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Design of novel biomimetic polymer gels with self-oscillating function

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Abstract

We report a novel biomimetic gel that undergoes autonomous swelling–deswelling oscillations without on–off switching of external stimuli, similar to heartbeat. The mechanical oscillation of gel was produced via oscillating chemical reaction, called the Belousov–Zhabotinsky (BZ) reaction. We have prepared an ionic gel consisting of the cross-linked poly(N-isopropylacrylamide) chain to which ruthenium tris(2,2′-bipyridine), a catalyst for the BZ reaction, was covalently bonded. The BZ reaction occurring within the gel matrix generates periodic redox changes of the catalyst moiety. This chemical oscillation is converted into the mechanical oscillation of the polymer network. As a result, the gel exhibits a periodical swelling–deswelling change. The self-oscillating behaviors of the gel were investigated in detail. When the gel size is smaller than the chemical wavelength, the redox change occurs homogeneously in the gel. In this case, the volume change is isotropic and the mechanical oscillation synchronizes with chemical oscillation without a phase difference. The period and amplitude can be controlled by changing the outer substrate concentrations. In the case of rectangular shape, chemical wave propagates along the length of the gel. The wavelength and velocity depend on the reaction rate of autocatalytic process as well as the diffusivity of the activator. The dynamic behavior that locally shrunken (or swollen) parts propagate was observed, similar to the peristaltic motion of worms. By using lithography technique, a ciliary motion actuator made of the gel has been demonstrated. These self-oscillating gels may be useful in a number of important applications to intelligent biomaterials such as pulse generator or chemical pacemaker, auto-mobile actuators or micropumps with peristaltic motion, device for signal transmission, etc. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Polymer gels; Biomimetics; Intelligent materials; N-isopropylacrylamide; Phase transition; Swelling; Self-oscillation; Nonlinear chemistry; BZ reaction

1. Introduction

Polymer gel is a jelly-like soft material made of a cross-linked three-dimensional polymer network containing solvent. Over the last two decades, many researchers have developed stimuli-responsive polymer gels that change volume abruptly in response to a change in their surroundings; for example, solvent composition [1,2], temperature [2,3], pH [4], and supply of electric field [5], etc. Their ability to swell and deswell according to conditions makes them an interesting proposition for use in new intelligent materials. In particular, applications for biomedical fields, e.g. actuator (artificial muscle) [6,7], self-regulating drug delivery systems [8–10], purification of chemical or bioactive agents [11,12], cell culture [13], on–off regulation of enzymatic reactions [14], biosensor [15] etc. are extensively studied. One of the strategies of these applications is

to develop biomimetic materials system with stimuli-responding function; i.e. the systems that the materials sense the environmental changes by themselves and go into action. For these systems, the on–off switching of external stimuli is essential to instigate the action of the gel. Upon switching, the gels provide only one unique action, either swelling or deswelling.

In contrast to these temporary responses to stimuli, there are many physiological phenomena in our body that continue their own native cyclic changes; examples are heartbeat, brain waves, the pulsatile secretion of hormones, etc. If such self-oscillation could be achieved for gels, possibilities would emerge for new biomimetic intelligent materials that exhibit rhythmical motion. Recently, we have developed such a self-oscillating gel [16–19]. It spontaneously exhibits cyclic swelling and deswelling under constant conditions, requiring no switching of external stimuli. Its action is similar to that of a beating heart muscle. In this paper, the self-oscillating behaviors of the gel have been discussed.

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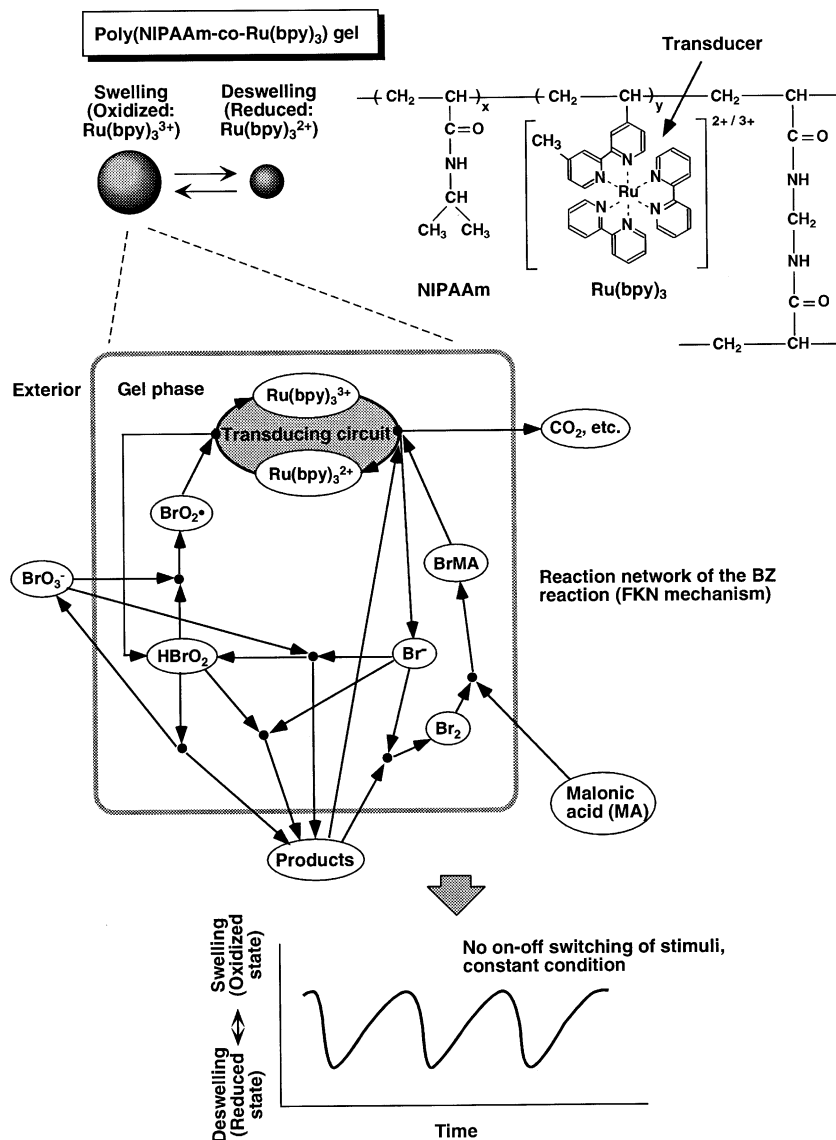*E-mail address:* yoshida@bmw.t.u-tokyo.ac.jp (R. Yoshida).

Fig. 1. Self-oscillation of poly(NIPAAm-co-Ru(bpy)$_3$) gel coupled with the Belousov–Zhabotinsky reaction.

2. Design of self-oscillating gel

2.1. Oscillating chemical reaction: the Belousov–Zhabotinsky reaction

The mechanical oscillation is driven by the energy of a chemical reaction, called the Belousov–Zhabotinsky (BZ) reaction [20–22], within the gel (Fig. 1). The BZ reaction is an oscillating reaction that spontaneously generates rhythmical changes through its redox potential. The reaction was discovered by Belousov who was looking for an inorganic analog of the Krebs cycle (TCA cycle; a key metabolic process in which citric acid is an intermediate), and then modified by Zhabotinsky. The overall process of the BZ reaction is the oxidation of an organic substrate such as citric or malonic acid by an oxidizing agent (bromate) in the presence of metal catalyst under acidic condition. The

metal ion or the metal complex with high redox potentials (1.0–1.4V/SHE), such as cerium ion, ferroin, or ruthenium tris(2,2′-bipyridine) (Ru(bpy)$_3$) are widely used as a catalyst. In the course of the reaction, the catalyst ion periodically changes its charge number to oscillate between the oxidized and reduced states for several hours as long as the substrate exists. When the solution is homogeneously stirred, the color of the solution periodically changes, like a neon sign, based on the redox changes of the metal catalyst. When the solution is placed as a thin film in stationary conditions, concentric or spiral wave patterns develop in the solution. The wave of oxidized state propagating in the medium at a constant speed is called 'chemical wave'.

The BZ reaction has a reaction network similar to TCA cycle. The oscillation mechanism has been explained by the models composed of three cyclic sub-processes (FKN mechanism) [21,22]; consumption of bromide ion (called

'process A'), autocatalytic reaction of bromous acid with oxidation of the catalyst (process B), and organic reaction with reduction of the catalyst (process C). These mechanisms lead to several phenomena such as oscillations and excitability, traveling reaction fronts, target patterns, spiral and scroll waves, bifurcation and chaos, etc. These phenomena are related to important processes in biology. The significance of the BZ reaction has been recognized as a chemical model for understanding some aspects of biological phenomena, such as glycolytic oscillations or biorhythms [23], cardiac fibrillation [24], self-organization of amoeba cells [25], pattern formation on animal skin [26,27], visual pattern processing on retina [28], etc.

2.2. Preparation of poly(NIPAAm-co-Ru(bpy)₃) gel undergoing redox changes

We prepared a copolymer gel which consists of *N*-isopropylacrylamide (NIPAAm) and Ru(bpy)$_3$ [16,17]. Ru(bpy)$_3$, acting as a catalyst for the BZ reaction, is pendent to the polymer chains of NIPAAm (Fig. 1). It is well known that homopolymer gels of NIPAAm have thermosensitivity and undergo an abrupt volume-collapse when heated at around 32 °C; i.e. thermally induced volume phase transition [2,3]. Fig. 2 shows the temperature dependence of swelling ratio for the poly(NIPAAm-*co*-Ru(bpy)$_3$) gel when the Ru(bpy)$_3$ sites were kept in the reduced (Ru(II)) and oxidized (Ru(III)) states in aqueous solutions containing Ce(III) and Ce(IV) (powerful oxidizing agent) ions, respectively. The oxidation of the Ru(bpy)$_3$ moiety caused not only an increase in the swelling degree, but also a rise in the transition temperature. These characteristics may be interpreted by considering an increase in the cationic changes bound to the network due to the oxidation of Ru(II) to Ru(III) in the

Ru(bpy)$_3$ moiety. This phenomenon is identical with that generally observed in NIPAAm-based polyelectrolyte gels when their ionic charges were increased [4]. As a result, we may expect that our gel undergoes a cyclic swelling–deswelling alteration when the Ru(bpy)$_3$ moiety is periodically oxidized and reduced under constant temperature.

3. Swelling–deswelling oscillation of the gel with periodical redox changes

3.1. Self-oscillation of the miniature gel

The poly(NIPAAm-*co*-Ru(bpy)$_3$) gel was cut into a cubic shape (each length of about 0.5 mm) in pure water, and then immersed into an aqueous solution containing malonic acid (MA), sodium bromate (NaBrO$_3$), and nitric acid (HNO$_3$) at constant temperature (20 °C). This outer solution comprised the reactants of the BZ reaction, with the exception of the catalyst. Therefore, the redox oscillation does not take place in this solution. However, as it penetrates into the gel, the BZ reaction is induced within the gel by the Ru(bpy)$_3$ copolymerized as a catalyst on the polymer chains. Under reaction, the Ru(bpy)$_3$ in the gel network periodically changes between 2 + and 3 + states. In the miniature gel whose size is smaller enough than the wavelength of chemical wave (typically several mm), the redox change of ruthenium catalyst can be regarded to occur homogeneously without pattern formation. We observed the oscillation behavior under a microscope equipped with a CCD camera and video recorder. Color changes of the gel accompanied with redox oscillations (orange: reduced state, light green: the oxidized state) were converted to 8-bit grayscale changes (dark: reduced, light: oxidized) by image processing. Due to the redox oscillation of the immobilized Ru(bpy)$_3$, mechanical swelling–deswelling oscillation of the gel autonomously occurs with the same period as for the redox oscillation (Fig. 3). The volume change is isotropic and the gel beats as a whole, like a heart muscle cell. The chemical and mechanical oscillations are synchronized without a phase difference (i.e. the gel exhibits swelling during the oxidized state and deswelling during the reduced state).

3.2. Control of oscillation period and amplitude

In order to enhance the amplitude of swelling–deswelling oscillations of the gel, we attempted to change the period and amplitude of the redox oscillation by varying the initial concentration of substrates of the BZ reaction. It is a general tendency that the oscillation period increases with the decrease in concentration of substrates. For the bulk solution system consisting of MA, NaBrO$_3$, HNO$_3$ and Ru(bpy)$_3$Cl$_2$, we obtained the following empirical relations between the period (*T*[s]) and initial molar concentration of
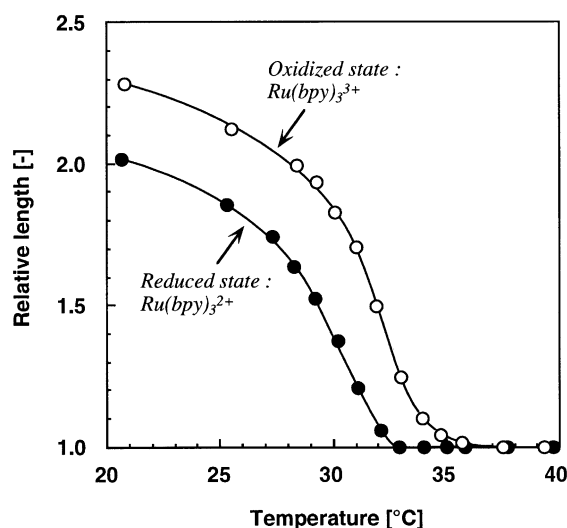

Fig. 2. Temperature dependence of normalized length for poly(NIPAAm-*co*-Ru(bpy)$_3$) gel under oxidizing and reducing conditions. The normalization was performed by use of the original gel length, which was determined at 45 °C.
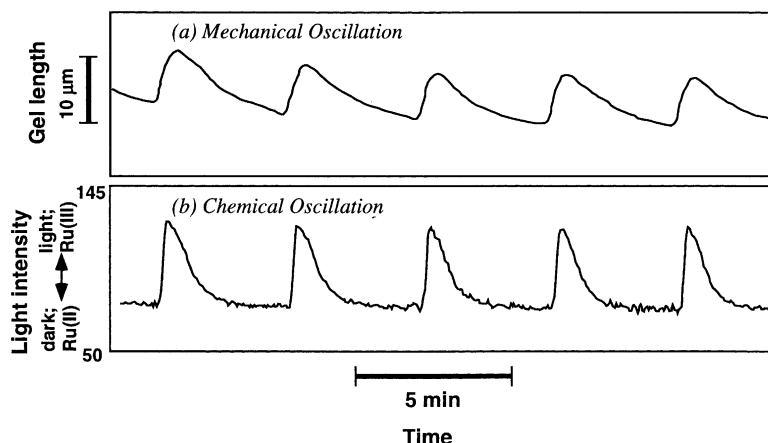
Fig. 3. Periodical redox changes of the cubic poly(NIPAAm-*co*-Ru(bpy)$_3$) gel (lower) and the swelling–deswelling oscillation (upper) at 20 °C. Transmitted light intensity is expressed as an 8-bit grayscale value. Outer solution: [MA] = 0.0625 M; [NaBrO$_3$] = 0.084 M; [HNO$_3$] = 0.6 M.

substrates [29] (Fig. 4):

$$T = 2.97[MA]^{-0.414}[NaBrO_3]^{-0.796}[HNO_3]^{-0.743} \quad (1)$$

T is most sensitive to [BrO$_3^-$]. This is due to the fact that the process A in the FKN mechanism, corresponding to the consumption of bromide ions (resting state), becomes a dominant factor in increasing the period. For the gel system, the oscillating profiles of the swelling–deswelling changes as well as the redox changes were studied as a function of the substrate concentrations by using an image-processing method. It was found that both period and amplitude of chemical oscillation varied depending on the substrate concentration. We obtained the following empirical relations for the gel system [30]:

$$T = 60.3[MA]^{-0.155}[NaBrO_3]^{-0.436}[HNO_3]^{0.469} \quad (2)$$

This concentration dependence is different from not only that for bulk solution system (Eq. (1)), but also that for reaction–diffusion system using the same poly(NIPAAm-*co*-Ru(bpy)$_3$) gel with a rectangular shape [29]. The reason

may be as follows. (1) In the case of the miniature gel, the dilution of intermediates from the gel into the surrounding aqueous phase must be more remarkable. The dilution effect, especially that for the activator (HBrO$_2$), leads to an increase in the period of chemical oscillations. (2) In addition, concentration change of substrates or products within the gel phase resulting from the swelling–deswelling oscillations may have some effects on the chemical oscillations (i.e. feedback effect).

The variation in chemical oscillation leads to a change in the swelling–deswelling oscillation; i.e. the swelling–deswelling amplitude (the change in gel length, Δd) increases with an increase in the period and amplitude of the redox changes. Empirically, the relation between Δd (μm) and the substrate concentrations can be expressed as follows:

$$\Delta d = 2.38[MA]^{-0.392}[NaBrO_3]^{0.059}[HNO_3]^{0.764} \quad (3)$$

As a result, it is apparent that the swelling–deswelling amplitude of the gel is controllable by changing the initial concentration of substrates. So far, the swelling–deswelling amplitude with ca. 20% to the initial gel size was obtained as a maximum value. The waveform of redox changes showed a tendency to deform to rectangular shape with a plateau period when the amplitude of swelling–deswelling oscillation increased [30]. From this result, it is supposed that not only energy transformation from chemical to mechanical change, but also feedback mechanism from mechanical to chemical change acts in the synchronization process.

4. Self-oscillating behaviors with the propagation of chemical wave

4.1. Peristaltic motion of the gel
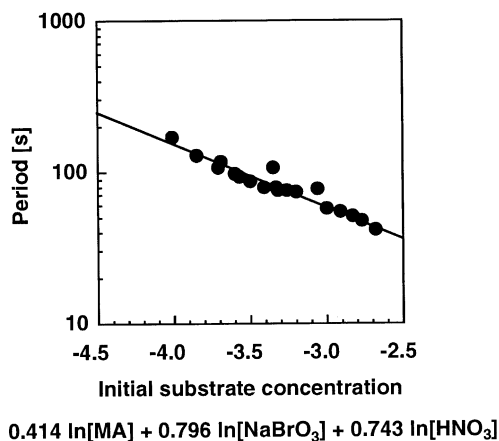
A rectangular piece of the gel (1 mm × 1 mm × 20 mm)

Fig. 4. Period as a function of the initial concentrations of malonic acid, sodium bromate, and nitric acid for the bulk solution system.

was immersed in the aqueous solution containing the three reactants of the BZ reaction. By coupling chemical oscillation with the diffusion of a reaction intermediate ($HBrO_2$) through the gel phase, a periodical pattern with different colors (i.e. different redox states) develops along the length of a rectangular gel. The pattern travels with time so that we can see the stripes moving at a constant speed (typically several tens of micrometers per second), like a series of waves along the gel. This phenomenon is known as the 'chemical wave'.

Since a change in the charge number of $Ru(bpy)_3$ induces volume change of the gel, Ru(II) and Ru(III) zones in the chemical wave represent simply the shrunken and swollen parts of the cycle, respectively. The locally swollen and shrunken parts move in the direction of the gel length along with the chemical wave. The propagation of the chemical wave makes the free end of the gel move back and forth at a rate corresponding to the wave propagation speed. As a result, the total length of the gel periodically changes [31].
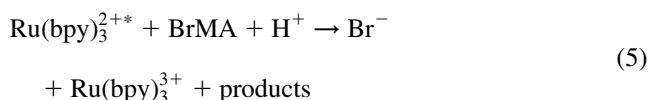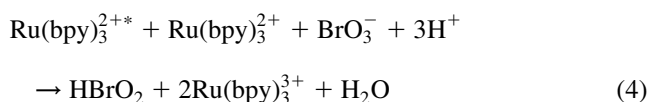
Fig. 5 demonstrates such an oscillating behavior of the rectangular poly(NIPAAm-*co*-Ru(bpy)$_3$) gel. The spatio-temporal pattern was constructed as follows. From the recorded video images of the rectangular gel, one-pixel line along the length was sampled at a suitable time interval (3 s) and sequentially lined up as a function of time through an image-processing method using a computer. The free end of the rectangular sample gel moves back and forth with the propagation of the chemical wave, through which the overall length of the gel undergoes a cyclic extension–contraction change within ca. 100 μm. Under a steady state, the free end begins to shrink when arriving the oxidizing front (light color) of the wave, while arrival of the reducing front with a dark color allows the gel to swell. It should be noted

that this observation is in contrary to the prediction from Fig. 2; that is, an 'anti-phase mode' between the chemical and mechanical oscillations was observed.

It was demonstrated by the mathematical model simulations that the change in the overall gel length is equivalent to that in the remainder of gel length divided by the wavelength of the chemical wave, because the swelling and the deswelling cancel each other per one period of oscillations under steady oscillating conditions [31]. The dynamic behavior that locally shrunken (or swollen) parts propagate is similar to the peristaltic motion observed in worms.

4.2. Control of chemical wavelength by laser irradiation to the pacemaker site

It is well known that the period of oscillation is affected by light illumination for the $Ru(bpy)_3^{2+}$-catalyzed BZ reaction. The excited state of the catalyst ($Ru(bpy)_3^{2+*}$) causes new reaction process: production of activator (Eq. (4)), or production of inhibitor (Eq. (5)), which depends on the solute compositions [32]

$$Ru(bpy)_3^{2+*} + Ru(bpy)_3^{2+} + BrO_3^- + 3H^+$$

$$\rightarrow HBrO_2 + 2Ru(bpy)_3^{3+} + H_2O \tag{4}$$

$$Ru(bpy)_3^{2+*} + BrMA + H^+ \rightarrow Br^-$$

$$+ Ru(bpy)_3^{3+} + products \tag{5}$$

Therefore, (i) we can intentionally make a pacemaker with a desired period (wavelength) by local illumination of laser beam on the gel, or (ii) we can change the period (wavelength) by local illumination on the pacemaker, which was already present in the gel.
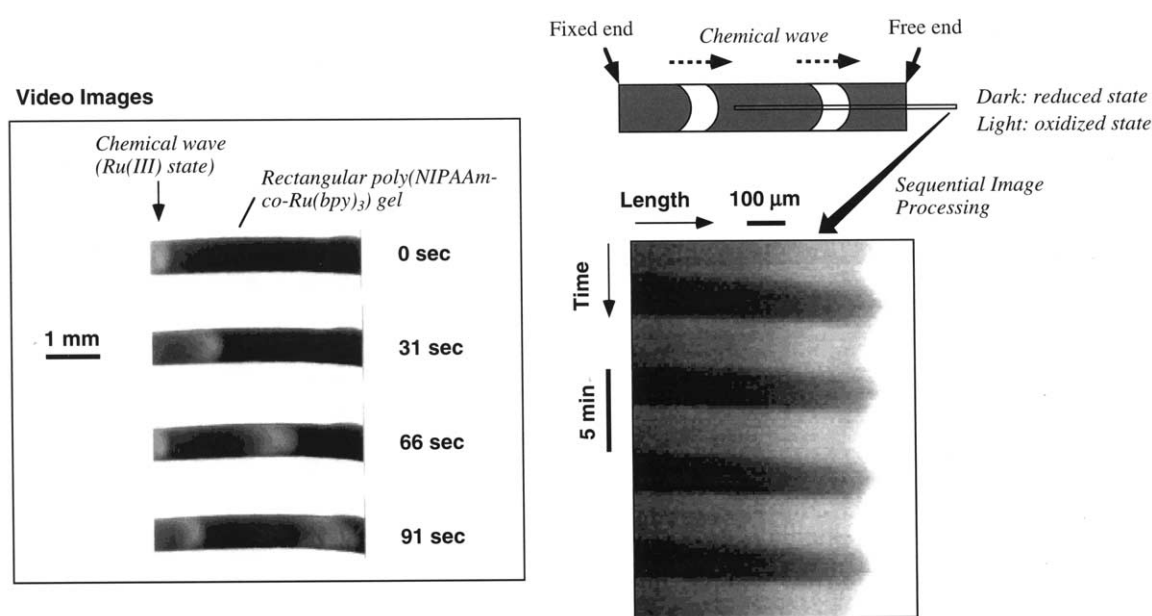

Fig. 5. Spatio-temporal pattern of oscillating behavior constructed from image-processing for the rectangular poly(NIPAAm-*co*-Ru(bpy)$_3$) gel.
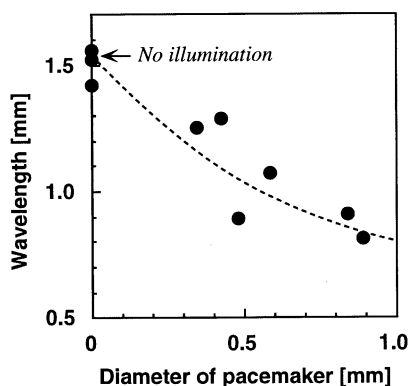
Fig. 6. Relation between the diameter of pacemaker and the wavelength of chemical waves.

Fig. 7. Velocity of chemical waves in the PNIPAAm gel vs. the square root of the product of proton and bromate concentrations at 20 °C.

In the rectangular gel, the corner often becomes a pacemaker from which chemical waves start to propagate. Therefore, the self-oscillating behaviors of the gel can be controlled by irradiating laser light locally to the pacemaker site of gels. Fig. 6 shows the effect of laser irradiation on the pacemaker under the condition that photo-illumination produces activator. The size of pacemaker was altered by changing the diameter of irradiated region on the gel through the pinhole on the way of light path. It was found that the wavelength of traveling waves in the gel decreased as the size of pacemaker increased. The results were in good agreement with a theoretical model simulation [33]. This result means that we can control the macroscopic swelling–deswelling behavior of the gel by local perturbation, i.e. small signal can be amplified to macroscopic change.

4.3. Measurement of solute diffusivity in gel by utilizing the chemical wave

The chemical wave is driven by the diffusion of $HBrO_2$ into the reduced state ahead of the front. The wave velocity of the BZ reaction is theoretically given by [22]

$$v \propto \left(4k_5 D[H^+][BrO_3^-]\right)^{1/2} \qquad (6)$$

where k_5 is the rate constant of the autocatalytic reaction of $HBrO_2$, D is the diffusion coefficient of activator ($HBrO_2$). We measured the velocity of chemical wave propagating in the thermosensitive homopolymer gel of NIPAAm in which the Ru(bpy)$_3$ catalyst was physically adsorbed at several temperatures. Fig. 7 shows the dependence of the wave velocity on the square root of the initial concentration product ($[H^+][HBrO_3^-]$)$^{1/2}$. As predicted from Eq. (6), the wave velocity increases in proportion to the square root of the product of proton and bromate concentrations. According to Eq. (6), the slope of v vs. ($[H^+][HBrO_3^-]$)$^{1/2}$ plots represents $(4k_5 D)^{1/2}$. From the slope, therefore, we can calculate the diffusivity (D) in the PNIPAAm gel at each temperature. The precision of the obtained diffusivites was evaluated by comparison with the values which were determined by conventional permeation method using gel membrane
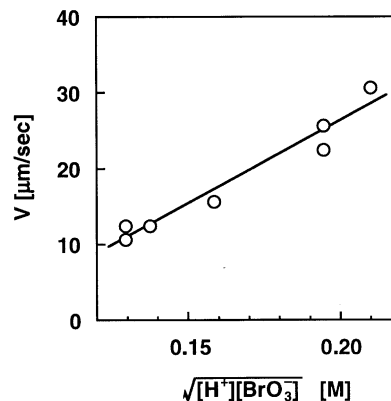
[34]. The diffusivities obtained from the two measuring methods gave a good agreement at various temperatures. The new method utilizing the BZ wave would be useful for the estimation of solute diffusivity for many kinds of gels and the analysis of their structures.

4.4. Ciliary motion actuator using self-oscillating gel

One of the promising fields of the MEMS is microactuator array or distributed actuator systems. The actuators, that have a very simple actuation motion such as up and down motion, are arranged in an array form. If their motions are random, no work is extracted from this array. However, by controlling them to operate in a certain order, they can generate work as one system. One of the typical examples of this kind of actuation array is a ciliary motion microactuator array. There have been many reports to realize it. Although various actuation principles have been proposed, all the previous works based on the same concept that the motion of actuators were controlled by external signals. If the self-oscillating gel plate with microprojection structure array on top is realized, it is expected that the chemical wave propagates and creates dynamic rhythmic motion of the microprojection structure array (Fig. 8(a)). This is the structure of proposed new ciliary motion array that exhibits spontaneous dynamic propagating oscillation.

The gel plate with microprojection array was fabricated by molding technique [35]. First, the moving mask deep-X-ray lithography technique was utilized to fabricate the PMMA plate with truncated conical shape microstructure array. This step was followed by the evaporation of Au seed layer and subsequent electroplating of nickel to form the metal mold structure. Then, a PDMS mold structure was duplicated from the Ni metal mold structure and utilized for gel molding. The formation of gel was carried out by vacuum injection molding technique.

The structure with the height of 300 μm and bottom diameter of 100 μm were successfully fabricated by the proposed process (Fig. 8(b)). The propagation of chemical reaction wave and dynamic rhythmic motion of the
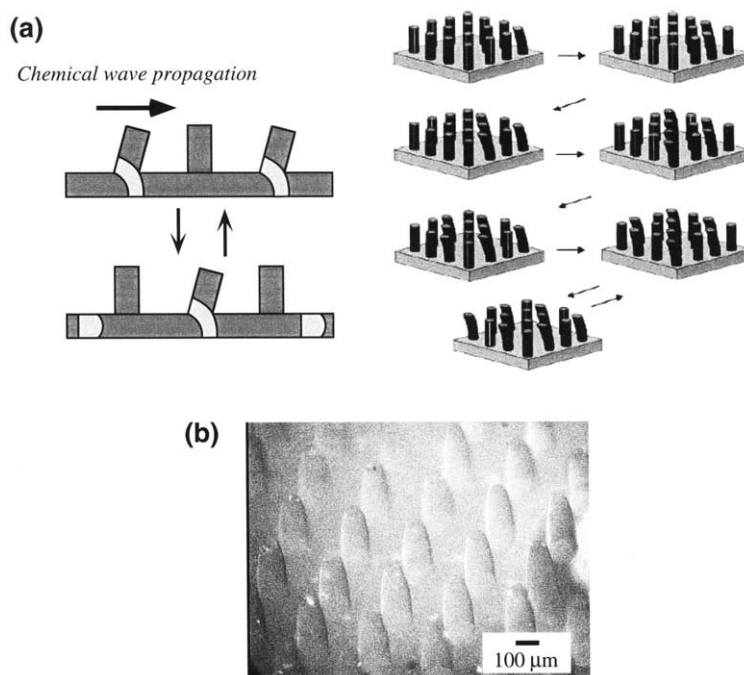
Fig. 8. (a) Concept of ciliary motion actuator using the self-oscillating gel and (b) the microprojection structure array on the gel surface fabricated by X-ray lithography technique.

microprojection array were confirmed by chemical wave observation and displacement measurements [35]. The propagation speed of the chemical wave was 1700 μm/min. The oscillation frequency and height change were 0.0055 Hz and 4 μm, respectively. The feasibility of the new concept of the ciliary motion actuator made of self-oscillating polymer gel was successfully confirmed.

5. Concluding remarks

Novel biomimetic polymer gels with self-oscillating function have been developed. The gel has a cyclic reaction network in itself, which is similar to metabolic reaction, and generates periodic mechanical energy from the chemical energy of the BZ reaction. The self-oscillating behavior can be controlled by changing the reaction condition or geometric design of the gel. The self-oscillating gel may be useful in a number of important applications such as pulse generator or chemical pacemaker, self-walking (auto-mobile) actuators or micropumps with autonomous beating or peristaltic motion, device for signal transmission utilizing propagation of chemical waves, oscillatory drug release synchronized with cell cycles or human biorhythms, etc. Research into the mechanism of the oscillating behavior as well as the practical applications continues.

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