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Bioresponsive DNA-co-polymer hydrogels for fabrication of sensors

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ABSTRACT

Bioresponsive hydrogels that include DNA within a non-DNA network (DNA-co-polymer hydrogels) constitute a group of soft materials possessing selective recognition ability hosted by the included DNA structure. They are furthermore characterized by the changes to the hydrogel properties which follow the recognition of the biological analyte. Such hydrogels can be synthesized with desired recognition ability through the selection of particular nucleotide sequence that is recognizing or binding ions, small molecules, biomolecules or parts of larger entities. The binding of the label-free analyte triggers a response of the hydrogel, such as changes in its swelling volume, mass, optical or mechanical properties. The hydrogel response is mediated by changes in network parameters such as charge density, crosslinking density or a combination of these associated with the interaction with the analyte. Bioresponsive DNA polymer hydrogels have found wide application in biosensors due to their versatile nature.

1. Introduction

In nature, nucleic acids are essential molecules in carrying genetic information, responsible for its transmission and translation. The hereditary functionality of nucleic acids was demonstrated more than 70 years ago, and has been widely penetrating the field of molecular biology since then. The facts that DNA adopts a double helical structure stabilized by the base-pair (bp) couples A and T and G and C between the opposing strands; that the two single-stranded constituents are antiparallel; and that the helix is topologically linear; are key features in such a context. The field of DNA nanotechnology has evolved based on the versatility of the DNA molecular structure combined with the capability to synthesize specified bp sequences. Thus, molecular constructs such as tiles, lattices, origamis with vast variety of geometries, nanoscale cubes with locks that can be opened with specific cues, and dynamic structures, have been reported [1–5]. The field of DNA-co-polymer hydrogels, i.e. DNA structures integrated into non-DNA polymer based hydrogels has emerged in the past 20 years following the first report on end-attachment of oligonucleotides amino modified at their 5′ end to a water soluble synthetic (vinyl) polymer [6••]. The aim of this first report was to include single-stranded (ss), bp complementary oligonucleotides grafted to polymers so that they formed additional DNA-based non-covalent crosslinks. The temperature dependence of the hybridization and denaturation of complementary oligonucleotides was then reflected in the temperature dependent crosslinking density of the hydrogel. It was reported that hybridization of the oligodeoxythymidylate (oligoT) and oligodeoxyadenylate (oligoA) did occur in a cast film subsequently immersed in water. This first hybrid DNA-co-polymer study exploited the specific oligonucleotide hybridization reaction as an effector of thermo-sensitive crosslinker functionality of the hydrogel material. Following this initial study, various other functionalities as hosted by the DNA and structural transitions associated with the particular sequence and its recognition have been reported. Incorporation of DNA as the sensing moiety within hydrogels allows for detection of variety of biomolecules. The changes to the gel-bound DNA brought on by the external stimulus lead to a response of the hydrogel. This can include changes in the local structure, overall swelling volume and mass as well as altered mechanical and optical properties. The hydrogel response can be monitored with the use of an appropriate readout platform, thus exploiting the responsive hydrogel as the recognition and transducing functionality in a sensor. This field of DNA-co-polymer hydrogels and their applications are distinct from hydrogels made only of DNA, e.g., by chemical crosslinking of DNA to yield ionic hydrogels with their characteristic properties [7–9]. Although the hybrid DNA-co-polymer field is not as rich in structural DNA motives so far included in the DNA Nanotechnology field, there is an increasing versatility. Recent reviews of hybrid DNA-co-polymer field and mechanisms important for these [10–12], provide an extensive source of relevant literature. In the following account, we focus on hybrid DNA-co-polymers with potential for sensing applications, the design principles exploited to support the specific sensing, how the changes in the integrated DNA structures mediate physical changes affecting the hydrogel and how this can be monitored at the hydrogel level. This will be followed by a brief account of selection procedures for specific DNA sequences and possible alternatives to the DNA with potentially similar versatility.

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2. Hydrogels – handles to include DNA as transducing elements

Successful transformation of changes in a DNA higher order structures to a detectable change in the hydrogel which it is integrated into depends on details in how the DNA structure is included, how the DNA transforms into changes of the hydrogel and how this is determined. In the following, general aspects of transforming hydrogels to responsive hydrogels where changes in DNA higher order structures are mechanistic are outlined. The various effect mediators are outlined based on the Flory-Rehner-Donnan theory of hydrogel swelling, with critical network parameters to be exploited for DNA-polymer hybrid swelling responses. In this account, the equilibrium state is governed by zero total osmotic pressure (Π) of the hydrogel. The total osmotic pressure for the hydrogel swelling state is given by three contributions originating from different molecular mechanisms. The first contribution originates from mixing of solvent and the polymer (Π_{mix}), the second from the elastic retraction occurring on polymer chain deformation (Π_{elas}) and the third originates from concentration differences of ions ΔC_{tot} in the hydrogel relative to its immersing solution (Π_{ion}). Within this theory, the total osmotic pressure is given by [13–17]:

$$\begin{aligned}\Pi &= \Pi_{mix} + \Pi_{elas} + \Pi_{ion}\\ \Pi_{mix} &= \frac{RT}{V_1}\left(\ln\varphi_1 + \varphi_2 + \chi{\varphi_2}^2\right)\\ \Pi_{elas} &= \frac{\upsilon RT}{V_0}\left(\frac{\varphi_2}{2\varphi_{2,0}} - \left(\frac{\varphi_2}{\varphi_{2,0}}\right)^{1/3}\right)\\ \Pi_{ion} &= RT\Delta C_{tot}\end{aligned} \tag{1.1}$$

where R is the molar gas constant, T is the absolute temperature, V_1 is the molar volume of the solvent, φ_1 and φ_2 are the volume fractions of the solvent and polymer phase, respectively, χ is the Flory-Huggins interaction parameter for intersegment contacts, V_0 is the volume of the hydrogel in the reference state, and υ is the molar number of elastic active polymer chains in reference to volume fraction $\varphi_{2,0}$ of the hydrogel. The term ΔC_{tot} describing the difference in molar concentration of mobile ions between the gel and the immersing aqueous solution can be estimated exploiting the theoretical expression for the Donnan equilibrium governing the ionic balance and using the relevant information on the electrolytes and molecular parameters of the network as reported [13,15].

In swelling equilibrium, when the ionic hydrogel is immersed in a solution with its electrolyte content, the volume fraction φ_2 will adjust to yield zero osmotic pressure. Inclusion of DNA within a polymer network possessing DNA recognition capacity is typically carried out with a small fraction of DNA relative to the polymer it is connected to. Furthermore, it is designed in such a way that the specific recognition and binding transforms into a hydrogel response based on either one, or a combination of effects working through the additive contributions governing the equilibrium swelling state (Eq. (1.1)). A change in DNA-co-hydrogel swelling mediated by affecting the mixing term can possibly be carried out by binding of components with altered hydrophobic nature. Such changes in basic physicochemical properties associated with binding the DNA component of the hydrogel are less discussed in the literature.

The second term represents the elastic restoring force of the network, limiting the overall expansion of DNA-co-polymer network. To have this mechanism playing a role associated with DNA-structural changes requires that the DNA structure undergoing a change on recognition is topologically connected to the polymer network. Or in other words, molecular binding events to a DNA grafted to the network with one end only are not directly affecting the crosslinking density of the network, and for this reason cannot transform the binding event to a change in the thermodynamics of the network through changes in the elastic part. On the other hand, DNA strand or complex of strands that is connected to the network by both its 3′ and 5′ ends, can transform binding events to changes in the term describing the elastic properties due to an altered end-to-end distance and thereby changes in crosslink density.

Exploitation of changes in properties governing the electrostatic contribution to the swelling equilibrium is the third option. Estimation of ΔC_{tot} and how this is related to alterations in changes in charge density driven by DNA based recognition processes can be carried out by exploiting the equilibrium condition for the salt. This can be estimated starting from

$$\Delta C_{tot} = (c_+ + c_-) - (c'_+ + c'_-) \tag{1.2}$$

where c is the concentration of ions and subscripts indicate the positive or negative ions, the prime depicts the immersing solution and the unprimed that within the gel. Within the theory of the infinite bath, the Donnan equilibrium requires electroneutrality in both compartments and equal chemical potential of the mobile ionic species across the gel-immersing solution interface [14,18]. Thus, the following equations are obtained:

$$z_+ c'_+ = z_- c'_- \tag{1.3}$$

$$z_+ c_+ = z_- c_- + z_p c_p \tag{1.4}$$

$$\gamma_\pm^2 c_+ c_- = \gamma'^2_\pm c'_+ c'_- \tag{1.5}$$

where z depict the valences of the cations, anions and polymer indicated by the subscripts +, − and p, respectively, the prime depict the immersing solution and the unprimed that within the gel. Furthermore, $\gamma_\pm^2$ and $\gamma'^2_\pm$ are the mean activity coefficients of the salt inside and outside of the gel raised to the second power. Structural changes of the DNA associated with the recognition process yield changes in the $z_p\, c_p$ parameter, which conventionally also is written:

$$z_p c_p = \frac{\rho\varphi_2}{M_2} \tag{1.6}$$

where ρ is the mass density of the dry polymer network and M_2 is the molar mass of the polymer, including connected DNA, per unit charge. The term $z_p\, c_p$ represents the counterions needed to balance the charged groups on the network, and possible ways to include Manning condensation in the calculation of these have been described [19]. Changes in the charge density of the DNA conjugated to the polymer network associated with the recognition process, can be expected to yield a contribution to the thermodynamics of the swelling, thus inducing a change in the equilibrium swelling state.

3. Changes in DNA higher order structures exploited in DNA-polymer hydrogel swelling changes

DNA is today recognized to have a wide repertoire of higher order structures far beyond the classical antiparallel duplex structure reported by Watson and Crick more than 60 years ago. So far, only a small fraction of such higher order structures have been exploited as recognizing and transducing element in DNA-polymer hydrogels. The DNA structural elements can exploit changes in crosslink density, equilibrium length of the DNA supported part connecting to other polymer chains (e.g., the elastically active network chains), and changes in the charge density of the ionic hydrogel properties as a consequence of the transformative molecular designs. The covalent integration of DNA into hydrogels is a necessary part in realizing the DNA-co-polymer hydrogels. Copolymerization strategies for including DNA strands into acrylamide based materials have been described and are increasingly being exploited due to the commercial availability, including custom designed bp sequences [20–22]. Such an experimental toolbox allows the realization of crosslinks, or elastically active network strands made up of oligonucleotides, alongside covalent crosslinks included by addition of bis