

Self-Oscillating Polymer Gels as Novel Biomimetic Materials

Ryo Yoshida

Abstract— Stimuli-responsive polymer gels and their application to smart materials have been widely studied. On the other hand, as a novel biomimetic gel, we developed gels with an autonomous self-oscillating function like a heart muscle, which was firstly reported in 1996. We designed the self-oscillating polymers and gels by utilizing the oscillating reaction, called the Belousov-Zhabotinsky (BZ) reaction as a chemical model of the TCA cycle. The self-oscillating polymer is composed of a poly(*N*-isopropylacrylamide) network in which the metal catalyst for the BZ reaction is covalently bonded. In a closed solution containing the reactants other than the catalyst, the polymer gel undergoes spontaneous cyclic swelling–deswelling changes without any on–off switching of external stimuli. Their potential applications include several kinds of functional material systems, such as biomimetic actuators and mass transport surface. Here recent progress on the novel polymer gels is introduced.

I. INTRODUCTION

A. Background

In the field of polymer science, polymer gels have made rapid progress during the past 30 years. Since the discovery of “volume phase transition” phenomena by Tanaka [1] as a turning point, many kinds of stimuli-responsive polymer gels that exhibit reversible swelling-deswelling change in response to environmental changes such as solvent composition, temperature, pH change, etc. have been developed. Especially, from the late 1980’s, new functional gels called “intelligent gels” or “smart gels” have been created, and their applications to biomaterials and biomimetic materials such as actuator (artificial muscle), drug delivery systems (DDS), tissue engineering, purification or separation systems, biosensor, shape memory materials, molecular recognition systems, etc. [2-5]. have been exploited. In these researches, a concept of “chemo-mechanical gels” to convert chemical energy of chemical/biochemical reaction to mechanical energy of gels has been proposed since a long time ago, as a model of artificial muscles to realize soft actuators. Further, gels have played important roles in the field of micromachines and nanotechnology recently. Not only new synthetic methods to give unique functions by molecular design in nano-order scale including supramolecular design, but also the design and construction of micro or nanomaterial systems with the biomimetic functions have been attempted.

Considering development of gels to bio/biomimetic materials, one of characteristic and important behaviors in living systems is autonomous oscillation, that is, spontaneous changes with temporal periodicity (called “temporal structure”) such as heartbeat, brain waves, pulsatile secretion

of hormone, cell cycle, and biorhythm. Although many stimuli-responsive polymer and gel systems inspired by living systems have been studied so far, there are few studies on polymer and gel systems undergoing self-oscillation under constant condition without any on-off switching of external stimuli. If such autonomous systems can be realized by using completely synthetic polymers, unprecedented biomimetic materials may be created.

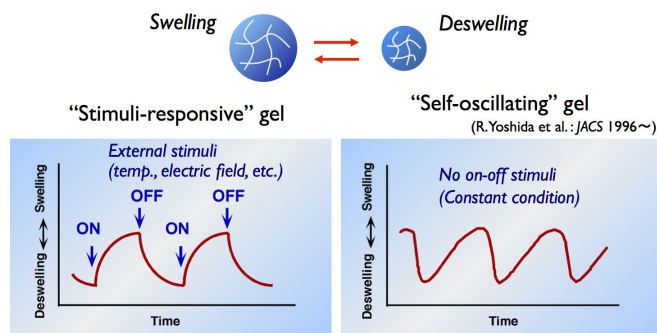


Fig.1 Stimuli-responsive and self-oscillating gels.

B. Design of self-oscillating polymer gels

From this viewpoint, we have studied the polymer gels with autonomous function. In contrast to conventional stimuli-responsive gels, we have developed “self-oscillating” polymer gels that autonomously undergo periodic swelling/deswelling oscillation without on-off switching of external stimuli in a closed solution (Fig.1). For the design of the gel, the Belousov-Zhabotinsky (BZ) reaction [6,7], which is well-known as an oscillating reaction which spontaneously exhibits temporal rhythm and spatial pattern, was focused. The overall process is the oxidation of an organic substrate, such as malonic acid or citric acid, by an oxidizing agent (bromate ion) in the presence of a metal catalyst under acidic condition. While the reaction proceeds, the catalyst undergoes spontaneous redox oscillation, showing periodical changes in color of the solution under stirring condition and concentric or spiral wave patterns under stationary condition. The wave of oxidized state propagating in the medium is called a “chemical wave”. The reaction is often analogically compared with the TCA cycle which is a key metabolic process taking place in the living body, and it is recognized as a chemical model for understanding several autonomous phenomena in biological systems.

We attempted to convert the chemical oscillation of the BZ reaction into a mechanical change in gels and generate an autonomous swelling-deswelling oscillation under non-oscillatory outer conditions. For this purpose, we prepared the gel composed of poly(*N*-isopropylacrylamide) (PNIPAAm) and ruthenium tris(2,2′-bipyridine) ($\text{Ru}(\text{bpy})_3$) which is covalently bonded to the PNIPAAm network (Fig.2). PNIPAAm is a well-known thermosensitive polymer which

R. Yoshida is with the Department of Materials Engineering, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan (e-mail: ryo@cross.t.u-tokyo.ac.jp).

exhibits a lower critical solution temperature (LCST) while $\text{Ru}(\text{bpy})_3$ acts as a catalyst for the BZ reaction. By redox changes in the $\text{Ru}(\text{bpy})_3$ moiety, the hydrophilicity as well as the LCST of the poly(NIPAAm-co- $\text{Ru}(\text{bpy})_3$) changes, which results in changing swelling ratio of the gel. Consequently, by immersing the gel in a catalyst-free BZ reaction solution at constant temperature, the BZ reaction occurs in the gel and the gel undergoes a cyclic swelling-deswelling change. Since the first report in 1996 [8], by using self-oscillating gels, we have developed many kinds of applications to biomimetic or smart materials [9-34].

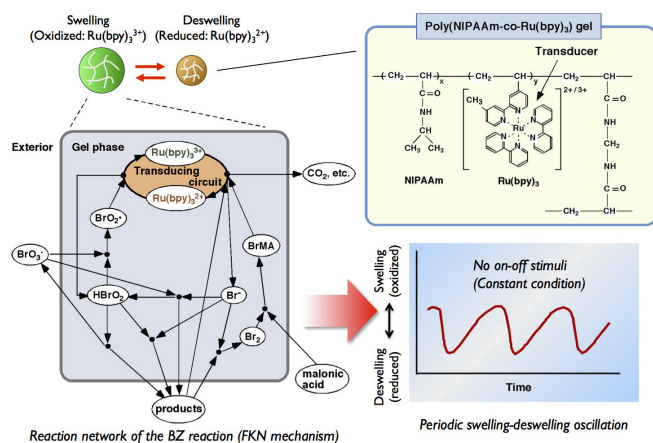


Fig.2 Mechanism of self-oscillation in gels.

II. SELF-OSCILLATING BEHAVIORS OF THE POLYMERS AND GELS

When the gel is enough small, redox changes occur homogeneously in the gel without pattern formation [10]. Then the swelling-deswelling change of the gel becomes isotropic. On the other hand, when the gel size is large, chemical waves spontaneously evolve and propagate in the gel due to the reaction-diffusion mechanism. Then locally swollen and shrunken regions propagate with the chemical waves, and peristaltic motion similar to that of a living worm or intestine can be induced [11-13]. By utilizing peristaltic motion of the self-oscillating gel, autonomous mass transport has recently been demonstrated as mentioned later. The period and amplitude of the oscillation can be controlled by changing substrate concentration and temperature. Further, on-off regulation of the self-oscillation by external stimuli such as temperature change, addition and removal of organic acid, photo-irradiation is possible [9]. For example, spirobenzopyran was copolymerized into the poly(NIPAAm-co- $\text{Ru}(\text{bpy})_3$) as the photochromic site [33]. Photochromism of the spirobenzopyran occurs and the LCST of the polymer solution shifts to lower temperature with isomerization by photo-irradiation. As a result, on-off switching of the soluble-insoluble self-oscillation for the polymer solution is possible by photo-irradiation.

III. DESIGN OF BIOMIMETIC SOFT-ACTUATORS

By utilizing such macroscopic swelling-deswelling oscillation of the gel, novel biomimetic actuators may be created. As applications to autonomous biomimetic actuators, ciliary motion actuators (artificial cilia) [14] and self-walking gels [15], etc. were realized (Fig.3). Further, self-propelled

motion of gels was theoretically demonstrated and experimentally realized by utilizing the gels [16]. Control of the motion by preparing a composite gel made of self-oscillating and non-active gels was also attempted [17].

Typically, there are several strategies to improve the response of gels, such as introducing porous microstructures, decreasing the size of the gels, and introducing grafted side chains with freely mobile ends on the backbone networks of gels. For example, it was demonstrated that the comb-type grafted PNIPAAm gels exhibited a fast deswelling response to temperature change by the guiding effect of hydrophobic interaction between side chains that have freely mobile ends [35]. These network-arranged designs are expected to be applicable for improving the swelling/deswelling kinetics to the redox change in the self-oscillating gel. We designed a novel comb-type self-oscillating gel that has $\text{Ru}(\text{bpy})_3$ on both the main and side chains. Different from the conventional type of self-oscillating gels in which $\text{Ru}(\text{bpy})_3$ is immobilized only on main chains, faster swelling/deswelling changes are expected because the grafted side chains with freely mobile ends can respond to the redox change of $\text{Ru}(\text{bpy})_3$ more quickly than the main chains. As a result, self-oscillation with a larger swelling-deswelling amplitude will be achieved.

In a living muscle, there exists hierarchical structure to amplify the microscopic movements of actin-myosin to macroscopic displacements. Such a hierarchical structure was introduced into the self-oscillating gel to get large amplitude of swelling/deswelling oscillation. The soft actuators assembled from self-oscillating submicron-sized hydrogel particles (microgels) were designed and obtained by assembling the pre-existing microgel particles [18]. Large displacements due to cooperative dispersing/flocculating motion of constituent microelements were exhibited.

IV. DESIGN OF AUTONOMOUS MASS TRANSPORT SYSTEMS

A. Self-driven gel conveyer: Autonomous transportation on the self-oscillating gel surface by peristaltic motion

In order to realize self-driven gel conveyer as novel autonomous mass transport system, we attempted to transport an object by utilizing the peristaltic motion of the self-oscillating gel (Fig.3) [19-22]. A model object, a cylindrical or spherical poly(acrylamide) (PAAm) gel was put on the surface of self-oscillating gel sheet. It was observed that the object was transported on the gel surface with the propagation of the chemical wave as it rolled (see the photograph in Fig.3). We have proposed a model to describe the mass transport phenomena based on the Hertz contact theory, and the relation between the transportability and the peristaltic motion was investigated.

B. Self-oscillating polymer brushes

Recently, surface modification techniques for polymer chains have made a lot of progress with the development of new polymer synthesis methods. In particular, surface-initiated atom transfer radical polymerization (SI-ATRP) is one of the most effective modification methods for preparing a well-defined dense polymer brush structure, or polymer brush, on substrates. Thus, a self-oscillating polymer brush prepared by SI-ATRP can be expected to create a new self-oscillating surface with autonomic function

like a cilia, which will lead to potential applications to transporting systems for nano-materials or flow control in micro fluidics. We have prepared a self-oscillating polymer brush on glass a substrate by SI-ATRP. The BZ reaction occurred on the self-oscillating polymer brush surfaces, and the propagation of the chemical wave was observed in the polymer brush layer on the inner surface of a glass capillary. We were able to demonstrate a self-oscillating surface to generate spontaneous periodic changes by using synthetic polymers, as a novel autonomous functional surface which has potential applications in systems such as nano-transport systems.

C. Autonomous intestine-like motion of tubular self-oscillating gel

Further, to construct autonomous mechanical pumping systems like an intestine, we fabricated the self-oscillating gel in a tubular shape [23] (Fig.3). Tubular self-oscillating gels were fabricated by photopolymerization. In the gel tube, it was observed that a model object (gas bubble) was autonomously transported. Mass transport by peristaltic pumping of the tubular self-oscillating gel was successfully demonstrated. Potential applications to artificial intestines, artificial digestive tracts, etc. can be expected. And also, there is a possibility of autonomous flow of an inner fluid. We are investigating an application to a novel micropump for microfluidic systems.

V. DEVELOPMENT TOWARD FUNCTIONAL FLUIDS

In the case of the uncrosslinked linear polymer and the submicron-sized gel beads, as shown in Fig.3, the polymer solution and the microgel dispersion exhibit autonomous viscosity oscillation as well as optical transmittance oscillation [24-30]. It is expected that these polymer solutions and microgel dispersions are applied as novel

functional fluid. And also, we realized autonomous viscosity oscillations of a polymer solution based on different mechanisms [31]. It is known that a terpyridine ligand binds or dissociates a Ru metal ion depending on the redox states of the Ru metal ion. Generally, when the Ru metal ion is in the reduced Ru(II) state, the Ru(II) metal ion forms bis-complexes with terpyridine ($\text{Ru}(\text{terpy})_2$). However, when the Ru metal ion is in the oxidized Ru(III) state, the Ru(III) metal ion forms monocomplex with terpyridine ($\text{Ru}(\text{terpy})$) [36]. If the Ru-terpyridine complex acts as a catalyst of the BZ reaction, the redox oscillation may cause periodical binding/dissociation of the Ru-terpyridine complex.

We achieved autonomous viscosity oscillation by reversible complex formation of terpyridine-terminated Tetra PEG in the BZ reaction [31]. Then the BZ reaction induces the periodical binding/dissociation of the Ru-terpyridine complex and causes periodical molecular changes and results in viscosity changes (Fig.3). Remarkable changes like a sol-gel transition could be possible by controlling molecular design. It was confirmed that octa-PEG was much more effective than the tetra-PEG system in providing a large amplitude of oscillation as well as a higher viscosity. This result is qualitatively explained by the tree-like structure theory, which predicts the relationship between the rate of reaction at gelation point and the branch number of the polymer. We are investigating molecular design of terpyridine-terminated PEG for causing sol-gel oscillation.

Further, a novel block copolymer that could undergo spontaneous unimer-micelle oscillation under constant conditions was prepared [34]. This is the first report on a synthetic block copolymer that exhibits “temporal structure,” undergoing self-oscillation between unimer and micelle, as an example of a dissipative structure.

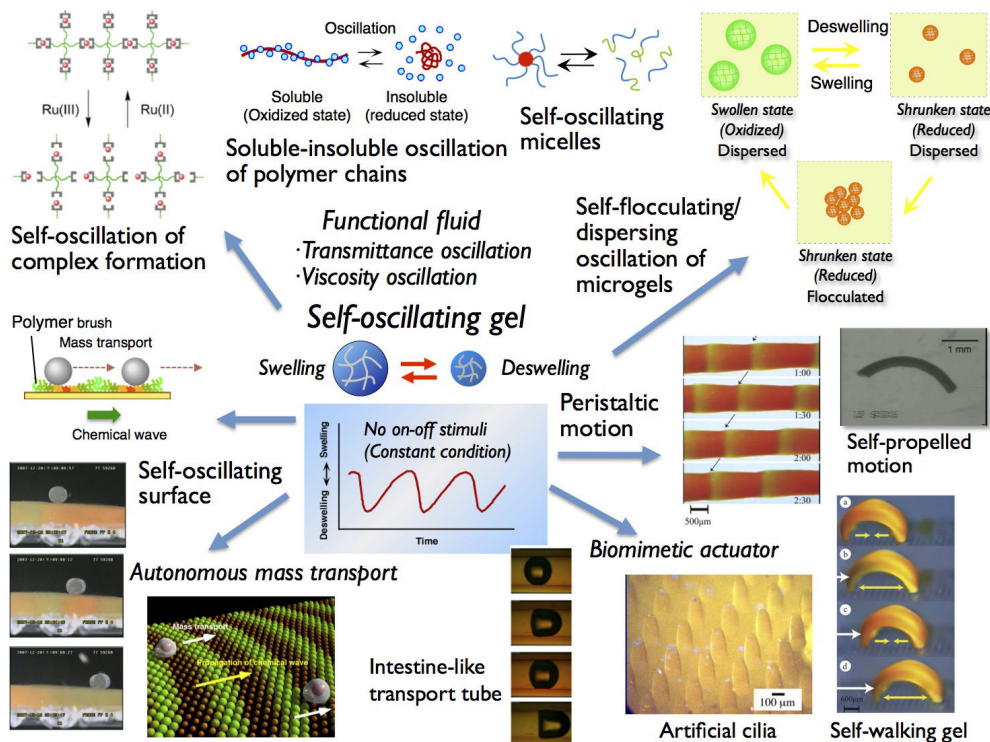


Fig.3 Development of self-oscillating polymer gels.

VI. CONCLUSION

As mentioned above, we proposed novel chemo-mechanical systems to convert chemical oscillation of the BZ reaction to mechanical changes of polymer and gel, and succeeded in realizing such an energy conversion system producing autonomous self-oscillation of polymer gel like a heart muscle. Here these recent progress on the self-oscillating polymers and gels and the design of functional material systems were summarized. Now polymer design toward biomedical applications is also attempted [25, 32]. As an innovative study to propose novel potential of polymer gels and achieve an autonomous behavior by coupling chemical and mechanical oscillations in polymer systems, the study has attracted much attention in the many research fields of polymer science, material science, physical chemistry, theoretical simulation, biophysics, etc. We continue to advance our research by studying new polymer systems.

REFERENCES

- [1] T. Tanaka, "Collapse of gels and the critical endpoint", *Phys. Rev. Lett.*, 40, 820-823, 1978.
- [2] R. Yoshida, "Design of functional polymer gels and their application to biomimetic materials", *Curr. Org. Chem.*, 9, 1617-1641, 2005.
- [3] R.M. Ottenbrite, K. Park, T. Okano and N.A. Peppas (Eds), *Biomedical Applications of Hydrogels Handbook*, Springer, New York, 2010.
- [4] T. Miyata, "Stimuli-responsive polymer and gels": in *Supramolecular Design for Biological Applications*, Yui N (Ed.), CRC Press, Boca Raton, pp.191-225, 2002.
- [5] A. Lendlein and V.P. Shastri, "Stimuli-sensitive polymers", *Adv Mater* 22, 3344-3347, 2010.
- [6] R.J. Field and M. Burger (Eds.), "*Oscillations and Traveling Waves in Chemical Systems*", John Wiley & Sons, New York, 1985.
- [7] I.R. Epstein and J.A. Pojman, "*An Introduction to Nonlinear Chemical Dynamics: Oscillations, Waves, Patterns, and Chaos*", Oxford University Press, New York (1998).
- [8] R. Yoshida, T. Takahashi, T. Yamaguchi and H. Ichijo, "Self-oscillating gel", *J. Am. Chem. Soc.* 118, 5134-5135, 1996.
- [9] R. Yoshida, "Self-oscillating gels driven by the Belousov-Zhabotinsky reaction as novel smart materials", *Adv. Mater.*, 22, 3463-3483, 2010.
- [10] R. Yoshida, M. Tanaka, S. Onodera, T. Yamaguchi and E. Kokufuta, "In-phase synchronization of chemical and mechanical oscillations in self-oscillating gels", *J. Phys. Chem. A*, 104, 7549-7555, 2000.
- [11] S. Maeda, Y. Hara, R. Yoshida and S. Hashimoto, "Peristaltic motion of polymer gels", *Angew. Chem. Int. Ed*, 47, 6690-6693, 2008.
- [12] S. Shinohara, T. Seki, T. Sakai, R. Yoshida and Y. Takeoka, "Chemical and optical control of peristaltic actuator based on self-oscillating porous gel", *Chem. Commun.*, 4735-4737, 2008.
- [13] S. Shinohara, T. Seki, T. Sakai, R. Yoshida and Y. Takeoka, "Photoregulated wormlike motion of a gel", *Angew. Chem. Int. Ed.*, 47, 9039-9043, 2008.
- [14] O. Tabata, H. Kojima, T. Kasatani, Y. Isono and R. Yoshida R, "Chemo-mechanical actuator using self-oscillating gel for artificial cilia", *Proceedings of the International Conference on MEMS 2003*, pp.12-15, 2003.
- [15] S. Maeda, Y. Hara, T. Sakai, R. Yoshida and S. Hashimoto, "Self-walking gel", *Adv. Mater.*, 19, 3480-3484, 2007.
- [16] O. Kuksenok, V.V. Yashin, M. Kinoshita, T. Sakai, R. Yoshida and A.C. Balazs, "Exploiting gradients in cross-link density to control the bending and self-propelled motion of active gels", *J. Mater. Chem.*, 21, 8360-8371, 2011.
- [17] V.V. Yashin, S. Suzuki, R. Yoshida and A.C. Balazs, "Controlling the dynamic behavior of heterogeneous self-oscillating gels", *J. Mater. Sci.*, 22, 13625-13636, 2012.
- [18] D. Suzuki, T. Kobayashi, R. Yoshida and T. Hirai, "Soft actuators of organized self-oscillating microgels", *Soft Matter*, 8, 11447-11449, 2012.
- [19] Y. Murase, S. Maeda, S. Hashimoto and R. Yoshida, "Design of a mass transport surface utilizing peristaltic motion of a self-oscillating gel", *Langmuir*, 25, 483-489, 2009.
- [20] Y. Murase, M. Hidaka and R. Yoshida, "Self-driven gel conveyor: Autonomous transportation by peristaltic motion of self-oscillating gel", *Sensors and Actuators B*, 149, 272-283, 2010.
- [21] Y. Murase, R. Takeshima and R. Yoshida, "Self-driven gel conveyor: effect of interactions between loaded cargo and self-oscillating gel surface", *Macromol. Bioscience*, 11, 1713-1721, 2011.
- [22] R. Yoshida and Y. Murase, "Self-oscillating surface of gel for autonomous mass transport", *Colloids and Surfaces B: Biointerfaces*, 99, 60-66, 2012.
- [23] Y. Shiraki and R. Yoshida, "Autonomous intestine-like motion of tubular self-oscillating gel", *Angew. Chem. Int. Ed.*, 51, 6112-6116, 2012.
- [24] R. Yoshida, T. Sakai, S. Ito and T. Yamaguchi, "Self-oscillation of polymer chains with rhythmical soluble-insoluble changes", *J. Am. Chem. Soc.*, 124, 8095-8098, 2002.
- [25] Y. Hara and R. Yoshida, "Self-oscillating polymer fueled by organic acid", *J. Phys. Chem. B*, 112, 8427-8429, 2008.
- [26] D. Suzuki, T. Sakai and R. Yoshida, "Self-flocculating/self-dispersing oscillation of microgels", *Angew. Chem. Int. Ed.*, 47, 917-920, 2008.
- [27] D. Suzuki and R. Yoshida, "Temporal control of self-oscillation for microgels by cross-linking network structure", *Macromolecules*, 41, 5830-5838, 2008.
- [28] D. Suzuki, H. Taniguchi and R. Yoshida, "Autonomously oscillating viscosity in microgel dispersions", *J. Am. Chem. Soc.*, 131, 12058-12059, 2009.
- [29] H. Taniguchi, D. Suzuki and R. Yoshida, "Characterization of autonomously oscillating viscosity induced by swelling/deswelling oscillation of the microgels", *J. Phys. Chem. B*, 114, 2405-2410, 2010.
- [30] Y. Hara and R. Yoshida, "A viscosity self-oscillation of polymer solution induced by the BZ reaction under acid-free condition", *J. Chem. Phys.*, 128, 224904, 2008.
- [31] T. Ueno, K. Bundo, Y. Akagi, T. Sakai and R. Yoshida, "Autonomous viscosity oscillation by reversible complex formation of terpyridine-terminated poly(ethylene glycol) in the BZ reaction", *Soft Matter*, 6, 6072-6074, 2010.
- [32] M. Hidaka and R. Yoshida, "Self-oscillating gel composed of thermosensitive polymer exhibiting higher LCST", *J. Controlled Release*, 150, 171-176, 2011.
- [33] T. Yamamoto and R. Yoshida, "Self-oscillation of polymer and photo-regulation by introducing photochromic site to induce LCST changes", *React. Func. Polym.*, in press.
- [34] T. Ueki, M. Shibayama and R. Yoshida, "Self-oscillating micelles", *Chem. Commun.*, in press.
- [35] R. Yoshida, K. Uchida, Y. Kaneko, K. Sakai, A. Kikuchi, Y. Sakurai and T. Okano, "Comb-type grafted hydrogels with rapid de-swelling response to temperature changes", *Nature*, 374, 240-242 (1995).
- [36] B.G.G. Lohmeijer and U.S. Schubert, "Supramolecular engineering with macromolecules: An alternative concept for block copolymers", *Angew. Chem. Int. Ed.*, 41, 3825-3829, 2002.