Self-Adjustable Adhesion of Polyampholyte Hydrogels

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Biological surfaces are very complex in nature. They have wide distribution in molecular species; including positive and negative charges, polar and non-polar groups.[1] A material to show adhesion to such biological surfaces should have the capability of creating enough adhesive interacting sites with these species in wet environment.[2] Conventional hydrogels usually have poor adhesion to biological surfaces.[3] This is because the adhesion in wet environment is usually based on the Columbic interaction that strongly depends on the charge combinations.[3,4] Many of the biological surfaces and hydrogels have net negative surface charge[5] and they are repulsive in water. Developing adhesives that possess the ability of quick, strong, and reversible adhesion to hydrogels and biological tissues regardless their net charge identity will substantially promote the application of hydrogels in biomedical applications. Several research groups have tried to develop different adhesive hydrogels based on surface modification,[6] mechanical interlocking,[7] making composites,[8] supramolecular recognition,[9] and nano-particles.[10,11] But these approaches have limitations in practical applications, such as lengthy and complicated way of processing, lack of water resistivity and universality, inability in non-residual removal, etc.[12]

The clue to develop adhesives working for hydrogels and biological tissues hides in nature. Bacteria cells, ubiquitous in environment, can attach with almost any surfaces including human tissues, regardless the diversity in the surface chemistry. The self-adjustable capability of the extracellular polymeric matrix (EPM) of bacteria cells has made this possible.[13,14] EPM can provide sufficient interacting sites for adsorption of species at interface in response to substrates mechanical and chemical properties through re-distribution of their charged groups.[15] Inspired from nature, we intend to find out a self-adjustable hydrogel adhesive for adhesion to hydrogels and tissues. A self-adjustable surface is such a surface which can offer its species for the formation of attractive interaction depending on substrate charges through dynamic reorganization process. A possible design for achieving such a self-adjustable

adhesive is a hydrogel composed of both positively and negatively charged monomers. Presence of both charges in the hydrogel is expected to create attractive interacting sites with any charged surfaces regardless of their charge identity to facilitate adsorption. But this seems to be tricky, because incorporation of both type charges in the same hydrogel sometime encounters strong self-ionic association, which will made it impossible for the formation of bonds with other species residing in different surfaces or in some cases imbalance in component inside hydrogel offers a strong net charge over the surface,[16] which will prevent their non-specific adhesion property. We can overcome this problem by choosing a neutral (charge balanced) polyampholyte (PA) hydrogel that has a fast ion-bonds exchange time.

A neutral PA carries equal amount of positive and negative charges on the polymer in random distribution.[17–20] When the charge balanced PA were synthesized at very high concentration, the opposite charges form dynamic ionic bonds of intra- and inter-chains. The inter-chain ionic bonds serve as physical crosslinking to form hydrogels.[21] Owing to such dynamic ionic bonding structure, the PA hydrogels show specific properties, such as deswelling in water, strong viscoelasticity, high toughness, and self-healing.[21,22] Beside these bulk properties, the dynamic ionic bonds of PA hydrogels on their surface are expected to create attractive interacting sites through the formation of polarization induced ion-bond complex formation with charged or polar species of counter surfaces, which can initiate the adhesion for physiological surfaces. According to previous studies, the molecular process of the complex formation is depicted as, when a neutral PA gel approaches a polyelectrolyte (PE) or protein species within their electric double layer, the neutral PA is polarized by the electric field of the polar species, which induces charge redistribution of the PA in such a way that opposite charges to that of polar species head to polar species and *vice vasa*.[17] This charge redistribution favors the ion complex formation between PA and polar species (**Scheme 1A**). Furthermore, since the ion complex formation accompanies with the release of the localized counter-ions of the PE to a more large volume, it leads to an entropy gain similar to the ion

complex formation between two oppositely charged PE hydrogels (**Scheme 1B**). Thus, this complex formation between PA and PE has both energetic and entropic origins. For a neutral PA gel, this mechanism applies similarly for positively charged and negatively charged PEs, which ensures the self-adjustability of PA hydrogel surface in response to the counter surface charges. The non-specific adhesion favors PA hydrogel to form ionic bonds with any charged surfaces, either positively or negatively, in similar to the function of extracellular polymeric matrix of bacteria cells for attaching with different substrates.

To test the idea, we used a chemically crosslinked PA gel, P(NaSS-*co*-DMAEA-Q). This gel is copolymerized from sodium 4-vinyl-benzenesulfonate (NaSS) and (2-acryloyloxyethyl)-trimethylammonium chloride quaternary (DMAEA-Q) with a small amount of chemical crosslinker.[21,22] Different from common hydrogels that usually swell in water to absorb abundant of water after preparation, the PA gel deswells in water by ~ 40 % in volume, and at the equilibrate state it only contains ~ 52 wt% of water as a result of ionic bond formation. The gel is very soft, highly stretchable, and viscoelastic (**Figure S1, Supporting Information**). The dynamic mechanical measurement showed a broad peak of loss factor tanδ around 300 rad/s, which gives a characteristic time τ_w= 1/300 ≃ 3 ms (**Figure S2, Supporting Information**). This characteristic time is considered as the average bond exchange time of the PA gel. The charge balanced PA hydrogel has almost zero Donnan potential, as confirmed by the microelectrode measurement (**Table 1**).

First, we tested the adhesion properties of the PA gel to fully swollen polyelectrolyte (PE) hydrogels with positive or negative charges. Since the PE hydrogels are too brittle to handle in their single network form, PE hydrogels were synthesized in double network (DN) structure to improve their mechanical strength.[23] These PE gels have high Donnan potential due to the existence of diffuse counter-ion layer (electric double layer) on the surface of the

gels (**Table 1**). The neutral PA hydrogel shows quick and strong adhesion to both positively and negatively charged hydrogels, as demonstrated by the adhesion tests of PA gel with PDMAEA-Q hydrogel and PNaSS gel, respectively (**Figure 1 and Movie S1, Supporting Information**). This result indicates that neutral PA hydrogel can adhere on the surface of PE hydrogels and their adhesion does not depend on the surface charge identity of the counter surfaces. More examples were tested using negatively charged PNaAMPS hydrogel, synthesized from sodium 2-acrylamido-2-methylpropanesulfonate (NaAMPS), and positively charged PDMAPAA-Q hydrogel, synthesized from *N*-[3-(*N*,*N*-dimethylamino)propyl]-acrylamidemethyl chloride quaternary (DMAPAA-Q) (**Scheme S1**). Similar strong adhesion of PA to these PE hydrogels was also observed (**Table 1**).

To further confirm that the adhesion of PA hydrogels is driven by Coulomb interaction, we also investigated the PA gel adhesion to neutral poly(vinyl alcohol) (PVA) hydrogel that has a weak negative Donnan potential in water (**Table 1**). Only weak adhesion of PA hydrogel is observed and interfacial failure occurred during the debonding of joints. These results indicate that the strong adhesion of the PA gel to charged gels has the electrostatic origin.
Biological tissues are charged systems but have more complicated surface nature than synthetic PE hydrogels. However, the self-adjustable mechanism of PA hydrogel should also work with the tissues. To confirm this, first, we tested the adhesion of the PA hydrogel to a piece of pork liver (**Figure 2A and Movie S2, Supporting Information**). We made two equal-notches on the surface of the liver, and hang the soft liver vertically (**Figure 2A(a)**). The notches opened apart by gravity as the tissue is very soft. A piece of PA gel was made in contact to the liver surface covering one of the notches. As a result, the PA gel stuck to the liver immediately to close the notch, and stayed there (**Figure 2A(b)**). The PA gel could be removed from and then stuck back to the liver repeatedly with no distinct changes in the appearance of both the PA gel and the tissue. In contrast, the negatively charged PNaAMPS

gel was slippery on the liver and slid down the liver surface (**Figure 2A(c)**), indicating no adhesion. On the other hands, the positively charged PDMAPAA-Q gel also immediately adhered to the liver first, but the liver surface became turbid gradually, suggesting the denaturation of the tissue surface (**Figure 2A(d)**). After several seconds, the positively charged gel also slipped down the denatured tissue surface. These results suggest that the liver tissue has a negative net surface charge and it is repulsive to the negatively charged PNaAMPS gel and attractive to the positively charged PDMAPAA-Q gel. The adhesive failure after the initial attachment of the positively charged gel may be related to the large stress mismatch at the junction built as a result of strong ion complexation. In addition, the diffusion of low molecular weight species, such as small ions, from the tissue to the gel across the interface might occur, which changes the microenvironment (such as the ionic strength) of the tissue and causes denaturation, and therefore causes changes in swelling of the tissue. A detailed study of the debonding mechanism of the positively charged gel to the liver tissue is beyond the scope of this study.

The adhesion of the neutral PA hydrogel does not cause any tissue damage probably owing to the mild dynamic ion-bond formation. We also found that the PA hydrogel can quickly join two separate pork muscles by its adhesive capability (**Movie S3, Supporting Information**). Based on the same self-adjustable mechanism, the PA gel strongly adheres to the glass substrate that carries negative charges in water.[24] Thus, we can assemble the oppositely charged PE hydrogels, biological tissues, and glass using PA gel as adhesive layers (**Figure 2B**). These results indicate that PA hydrogel can serve as an adhesive for reversible gluing of charged surfaces by forming the dynamic ion bond formation.

Next, we characterized quantitatively the adhesion strength by a lap shear test (**Figure 3A**). Debonding force-displacement curves for gels and pork tissues are shown in **Figure 3B**. The

adhesion of PA hydrogel to the PE gels was so strong that the failure occurred always in the PE gel's bodies outside of the joint, not at the interface of the joint (**Figure 3C**). While for pork heart tissues and neutral hydrogels, the debonding occurred at the interface. The critical energy release rate, G_c, was estimated from the method proposed by K. Kendall for long lap joint.[25] As the PE gels break in bulk, we could not obtain the true bonding strength of PA gel to PE gels. But at least they should have values higher than the data shown in **Figure 3D**. The G_c of PA to the pork tissue was found lower than the PE gels, probably due to lower surface charge density of the tissue than the strong PE gels. G_c to the neutral PVA gel was very low due to lacking of strong electrostatic interaction.

In summary, hydrogels are one of the most promising materials in life science. They are water-borne, soft, flexible, less cytotoxic, and therefore more biocompatible than other synthetic materials. Despite these intrinsic tissue compatible properties of hydrogels, their use is often limited in biomedical engineering by the poor adhesion with biological tissues. We have demonstrated here that a neutral PA hydrogel can act as wet adhesive material for the joining of PE hydrogels or biological tissues based on a self-adjustable ion-bond formation mechanism. This mechanism, driven by the Columbic interaction and the entropy gain of the counter-ion release, is specific for polyelectrolyte systems in aqueous environment. As the biological tissues are mainly composed of polyelectrolytes (such as polysaccharides on the cell surfaces) and polyampholytes (such as proteins), this self-adjustable mechanism also gives insight in understanding the biological adhesion. Thus, this work will open a new avenue for designing adhesive hydrogels for use in different disciplines of life science.

Experimental Section

Materials: Sodium, 4-vinyl-benzenesulfonate (NaSS), *N,N'*-methylenebisacrylamide (MBAA), 2-oxoglutaric acid (α-keto) were purchased from Wako Pure Chemical Industries

Ltd. (Japan). (2-acryloyloxyethyl)trimethylammonium chloride quaternary (DMAEA-Q; 79.0 wt%) was purchased from MT Aqua Polymer, Inc.(Japan) and *N*-[3-(*N*,*N*-dimethylamino)propyl] acrylamidemethyl chloride quaternary (DMAPAA-Q) from Kohjin Co. Ltd. (Japan). Sodium 2-acrylamido-2-methylpropanesulphonate (NaAMPS) was provided by Toagosei Co. Ltd. (Japan). Poly(vinyl alcohol) (PVA) was purchased from Nacalai Tesque Inc. (Japan). Fresh pork heart, muscle and liver tissues were purchased from a company, Nippon Food Packer Inc. (Japan), collected from hybrid pig (Landrace-Yorkshire-Duroc, weight- ~ 120 kg and age ~ 6 months) and used as received without any surface pretreatment or special drying.

Synthesis of neutral polyampholyte hydrogel: The chemically crosslinked PA hydrogel, P(NaSS-*co*-DMAEA-Q), was synthesized by free radical copolymerization. Aqueous solution containing 2.5 M monomers (= [NaSS]+[DMAEA-Q]), 0.1 mol% chemical cross-linker *N,N'*-methylenebisacrylamide (MBAA), 0.1 mol% UV initiator, α-keto (both in relative to the total monomer concentration) was prepared. The in feed molar ratio of NaSS to DMAEA-Q was 0.52:0.48 to obtain the charge balanced gel.[22] The solution was poured into glass mold consisting of two glass plates separated by a silicone spacer of 2.0 mm thick and irradiated by UV light in argon atmosphere for 8 h. After the polymerization, the hydrogel was placed in water for 7 days with continuous exchange of water at 12 h duration. During this process, the small counter-ions were washed away (dialysis) and the hydrogel deswelled by formation of dynamic ionic bonds between opposite charges of the polymer. The sample in swelling equilibrium was ~1.7 mm thick, and the water content was ~52 wt%. Detailed procedures were described in the literature.[21,22]

Synthesis of polyelectrolyte hydrogels: As the polyelectrolyte (PE) hydrogels in single network structure are extremely weak, double network (DN) hydrogels were synthesized from

the same charged monomer as the first and second network. Such DN structure improves the mechanical strength of the polyelectrolyte gels for some extend.[23] Four polyelectrolyte DN hydrogels of anionic type (PNaSS/PNaSS, PNaAMPS/PNaAMPS) and cationic type (PDMAEA-Q/PDMAEA-Q, PDMAPAA-Q/PDMAPAA-Q) were synthesized using NaSS, NaAMPS, DMAEA-Q, and DMAPAA-Q as monomers, respectively. For simplicity, these four DN gels were denoted as PNaSS, PNaAMPS, PDMAEA-Q, PDMAPAA-Q.
These hydrogels were prepared by following the processes described in literature.[23] The first network was polymerized from aqueous solution containing 1 M monomer, 3 mol% MBAA as crosslinker, and 0.1 mol% α-ketoglutaric acid as UV initiator (both in relative to the monomer). The solution was poured into glass mold consisting of two glass plates separated by a silicone spacer of 1 mm thick and irradiated by UV light in argon atmosphere for 8 h. The first hydrogel was immersed in the second aqueous solution containing 3 M monomer, 0.1 mol% crosslinker and 0.1 mol% initiator for 2 days to attain the swelling equilibrium. The sample was then irradiated by UV light again for 8 h to form the second network. The hydrogels were swollen in deionized water for 7 days with continuous exchange of water at 12 h duration.

Synthesis of PVA hydrogel: Neutral PVA hydrogel was prepared from PVA polymer following a process described in previous report.[26] Homogeneous solution of 10wt% PVA (M_w = 2000 and saponification value > 98 %) in DMSO/water (3:1, by weight) mixture solvent was prepared by heating the solution at 90 °C for 2 h. The solution was then degassed in vacuum oven and then poured into glass mold with 2 mm silicone spacer. The glass molds were allowed to stay in low temperature freezer (4°C) for 12 h. The frozen hydrogel was placed in deionized water for 7 days with continuous exchange of water.

Measurement of hydrogel Donnan potential: A neurophysiological recording technique was applied for measuring the Donnan potential of the hydrogels.[27] A glass tube microelectrode with a tip diameter < 1 μm consisting of a reversible silver/silver chloride electrode (Ag|AgCl) was prepared. An aqueous solution of 3 M KCl was inserted on it. Another glass microelectrode was used as reference electrode. The microelectrode was vertically inserted into gel surface that is immersed in 10^{-4} M NaCl solution at a constant speed for obtaining potential depth-profile. All measurements were performed at 25 °C.

Lap shear test: For measurement of PA hydrogel adhesion to hydrogels and biological tissues, lap shear joints were prepared, following a process frequently used for measuring adhesive strength of hydrogel based tissue adhesives.[12] Two ribbons of hydrogels (length l × width w= 75 ×25 mm^2) were cut by scalpel. They were brought into contact with a piece of PA hydrogel (l×w×h=20×25×1.7 mm^3), which form a junction contact area of 5 cm^2 (**Figure 3A**). The lap joint was slightly pressurized with finger for 30 s then the two ends of the gels were clamped to the tensile machine (TensilonRTC-1310A, Orientec Co.). The shear adhesive test was performed at a shear velocity of 100 mm/min. The same measurement was performed for the adhesion of PA gel to pork heart tissues. The critical energy release rate, G_c, was estimated from the measured adhesive failure force F, both for interfacial failure and substrate failure using the expression for long lap joints $G_c=(F/w)^2/(4Eh)$ [25], where E, h , and w denote the elastic modulus, thickness and width of substrate hydrogels respectively.

Tensile test: Tensile test of hydrogels and pork heart tissues was performed in Tensile tester (TensilonRTC-1310A, Orientec Co.) at velocity 100 mm/min. Dumbbell shape hydrogel samples having length 15 mm and width 3.5 mm were used for modulus measurement. The thicknesses of PNaSS, PNaAMPS, PDMAEA-Q, PDMAPAA-Q, PVA, and PA hydrogels were 3.1, 3.3, 4.7, 4.1, 2.3, and 1.7 mm respectively. For measuring the elastic modulus of

pork heart tissue, rectangular shape ($l \times w \times h$= 15 × 5.5 × 7 mm^3) samples were used. The tensile stress-strain plot of PA hydrogel used in this study has been shown in **Figure S1**.

Rheological test: For rheological characterization of PA hydrogel, frequency (ω) dependence of the storage modulus G', loss modulus G'', and loss factor tanδ were measured at different temperatures in an ARES rheometer (advanced rheometric expansion system, Rheometric Scientific Inc.). Frequency sweep was performed from 0.06 to 100 rad/s at a shear strain of 0.5 % in the temperature range 0.1–80.1 °C. In parallel plate geometry, disc-shaped samples having thicknesses of ~ 1.7 mm and diameters of 15 mm was used. The dynamic behaviors of the PA hydrogel at different temperatures and frequencies follow the principle of time-temperature superposition. A master curve was obtained after shifting all isotherms to a reference temperature, 25.1 °C (**Figure S2**).

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C. K. R. and J. P. G. developed the hypothesis and designed the study. C. K. R., H. L. G., A. B. I. performed the experiments. All authors analyzed and discussed the results. C. K. R. and J. P. G. wrote the paper. The authors thank Dr. Yoshinori Katsuyama for his support in collecting fresh tissues. This research was financially supported by a Grant-in-Aid for Scientific Research (S) (No. 124225006) from the Japan Society for the Promotion of Science (JSPS). C. K. R. and A. B. I. thank the MEXT for the scholarship.

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Scheme 1. Schematic illustration of adhesion mechanism between charged hydrogels. (A) The self-adjustable adhesion of a charge balanced polyampholyte (PA) to polyelectrolyte (PE) hydrogels with either positive or negative charges. (B) Adhesion between two oppositely charged PE gels.

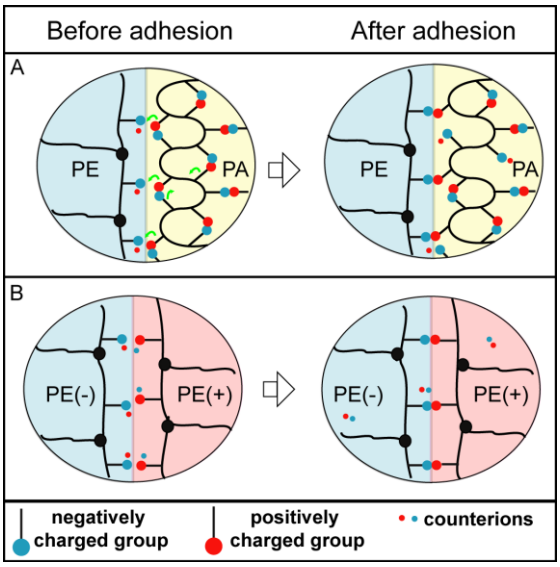


Table 1. Properties of different types of hydrogels and tissues, and their failure mode during adhesion test to PA gel, P(NaSS-*co*-DMAEA-Q).

Charge type of hydrogel	Name of hydrogel	Modulus (MPa)*	Donnan potential (mV)	Adhesion failure mode
Anionic	PNaSS	0.100±0.007	-163	Hydrogel failure
Anionic	PNaAMPS	0.236±0.001	-100	Hydrogel failure
Cationic	PDMAEA-Q	0.141±0.006	+158	Hydrogel failure
Cationic	PDMAPAA-Q	0.107±0.002	+139	Hydrogel failure
Neutral	PVA	0.042±0.001	-20	Interfacial failure
PA	P(NaSS-*co*-DMAEA-Q) (Self-adhesion)	0.076±0.004	-5	Interfacial failure
Tissue	Pork heart tissue	0.024±0.009	-	Interfacial failure

*The error ranges are the standard deviation of the average over three samples.

Figure 1. Demonstration of the self-adjustable adhesion of a PA hydrogel to charged hydrogels. The neutral PA hydrogel (P(NaSS-*co*-DMAEA-Q, dyed in yellow color) can adhere to both the negatively charged hydrogel (PNaSS, dyed in blue color) and the positively charged hydrogel (PDMAEA-Q, dyed in red color). A schematic illustration is represented to show the adhesion mechanism of the PA hydrogel to the oppositely charged gels. Small counter-ions of PE gels are not shown for clarity.

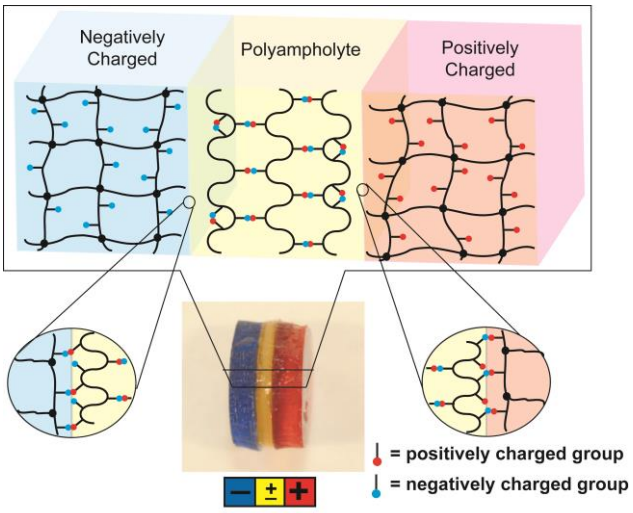


Figure 2. Adhesion of the PA hydrogel to biological tissues and hydrogels. (A) Adhesion behaviors of hydrogels with different charges to the surface of a piece of pork liver tissue. Two open notches of ~ 10 mm length were made on the tissue (a), and the neutral PA hydrogel adhered to the tissue and closed the notch (b), but the negatively charged PNaAMPS hydrogel was non-adhesive and slipped down the tissue surface (c); the positively charged PDMAPAA-Q hydrogel adhered to the tissue first, but the tissue surface quickly became turbid. After several seconds, the positive gel also slipped down the tissue surface (d). (B) Assembly of glass (white), negatively charged PNaAMPS hydrogel (blue), pork muscle tissue (pink), positively charged PDMAEA-Q hydrogel (red) through PA hydrogels P(NaSS-*co*-DMAEA-Q) (yellow). A movie to show the adhesion of PA hydrogel P(NaSS-*co*-DMAEA-Q), anionic PNaAMPS and cationic PDMAPAA-Q hydrogels on the surface of a piece of pork liver tissue is available in Supporting Information **Movie S2**.

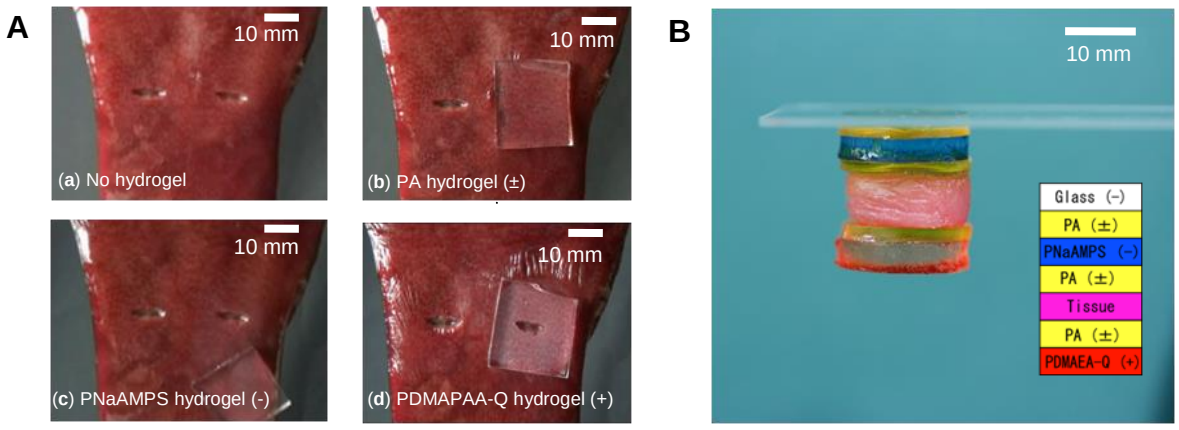
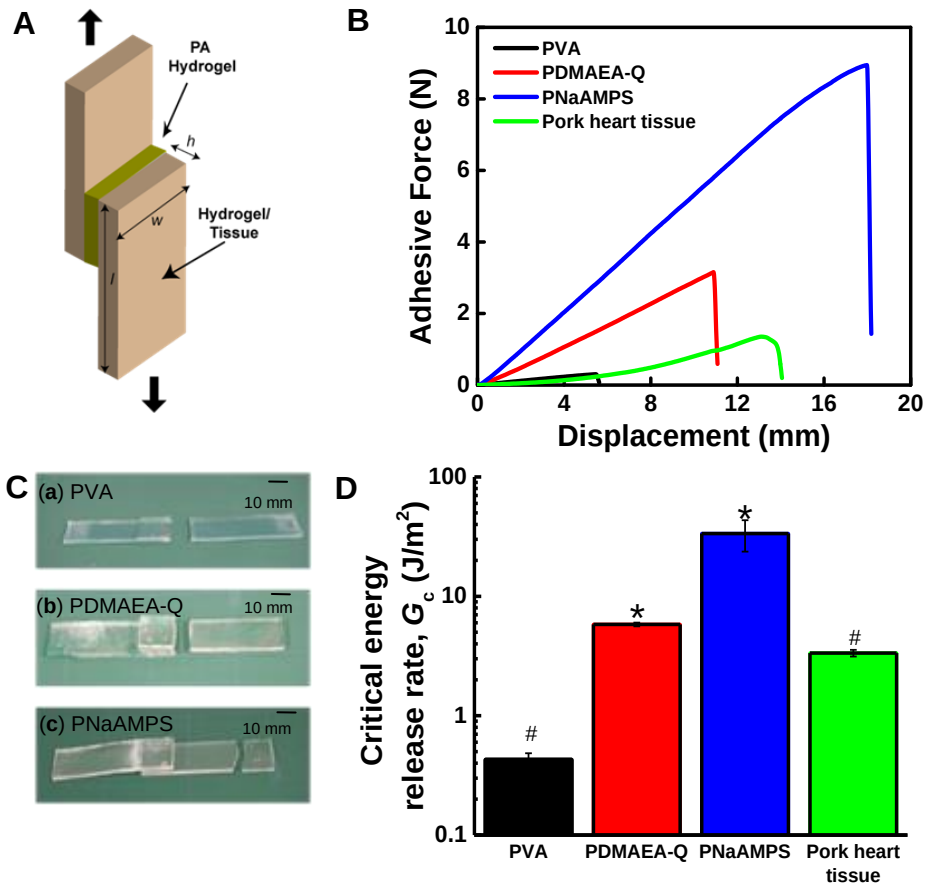


Figure 3. Lap shear test to measure the adhesion of PA hydrogel P(NaSS-*co*-DMAEA-Q) to various gels and soft tissue.(A) adhesion testing geometry; (B) force-displacement curves of adhesion to gels and tissue; (C) adhesion failure modes of gels; (a) PVA at interface, (b) PDMAEA-Q and (c) PNaAMPS hydrogels at gel bulk; (D) critical energy release rate G_c of shear adhesive joints. G_c calculated for interfacial failures were indicated by # and gel bulk failure by *. Each data point was averaged for three samples. The error bars show the standard deviation. Sample dimension ($l \times w \times h$): PA gel (20×25×1.7 mm^3), cationic hydrogel PDMAEA-Q (75×25×4.7 mm^3), anionic hydrogel PNaAMPS (75×25×3.3 mm^3), neutral hydrogel PVA (75×25×2.3 mm^3) and pork heart tissue (75×25×8.5 mm^3).



Supporting Information

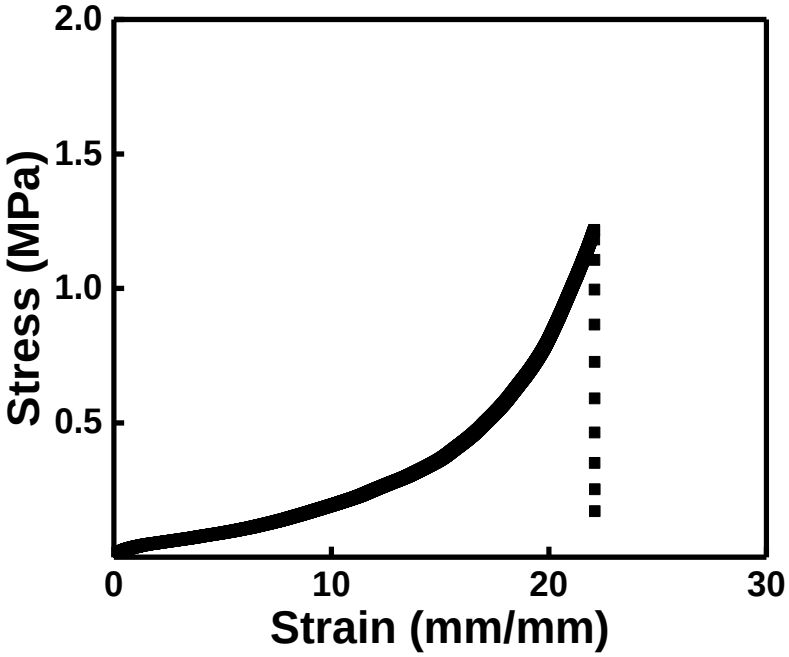


Figure S1. Tensile stress-strain behavior of the polyampholyte (PA) hydrogel, P(NaSS-*co*-DMAEA-Q) at stretching velocity of 100 mm/min.

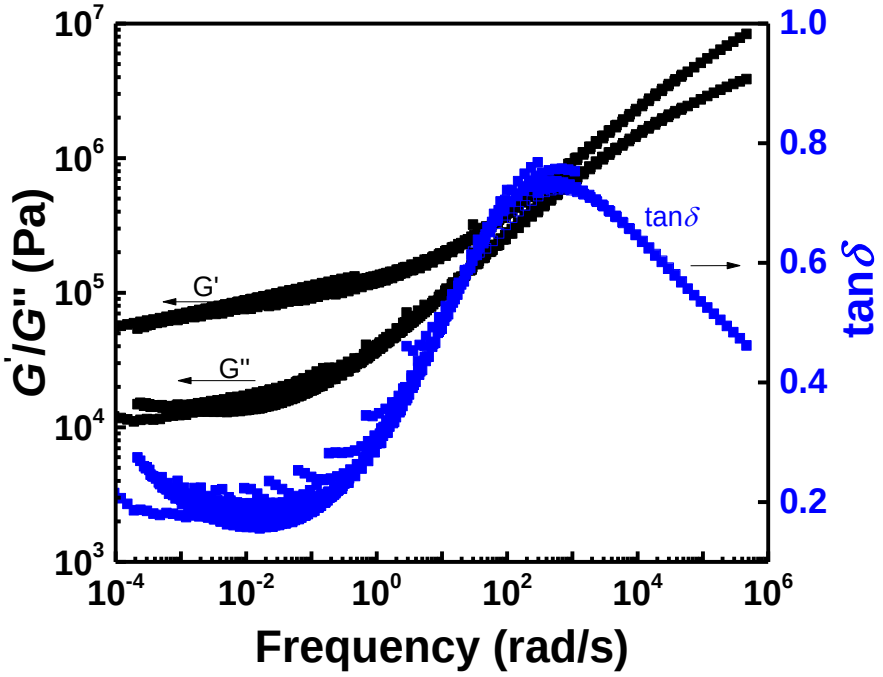
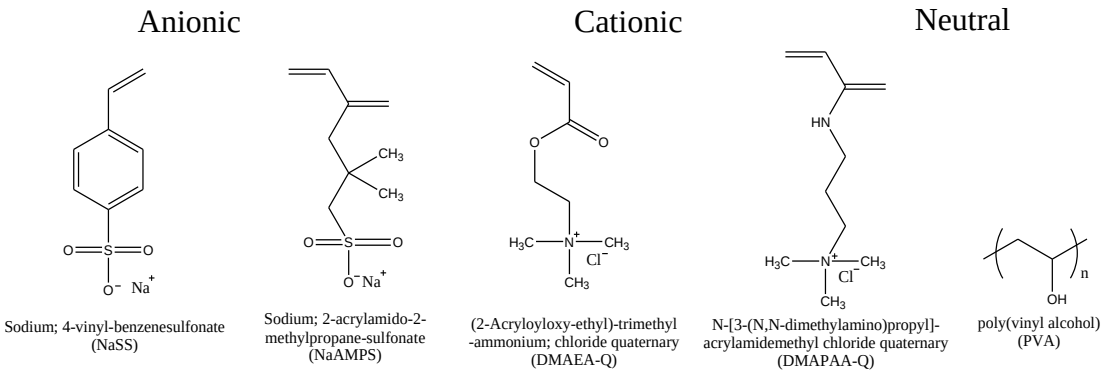


Figure S2. Rheological characterization of the PA hydrogel, P(NaSS-*co*-DMAEA-Q). *G′*, *G″* and tan*δ* represent storage modulus, loss modulus, and loss factor, respectively.



Scheme S1. Chemical structure of monomers and polymer used in this work.

Movies: Movies are available from the Wiley Online Library or from the author.

http://onlinelibrary.wiley.com/wol1/doi/10.1002/adma.201504059/suppinfo

Movie S1. Demonstration of adhesion of PA hydrogel (middle, yellow), P(NaSS-*co*-DMAEA-Q), to anionic PNaSS (left, blue) and cationic PDMAEA-Q (right, red) hydrogels in water.

Movie S2. Adhesion of PA hydrogel P(NaSS-*co*-DMAEA-Q), anionic PNaAMPS and cationic PDMAPAA-Q hydrogels on the surface of a piece of pork liver tissue.

Movie S3. Demonstration of adhesion of PA hydrogel, P(NaSS-*co*-DMAEA-Q) to pork heart tissue.