a broader range of permeability control than it would be achievable with size filtering strategies alone.

Further exploring the microscopic barrier function of biological hydrogels, a comparison to engineered synthetic hydrogels, and insights from theoretical modelling, might allow for the rational design of biomimetic materials that can mimic the barrier function of their biological counterparts (Box 4). In principle, the application of a polymer based hydrogel filter is not limited to biomedical problems, but could also be employed by any field that relies on the sorting of molecules or other nanoscopic particles.

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Box 1

Probing the local microenvironment in hydrogels

Hydrogels are mainly constituted by water, which fills the space between the hydrogel polymers. The average distance between distinct polymer strands is referred to as the hydrogel mesh size. In cases where the total polymer concentration and the length of individual polymer strands are known, this mesh size can be estimated mathematically. An exact measurement of hydrogel mesh sizes is, however, difficult to achieve. Hydrogel pore sizes as obtained from the analysis of electron micrographs are prone to artefacts that arise from the necessity to stain the hydrogel biopolymers with contrast-enhancing heavy metals or from the structural collapse of the hydrogel upon its processing required for electron microscopy. Therefore, particle tracking techniques[74, 75] are commonly used to probe the local microenvironment of hydrogels[3, 76] and a size cut-off is determined from the abrupt change in the transport behaviour of tracer particles with different sizes[36] (compare Fig. IA and C). However, the mesh size values obtained by this method may depend on many parameters including the shape, mechanical rigidity and surface modification of the tracer particles used[77, 78]. Both geometrical constraints and, in the case of non-inert particles, also binding events with the biopolymers can retard the diffusion of molecules (Fig. IB and C). Ideally, rigid and completely inert tracer particles are used for mesh size measurements (i.e. particles that show no binding interactions with the hydrogel components). Only such inert particles will be able to fully explore their microenvironment inside the hydrogel and thus report the correct mesh size.

Inside a hydrogel mesh, the local viscosity an inert diffusing particle encounters is typically close to the viscosity of water or buffer, depending on what liquid is used to hydrate the biopolymers. This microviscosity of a hydrogel should not be confused with the viscous modulus that is, for instance, obtained from diffusion measurements with particles that are larger than the hydrogel mesh size (Fig. IC), or from macroscopic shear rheometry. These techniques report a meso- or macromechanical material property of the hydrogel network from which the local diffusion behaviour of particles or molecules cannot be derived. For details on this particular problem we refer interested readers to [3] and [78].

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Box 2

Possible filtering mechanisms in biological hydrogels

Hydrogels can employ two generic strategies to trap molecules or particles and thereby modulate their diffusion behaviour (Figure II):

A. *size filtering*: the density of hydrogel polymers defines a molecular size cut-off above which the diffusion of particles is geometrically restricted.

B. *interaction filtering*: molecules that engage in strong binding interactions with the hydrogel polymers become trapped in the hydrogel matrix independent of their size.

Interaction filtering strategies seem to contribute to the filtering properties of

a) extracellular matrix	– type of interaction: electrostatic
b) mucus hydrogels	– type of interaction: electrostatic
c) nuclear pore hydrogels	– type of interaction: hydrophobic/electrostatic
d) bacterial biofilms	– type of interaction: electrostatic

In addition to electrostatic and hydrophobic forces, hydrogen bonds and specific binding interactions might also be used to establish attractive interactions in biological hydrogels.

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Box 3

Interaction filtering strategies establish extracellular microenvironments

Binding interactions between hydrogel polymers and diffusing molecules might not only be useful for regulating the exchange of material between different compartments, but could also contribute to several other biological processes that are associated with biopolymers (Figure III). For example, binding interactions with the extracellular matrix polymers could be the basis to establishing and maintaining gradients of growth factors in the connective tissue. Trapping molecules inside the mucus hydrogel matrix might help enrich the intestinal mucosa with nutrients for efficient uptake into the blood stream. Interactions with extracellular polymers in bacterial biofilms could play a role in quorum sensing by shaping the range and distribution of secreted or incoming quorum sensing molecules.

Independent of their location, the tunability of binding interactions should allow for a controlled release of stored molecules upon demand when those interactions are weakened. This can be achieved by, for instance, posttranslational modifications of protein surfaces, or by changing the local pH or salt concentration in the case of electrostatic interactions or, more generally, by the formation of non-interacting complexes (e.g. with transport receptors), as is the case in nuclear transport.

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Box 4

Outstanding questions

- Which types of binding interactions/molecular forces regulate the selective trapping of molecules in biological hydrogel barriers?
- How do combinations of interactions, for example electrostatic and hydrophobic, affect the translocation of particles?
- What are the biochemical substructures in biological hydrogels that establish selective binding interactions?
- Which role does protein glycosylation play in the selective filtering of biological gels?
- How does the human body adjust the permeability of hydrogel barriers?
- Do binding interactions also contribute to the regulation of other biological processes that are associated with biological hydrogels?

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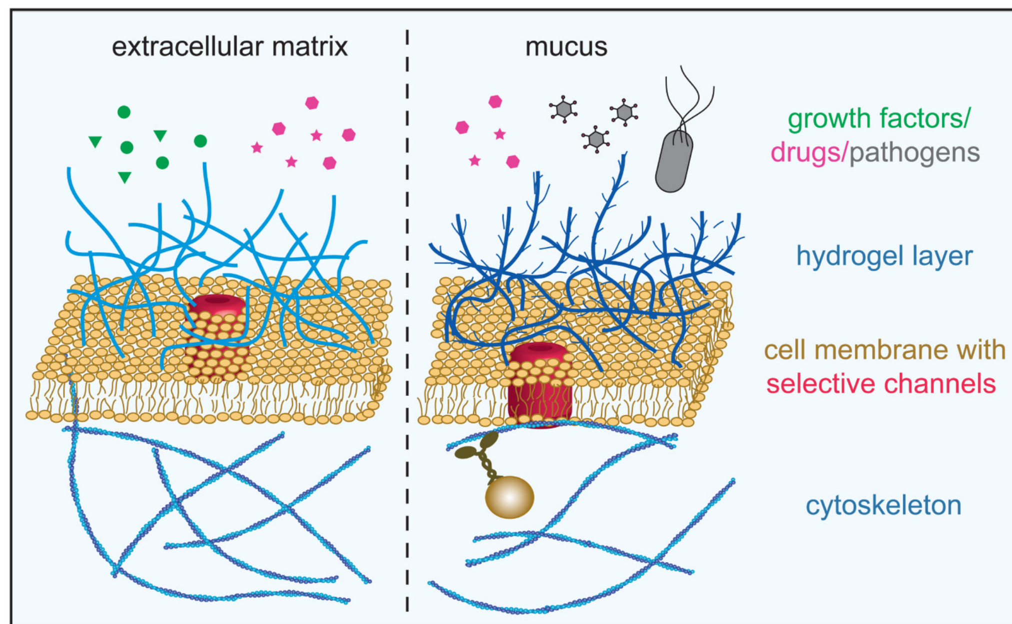

Figure 1.
The cell membrane/hydrogel barrier. Eukaryotic cells are surrounded by a plasma membrane, which mediates both compartmentation and the exchange of material with the extracellular space. This plasma membrane is typically externally coated with a hydrogel such as the extracellular matrix or mucus, which provides an additional permeability barrier. For example, extracellular hydrogels can prevent molecules or microscopic particles such as viruses or bacteria from reaching the plasma membrane. The detailed microscopic mechanisms by which macromolecules or pathogens are retained by biological hydrogels are still poorly understood.

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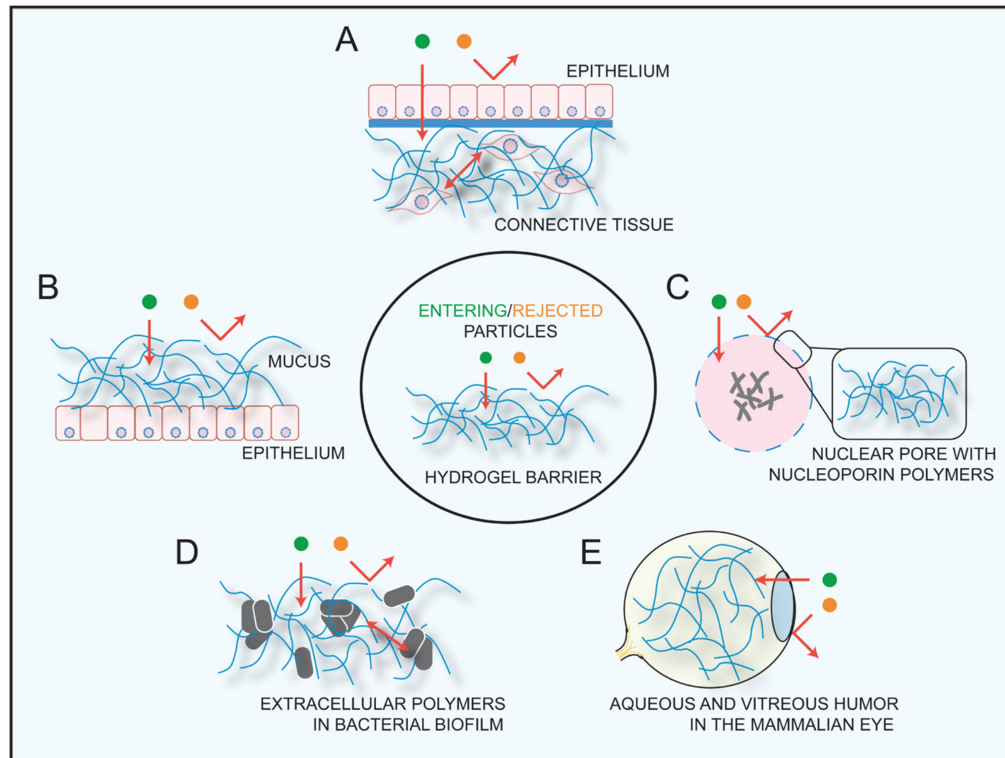

Figure 2.

Biopolymer based hydrogels control the translocation of microscopic objects and act as selective permeability filters. They allow the passage of certain molecules (green) whereas rejecting others (orange). (A) The epithelium is lined with a layer of mucin polymers, which form a hydrogel that shields the underlying cell layer from infectious agents such as viruses or bacteria. (B) Extracellular matrix systems such as the basal lamina or the connective tissue regulate the passage of molecules to and from the blood stream or between cells. (C) Nuclear pores are filled with nucleoporin polymers, which regulate the import and export of proteins into or out of the nucleus. (D) In bacterial biofilms, extracellular polymers effectively shield the bacteria from antibiotics while allowing nutrients to enter the biofilm. (E) The vitreous humour in the mammalian eye allows the penetration of certain antibiotics while blocking others.

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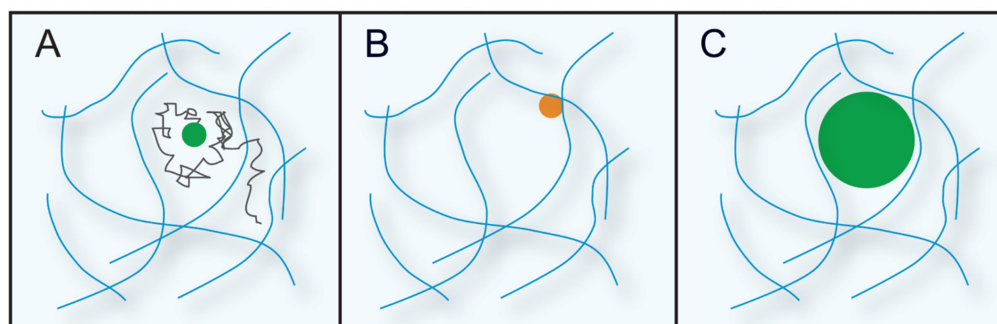

Figure I.

Microscopic particles can probe different hydrogel parameters. (A) Inert particles (green) that are small enough can diffuse inside the hydrogel matrix where they experience a local viscosity that is mainly dictated by the hydrogel solvent. (B) Particles that bind to hydrogel components (orange) will not be able to fully explore the local microenvironment and thus cannot report the correct hydrogel mesh size. (C) Large particles that are geometrically trapped in the hydrogel mesh will report the local viscoelasticity of the hydrogel and thus provide mechanical information about the hydrogel rather than probing its microstructure.

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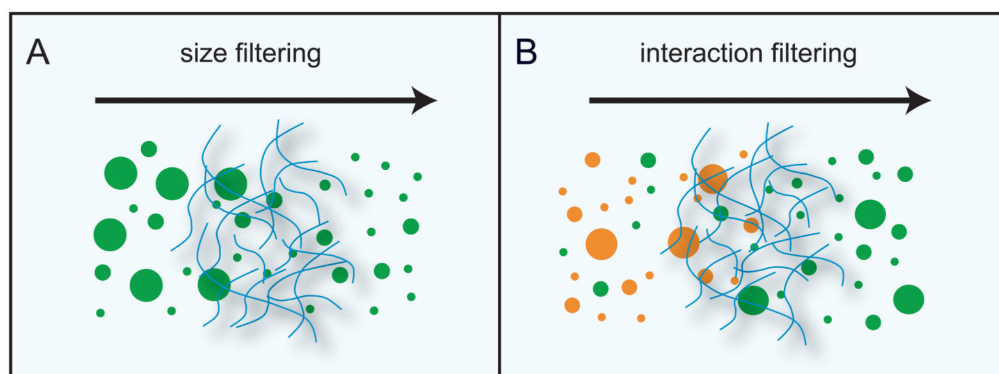

Figure II.
Two generic filtering principles can be employed by biopolymer based hydrogels: (A) Size filtering allows particles that are smaller than the cut-off size of the hydrogel to pass while larger objects are rejected. (B) Interaction filtering allows for distinguishing particles according to their surface properties: A subset of particles (orange) strongly interacts with the polymer matrix of the hydrogel and is trapped, while other particles (green) show only weak interactions and thus are allowed to pass.

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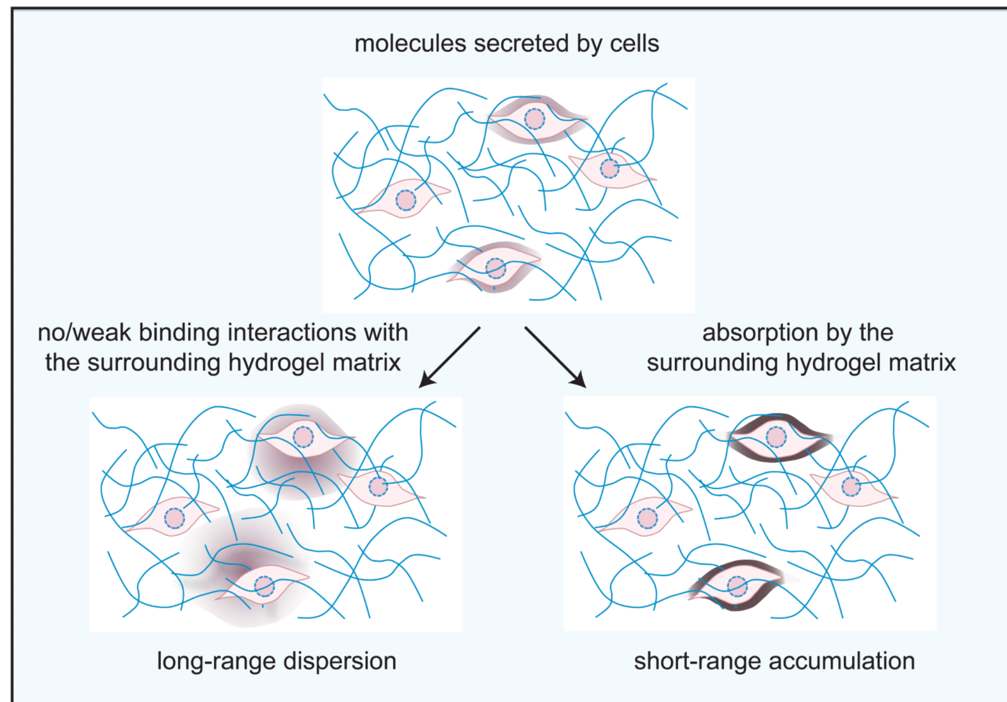

Figure III.
Binding interactions of diffusing molecules with hydrogel polymers could help establish and maintain gradients. In the absence of such interactions with the hydrogel, locally secreted molecules such as signalling molecules or growth factors would quickly spread by diffusion and cover a large area around the source cell. In contrast, when those molecules are trapped in the surrounding hydrogel polymer matrix by absorption events, they can locally accumulate and form a gradient. If those binding interactions are weakened, these gradients can be dissolved and the stored molecules are released without requiring enzymatic degradation of the polymer matrix.