

# 博士論文

## Stimuli-Responsive Hydrogels Packaging Anisotropic Electrostatics

(異方的な静電力学を内包する刺激応答性ヒドロゲル)

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# Stimuli-Responsive Hydrogels Packaging Anisotropic Electrostatics

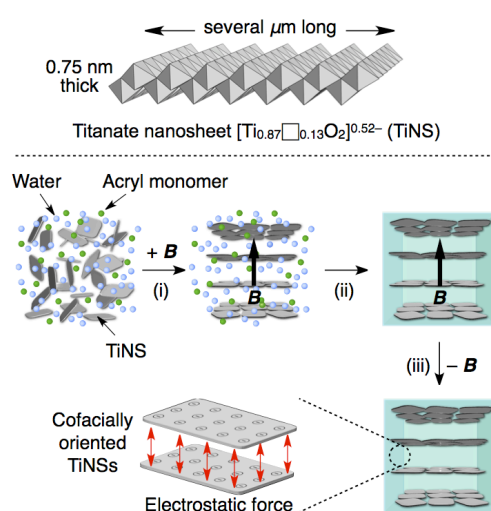
## 異方的な静電力学を内包する刺激応答性ヒドロゲル

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### Introduction

In the field of materials science, a long-standing topic is the development of muscle-like actuators that can convert chemical energies into large, quick, and unidirectional motions. For this aim, the most promising are hydrogels that exhibit abrupt volume changes in response to external stimuli, owing to their soft and water-rich structures similar to biological tissues, together with their operating temperatures close to body temperature. Although various hydrogel actuators have been developed so far, however, their actuation has inherent limitation in efficiency, because of their primitive actuation mechanism simply relying on the volume changes through the swelling and deswelling of gel networks. The kinetics of such volume changes is governed by the transport of water and subsequent rearrangement of polymer chains, and therefore is generally slow. In addition, the volume changes are usually isotropic and not suitable to produce anisotropic motion. The creation of unidirectional motion, such as one-way waling, is an even greater challenge for today's materials science, not confined to matters of hydrogels, where successful examples are limited to those using elaborated setups, such as ratchet mechanisms and directionally programmed stimuli. Furthermore, autonomous operation of such directional motion is an even greater challenge, although such motion is often observed for living organisms. Indeed, most artificial soft actuators go into action only when some stimuli are externally applied.

As a promising material to circumvent these limitations, Aida *et al.* recently reported an anisotropic hydrogel whose mechanical properties are dominated by 'embedded electrostatic repulsion' (**Scheme 1**).<sup>[1]</sup> This hydrogel is supported by a 3D network of an organic polymer incorporating unilamellar titanate nanosheets (TiNSs). This particular nanosheet, developed by Sasaki *et al.* in 1996,<sup>[2]</sup> consists only of surface atoms adopting a single-crystal-like 2D array and therefore is ultrathin (0.75 nm). It is also characterized by an exceptionally high aspect ratio ( $\sim 10^4$ ). TiNS is negatively charged and wrapped by tetraalkylammonium counterions to furnish an electric double layer in aqueous media. Unlike any other metal oxide nanosheets, TiNSs in an aqueous colloidal dispersion magnetically align cofacially (**Scheme 1**, i). This unprecedented orientation allows for the emergence of an anisotropic electrostatic repulsion among TiNSs. For minimizing the consequent thermodynamic instability, the aqueous dispersion adopts a quasi-crystalline structural order, wherein a uniformly large plane-to-plane nanosheet separation develops up to a macroscopic length scale. This magneto-induced temporal structural ordering can be fixed by transforming the dispersion into a hydrogel by in-situ vinyl



**Scheme 1.** Schematic representation of the preparation of a hydrogel containing cofacially oriented TiNSs.

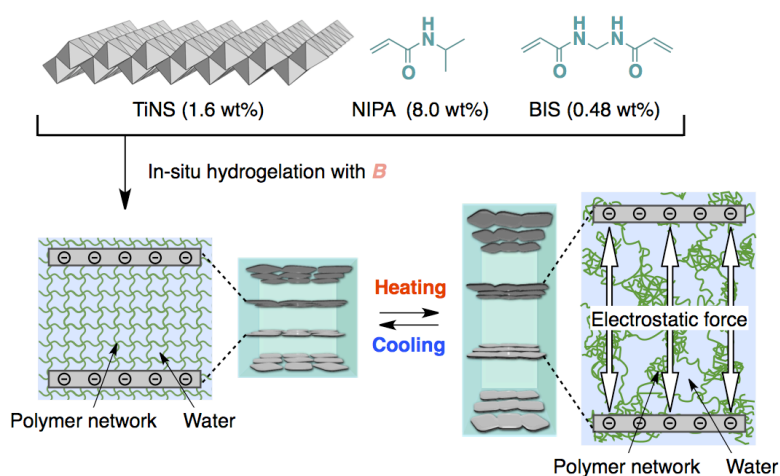
polymerization (**Scheme 1**, ii).<sup>[3]</sup>

Through the study of Aida *et al.*, the ‘embedded electrostatics’ was found to bring anomalous anisotropic mechanical features to the hydrogel (**Scheme 1**, iii), where the hydrogel easily deformed along a shear force applied parallel to the TiNS plane but was resistive against a compressive force applied orthogonally. Inspired by this work, the author envisioned that, if the 3D network of this hydrogel is composed of a stimuli-responsive polymer, the 3D network of the hydrogel would reversibly release and hold gelling water in response to external stimuli. Consequently, the polarity and dynamics of the gel matrix would be abruptly changed, which causes the switching of the intensity of the ‘embedded electrostatics’, thereby producing quick and anisotropic deformation of the hydrogel. In this philosophy doctoral (Ph.D.) thesis, the author describes stimuli-responsive hydrogels whose anisotropic actuation is driven by switching the intensity of embedded electrostatics acting among cofacially oriented TiNSs. In Chapter 1, thermoresponsive unidirectional actuation of a hydrogel is discussed, where the phase transition of a thermoresponsive gel network was used as a trigger to switch the electrostatic force. In Chapter 2, autonomous actuation of a hydrogel is discussed, where a self-oscillating system based on the Belousov–Zhabotinsky reaction was combined with the actuation mechanism dominated by embedded anisotropic electrostatics.

## Chapter 1. Unidirectional actuation of a hydrogel driven by tunable anisotropic electrostatic repulsion among cofacially oriented inorganic nanosheets

As described in Introduction, the author aimed at introducing a thermoresponsive anisotropic hydrogel with embedded electrostatic repulsion among cofacially oriented TiNSs. Water-soluble polymers gain hydrophilicity by hydration through dipole–dipole and hydrogen-bonding interactions with water molecules. When a water-soluble polymer such as poly(N-isopropylacrylamide)

[poly(NIPA)] is heated above a certain temperature in an aqueous medium, these dipole–dipole and hydrogen-bonding interactions are disrupted, resulting in dehydration and subsequent hydrophobic aggregation of the polymer chains. The electrostatic permittivity of water, which is lowered by association with poly(NIPA), recovers its intrinsic value upon liberation. This process is fully thermoreversible and known as the lower-critical solution temperature (LCST) phenomenon. When the system is cooled, the water molecules again hydrate the polymer chains and become less mobile. The author conjectured that the LCST phenomenon is applicable as a ‘trigger’ for switching the electrostatic permittivity of the matrix of a hydrogel. Accordingly,



**Scheme 2.** Hydrogel containing cofacially oriented TiNSs (TiNS//PNIPA). Schematic representation for the preparation of TiNS//PNIPA gel (top) and its anisotropic thermoresponsive deformation (bottom).

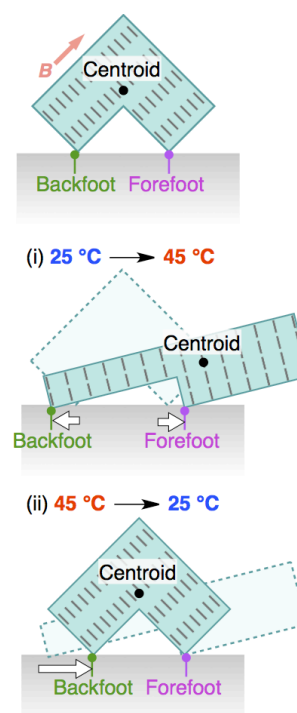
LCST phenomenon would reversibly change the degree of ion pairing between the electrolyte sheets and their counterions, eventually tuning the electrostatic repulsion among the electrolytes sheets (**Scheme 2**). Based on this simple design principle, in this work the author developed a hydrogel actuator that reversibly expands and contracts in the direction orthogonal to the electrolyte sheets.

For the components of such a thermoresponsive gel network, the author chose *N*-isopropylacrylamide (NIPA) as a monomer and *N,N'*-methylenebis (acrylamide) (BIS) as a crosslinker, whose lower critical transition temperature (LCST) is known to be 32–34 °C. The hydrogel containing cofacially oriented TiNSs (TiNS<sub>//</sub>-PNIPA) was prepared according to the method we recently reported (**Scheme 2**). Typically, an aqueous dispersion of 1.6 wt% TiNSs was hydrogelated in a 10 T magnetic flux by in-situ crosslinking polymerization of 8.0 wt% NIPAM and 0.48 wt% BIS. In the resultant hydrogel, TiNSs adopted a layered structure with a uniform plane-to-plane separation of 14 nm. A reference hydrogel containing randomly oriented TiNSs (TiNS<sub>random</sub>-PNIPA) was also prepared in the same manner but without using a magnet. As revealed by calorimetric measurement, these hydrogels exhibit a sharp phase transition at 32–34 °C, which is characteristic of poly(NIPA)-based hydrogels.

When TiNS<sub>//</sub>-PNIPA hydrogel was heated from 25 to 45 °C, it became opaque at ~32 °C due to the hydrophilic–hydrophobic transition of the gel network, and then underwent the anomalous deformation. To our surprise, the hydrogel expanded to ~150% in the direction orthogonal to the TiNS plane, unlike other poly(NIPA)-based hydrogels that generally shrink when heated above their LCST. Concomitantly to this expansion, the hydrogel contracted to ~80% in the in-plane directions of the TiNS plane. Accordingly, the volume of the hydrogel was maintained through the deformation. In addition, when the hydrogel thus deformed is cooled below 32 °C, the reverse deformation took place. Worth noting is that these deformations do not involve a long-range water transport and subsequent polymer rearrangement, and therefore are very quick, unlike the deformation of usual stimuli-responsive hydrogels. Furthermore, upon heating–cooling cycles, these deformations can be repeated without any detectable degradation. Such anomalous deformations occur only when TiNSs in the hydrogel are cofacially oriented. Indeed, a reference hydrogel containing randomly oriented TiNSs was heated above 32 °C, it did not exhibit such an anomalous deformation in the present time scale, but only gained its turbidity.

As described in the introductory part, the anomalous deformation of the TiNS<sub>//</sub>-PNIPA gel is most likely due to the release and holding of water molecules by the gel network, which cause the switching of electrostatic permittivity in the gel matrix. According to the theory of colloidal dispersions, the thickness of electrical double layers surrounding TiNSs gains as the permittivity of the medium increases, thereby increasing the intensity of electrostatic repulsive force among TiNSs. In order to confirm the hypothesized mechanism more directly, 2D small-angle X-ray scattering (2D SAXS) of the TiNS-oriented gel was measured with irradiating an X-ray beam parallel to the TiNS plane, so that the information on the plane-to-plane separation of the oriented TiNSs can be obtained. In the original state, the 2D SAXS image indicated that cofacially oriented TiNSs align with a uniform *d*-spacing of 14 nm. When the TiNS-oriented gel was heated up to 35 °C, the layered structure of TiNSs expanded with gaining its *d*-spacing from 14 to >19 nm. In the reverse cooling process, the layered structure reduced its *d*-spacing from >19 to 14 nm. The expansion and contractile of the layered structure could be repeated multiple times without serious structural degradation. Noteworthy, the TiNS<sub>//</sub>-PNIPA gel changed its macroscopic shape almost synchronously with the *d*-spacing of the layered structure, indicating the validity of the proposed mechanism.

Taking advantage of the unique actuation feature, the magnetically structured hydrogel realized unidirectional walking, not due to a ratchet mechanism but due to a dissymmetric structure embedded in it. For example, the magnetically structured hydrogel was simply processed into an L-shape, where the TiNS plane was orthogonal to one of the sides of the L-shape and was parallel to the other. Through the heating-induced deformation of the L-shaped gel, the forefoot and backfoot slid to the opposite directions, so that the net movement of the L-shaped gel was negligibly small. (Figure 1, i). However, through the cooling-induced deformation, the backfoot slid over a long distance, whereas the forefoot was almost fixed, because the centroid of the deformed hydrogel was nearer to the forefoot and therefore generated larger friction with the base at the forefoot than at the backfoot (Figure 1, ii). When the heating–cooling cycles were repeated, the L-shaped gel securely walked in one direction like a looper (Figure 1). Worth noting is that our hydrogel successfully converted a nondirectional thermal energy source into unidirectional motion.



**Figure 1.** Walking mechanism of an L-shaped TiNS<sub>7</sub>/PNIPA hydrogel.

## Chapter 2. Spatiotemporally controlled actuation of a hydrogel driven by the hybridization of anisotropically embedded electrostatics and a self-oscillating reaction

As described in Chapter 1, the author succeeded in developing a hydrogel actuator that exhibits large, quick, and unidirectional motion in response to external thermal stimuli. In terms of actuation efficiency and capability of converting nondirectional energy (thermal energy) into unidirectional ‘walking’ motion, this hydrogel actuator succeeded in reproducing the characteristic motion of living organisms. A remaining challenge for this hydrogel is “autonomy”, which is a crucial difference generally observed between artificial soft actuators and living organisms.

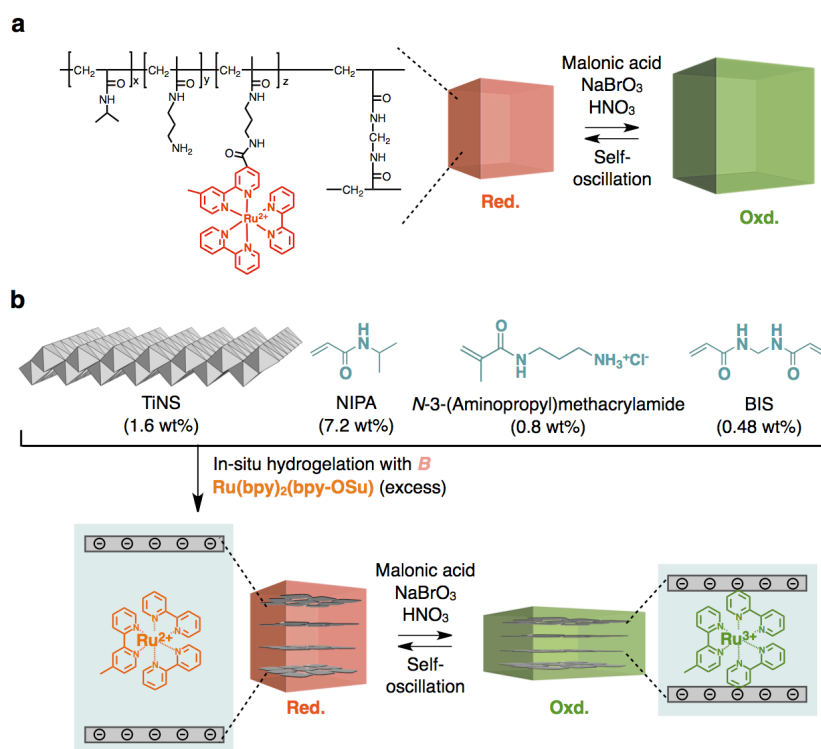
Recently, Yoshida *et al.* have developed self-oscillating hydrogels that periodically change their properties (volume, color, aggregation profiles, *etc.*) in the absence of continuous on–off switching of external stimuli.<sup>[4]</sup> For the design of such hydrogels, they utilize the Belousov–Zhabotinsky (BZ) reaction, where ruthenium catalysts periodically switch their valence ( $\text{Ru}^{2+} \rightleftharpoons \text{Ru}^{3+}$ ) through the ruthenium-catalyzed oxidative reaction of malonic acid by bromate in acidic media. In most of self-oscillating hydrogels, gel matrices are composed of poly(NIPA) covalently connected with ruthenium tris(2,2'-bipyridine) [ $\text{Ru}(\text{bpy})_3$ ]. When these hydrogels were immersed in solutions containing BZ substrates [malonic acid (62.5 mM), sodium bromate (84 mM), and nitric acid (0.3 M)] at 18 °C, the self-oscillation reaction autonomously proceeds. In response to the changes of  $\text{Ru}(\text{bpy})_3$  units ( $\text{Ru}^{2+} \rightleftharpoons \text{Ru}^{3+}$ ), hydrophilicity and LCST of gel matrices change, which causes the swelling and deswelling of the gel networks (Scheme 3, a). The author envisioned that both “anisotropy” and “autonomy” could be realized at the same time, if  $\text{Ru}(\text{bpy})_3$  moieties are covalently bound to the gel network embedded with cofacially oriented TiNSs so that the self-oscillating

system is coupled with the actuation mechanism dominated by embedded anisotropic electrostatics as described in Chapter 1. Although several design strategies have been developed for self-oscillating hydrogels to improve the magnitude and quickness of their deformation, the control of anisotropy still remains an unexplored realm.

According to the method established in Chapter 1 with some modification, the target hydrogel was synthesized, whose gel network embedded with cofacially oriented TiNSs was covalently modified with Ru(bpy)<sub>3</sub> units (TiNS<sub>//</sub>-NIPA-co-Ru(bpy)<sub>3</sub>) (Scheme 3, b). The hydrogel was processed in a rectangular shape, where one of the sides became orthogonal to the TiNS plane,

while the others are parallel to the TiNS plane. When the hydrogel was immersed in an aqueous medium containing the BZ substrates, the self-oscillating BZ reaction started in the hydrogel after a while. In order to evaluate the anisotropy of this autonomous actuation, the time-series image analysis of the hydrogel was performed along the perpendicular (i) and parallel (ii) directions to the TiNS plane. Thus, from each frame of the movie taking whole shape of the hydrogel, a one-line image along either of the two directions (i or ii) was extracted and lined up sequentially with time, so that two spatiotemporal patterns were constructed. When the hydrogel turned to the oxidized state (Ru<sup>3+</sup>-state) where the hydrogel appeared green, the hydrogel showed notable contraction in the direction orthogonal to the TiNS plane. Synchronously to the contraction, the hydrogel expanded in the in-plane directions to the TiNS plane. When the hydrogel turned to the reduced state (Ru<sup>2+</sup>-state) where the hydrogel appeared orange, the reverse deformation occurred. These deformations were autonomously repeated in an oscillatory manner without degradation.

Worth noting is that the actuation mechanism of the present hydrogel is totally different from that of conventional self-oscillating hydrogels based on the BZ reaction, in terms of volume change and anisotropy. In the case of conventional self-oscillating hydrogels oxidative state of the Ru(bpy)<sub>3</sub> units (Ru<sup>2+</sup> ⇌ Ru<sup>3+</sup>), which causes the changes in hydrophilicity and LCST of gel matrices and subsequent swelling and deswelling of their gel networks (Scheme 3, a). Therefore, such conventional hydrogels generally swell in the oxidized (Ru<sup>3+</sup>) state and shrunken in the reduced (Ru<sup>2+</sup>) state in an isotropic manner so long as the effects of their macroscopic shapes are negligible. In sharp contrast, the actuation of the present hydrogel



**Scheme 3.** a. Schematic illustration of the self-oscillating behavior of conventional self-oscillating hydrogel based on poly(NIPA) and Ru(bpy)<sub>3</sub>. b. Schematic representation for the preparation of the hydrogel containing Ru(bpy)<sub>3</sub> and cofacially oriented TiNSs (TiNS<sub>//</sub>-NIPA-co-Ru(bpy)<sub>3</sub>) (top) and anisotropic autonomous deformation (bottom).

does not involve swelling and deswelling of its gel network, but proceeds in an isovolumetric manner (**Scheme 3, b**). Considering the fact that the present hydrogel contracts in the direction orthogonal to the TiNS plane in the oxidized ( $\text{Ru}^{3+}$ ) state, which result in the contraction force between the plan-to-plan of TiNSs. It is assumed that a higher charge on the  $\text{Ru}(\text{bpy})_3$  of the polymer network can lead to produce a stronger ionic environment around TiNSs. According to the theory of colloidal dispersions, the thickness of electrical double layers surrounding TiNSs shortens as the ionic strength of the medium increases, thereby decreasing the intensity of electrostatic repulsive force among TiNSs. Also, in the oxidized state, an enhanced electrostatic repulsion among  $\text{Ru}(\text{bpy})_3$  moieties in the gel network, could be quenched temporarily by negatively charged TiNSs.

## Summary

The author succeeded in developing hydrogel actuators operated in unprecedented mechanism, which realizes efficient, unidirectional, and even autonomous motion. These hydrogels incorporates negatively charged inorganic nanosheets that are oriented cofacially with one another, where an anisotropic electrostatic repulsion emerges among the nanosheets. The oriented nanosheets are packaged by 3D polymer networks of stimuli-responsive polymers, which can switch the electrostatics in response to externally or internally controlled stimuli. These hydrogels, having many similarities to muscular tissues in actuation profiles and in mechanism, would contribute to the progress of studies on artificial soft actuators, both in fundamental and practical aspects.

## References

- [1] Liu, M.; Ishida, Y.; Ebina, Y.; Sasaki, T.; Hikima, T.; Takata, M.; Aida, T. *Nature* **2015**, *517*, 68.
- [2] Sasaki, T.; Watanabe, M.; Hashizume, H.; Yamada, H.; Nakazawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8329.
- [3] Liu, M.; Ishida, Y.; Ebina, Y.; Sasaki, T.; Aida, T. *Nat. Commun.* **2013**, *4*, 2029.
- [4] Yoshida, R.; Takahashi, T.; Yamaguchi, T.; Ichijo, H. *J. Am. Chem. Soc.* **1996**, *118*, 5134.