

Pulsating pH-Responsive Nanogels

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A novel method is presented for the design of robust, sustained nanochemomechanical oscillators. The approach is based on the switching of chemoresponsive nanogel beads between their collapsed and swollen state by coupling them to an appropriately chosen nonlinear reaction. The presented system utilizes a proton activated oscillatory reaction and pH-sensitive nanobeads of gel that provide more than an order of magnitude volume change. A key point of our approach is the control of the colloid stability of the nanobeads of gel in a wide range of experimental parameters (pH, ionic strength, temperature) without interfering with the swelling characteristics of the nanogel particles. This was achieved by utilizing the interaction of nanogels with ionic surfactants.

Introduction

Molecular motors, which transform chemical energy to mechanical work at a molecular scale, are ubiquitous in living systems. Motor molecules play a key role in muscular contraction, cell division, cellular traffic, material transport along the axons of nerve cells, etc.^{1,2}

To achieve artificial autonomous nanodevices two approaches have been developed until now. In the first case, the nanodevice is based on DNA supramolecular structures, which can undergo cyclic conformational changes. Autonomous behavior of DNA-based nanodevices has been achieved in only a few cases with the help of deoxyribozymes^{3–5} and enzymes,^{6,7} and very recently by means of an oscillatory reaction.⁸ A major limitation of these systems is that their environmental conditions must be compatible with biochemistry, thus ruling out the presence of any molecule that could cause the degradation or denaturalization of the biomolecules (e.g., oxidizing and reducing agents, heavy metal ions, too acidic or basic environment).

The other approach is based on the coupling of stimuli-responsive hydrogels and nonlinear chemical reactions.⁹ These systems are capable of generating oscillatory volume changes of the chemoresponsive gels. The prototype of this approach is provided by the pioneering work carried out by Yoshida and co-workers by using first a pH-sensitive and later a ruthenium-containing polymer gel.^{10,11} In the latter case, they prepared a copolymer gel of *N*-isopropylacrylamide (NIPAm) in which a ruthenium complex is bound to the polymer chain. The gel swells and deswells in the oxidized and the reduced states of the ruthenium complex, respectively. This ruthenium complex is a catalyst of the oscillatory Belousov–Zhabotinsky (BZ) reaction. During the course of the reaction the catalyst is oxidized and reduced periodically. Now, immersing the gel into the BZ mixture the gel undergoes periodical volume changes.

Yoshida and co-workers used ruthenium complex containing gels from millimeter size down to nanobeads with diameters around 100–150 nm.^{11–13} One of the limitations of this system is that the gel is in a swollen state even in the reduced state of the catalyst, which considerably decreases the available amplitude of the volume change. Furthermore, the change in the oxidation state of the catalyst, which goes from +2 to +3, provides relatively small stimuli. Altogether, the volume change

between the two states of the ruthenium containing nanobeads is limited to a factor of 2.

Sakai et al.¹⁴ have also investigated the cross-linking effect on the phase transition behaviors of ruthenium containing polymers by comparing the conformational changes of the linear polymer and the nanogel beads. Their results indicate that while the linear polymers change their conformation continuously, the gel beads undergo discontinuous volume change because the polymer chains are forced to behave cooperatively by the cross-linking. Recently, Yashin and Balazs presented a model for a polymer gel undergoing the BZ reaction.¹⁵

Chemomechanical oscillations have also been produced by coupling pH-responsive macrogels with proton activated bistable^{16,17} or oscillatory reactions.^{18,19} Ryan and co-workers used poly(methacrylic acid) gels and the bromate–sulfite–ferrocyanide pH-oscillator, which typically oscillates between pH 3 and 7.^{18,19} In their experiments the linear dimensions of the sample (a particle with volume of 1 μm^3) changed by a factor of 6 and the force generated by the gel was ~ 0.012 N.

Here, we present a novel approach for the development of a hydrogel-based chemomechanical system. The applied nanobeads of gel respond to pH stimulus and provide a robust swelling accompanied by a 12-fold volume increase. Furthermore, they retain their colloid stability over a wide range of experimental parameters (pH, ionic strength, temperature). By coupling them to a chemical oscillator a free running autonomous nanomotor is provided.

Experimental Conditions

Preparation of pNIPAm-co-AAc Microgel Latex. For the preparation of the nanogels, *N*-isopropylacrylamide (NIPAm), methylenebisacrylamide (BA), ammonium-persulfate (APS), acrylic acid (AAc), and sodium dodecyl sulfate (SDS) were used. These chemicals were provided by Aldrich and were used without further purification. Our procedure was based on the method developed by Wu et al.^{20,21} NIPAm (2.520 g), 0.190 g of cross-linker BA, and 38 mg of SDS were dissolved in 190 mL of distilled water. The temperature of the reactor was kept at 80 °C and the solution was intensively stirred. To remove oxygen, nitrogen gas was purged through the solution for 30 min. Then, 0.179 g of AAc dissolved in 5 mL of water was

mixed with the solution. Once the acrylic acid was added, the reaction was immediately initiated by injection of 56 mg of APS dissolved in 5 mL of water. The solution was stirred intensely for an additional 4 h at 80 °C while it was continuously purged with nitrogen. The latex was purified from unreacted monomers and surfactant by dialysis against distilled water for 4 weeks.

Nonlinear Chemical Reaction. In the continuous stirred tank reactor (CSTR) experiments H_2SO_4 (Chemolab 96%), NaBrO_3 (Fluka p.a.), sodium sulfite (Aldrich, 98%), and doubly distilled water were used to prepare the working solutions. The chemical state of the CSTR was monitored by a pH electrode. The temperature was kept at $35.0(\pm 0.1)$ °C. The CSTR (volume 18 mL) was continuously refreshed by constant flows of solutions of the initial reagents distributed in two separated reservoirs. One reservoir contained a solution of sodium bromate. The second reservoir contained a solution of sodium sulfite, nanogel beads, and SDS. Equal flows were pumped by a peristaltic pump (Gilson Miniplus 2) from the reservoirs and premixed just before being injected into the CSTR. The residence time of the reactor was $\tau = 5400$ s. Hereinafter, $[X]_0$ denotes the concentration that species X would have after mixing in the total inlet flow and prior to any reaction. The solutions were mixed with a small propeller. The reactor was stirred for 25 s in every 150 s to avoid interference with dynamic light scattering. This stirring was enough to avoid the appearance of large inhomogeneities in the reactor. The pH oscillations in this reaction are robust, and we did not observe high stirring sensitivity.

Dynamic Light Scattering. Dynamic light scattering measurements were performed by means of Brookhaven dynamic light scattering equipment consisting of a BI-200SM goniometer and a BI-9000AT digital correlator. An argon-ion laser (Om-Nichrome, model 543AP) operating at 488 nm wavelength and emitting vertically polarized light was used as the light source. The signal analyzer was used in real-time “multi tau” mode. In this mode, the time axis was logarithmically spaced over a time interval ranging from 0.1 μs to 0.1 s and the correlator used 218 time channels. The pinhole was 100 μm . In the CSTR the autocorrelation functions were measured between two stirred periods and each autocorrelation function was accumulated for 30 s.

The measured autocorrelation functions were analyzed by the second-order cumulant expansion methods. The samples were found to be highly monodisperse. The effective hydrodynamic diameter (d_h) was calculated by the Einstein–Stokes relation from the first cumulant.

Results and Discussion

To gain pH-responsive, monodispersed, soft nanobeads (hydrogel spheres with a diameter of a few hundred nanometers), we prepared a copolymer nanogel of NIPAm and AAc. The pNIPAm hydrogel is probably the most well-known temperature-responsive hydrogel. It exhibits a remarkable shrinking with increasing temperature and shows a volume-phase transition (VPT) around 33 °C. When acrylic acid is introduced into the polymer network, the temperature of the VPT is considerably increased. This means that at temperatures which are just above the temperature of the VPT of the uncharged polymer network, the charged copolymer is still in a highly swollen state (see Figure 1). Consequently, by switching the pH (thus driving the carboxylic groups, e.g., from a protonated to deprotonated state) the hydrogels can respond with more than an order of magnitude volume change.

However, when the size of the pNIPAm-co-AAc particles is monitored as a function of increasing temperature at low pH

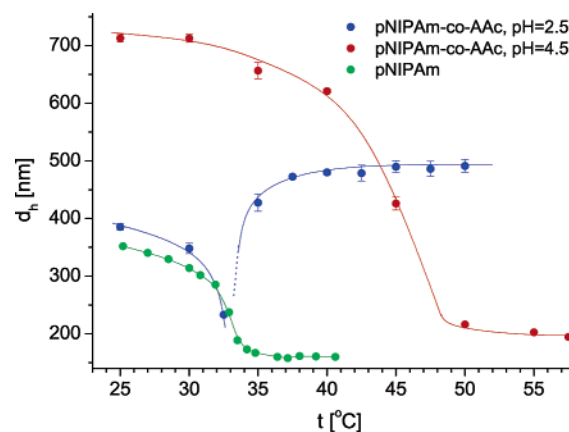


Figure 1. The hydrodynamic size of the nanogel beads in the function of temperature. Green circles indicate pNIPAm particles in distilled water (uncharged); red spheres denote pNIPAm-co-10% AAc nanobeads in distilled water (charged); blue spheres also denote pNIPAm-co-10% AAc nanobeads but in a pH 3.0 (HCl) medium (uncharged).

after the initial deswelling of the nanogel beads a sudden increase of the measured hydrodynamic size can be observed (Figure 1). This behavior can be interpreted in terms of the colloid stability of the particles. In the collapsed state of the nanogel beads the segment density within the particles is an order of magnitude larger than that in their swollen state giving rise to considerable interparticle attraction.^{22,23} This attractive interaction is counterbalanced by the repulsive interaction of the particles originating from the surface charge density of the collapsed nanobeads. Nevertheless, at low pH where the carboxylic groups are protonated, the surface charge density of the particles diminishes, leading to the observed aggregation (and eventually precipitation) of the nanogel particles.

To be able to use the pNIPAm-co-AAc nanogels for the development of robust, autonomous chemomechanical system, their colloid stability must also be ensured in the entire range of the applied experimental parameters (e.g., pH and ionic strength). Practically this means that the surface charge density of the nanogel beads must be high enough even at low pH to preserve their stability. However, this requirement seems to contradict the experimental conditions at low pH, where the carboxylic groups are protonated. To overcome this difficulty, we exploit the fact that the collapsed nanobeads are hydrophobic nanoparticles, which can adsorb surface active molecules on their surface. Thus, by adding an anionic surfactant to the system in an appropriate concentration, it can be achieved that while the internal charge density of nanobeads diminishes initiating the collapse of the nanobeads, the surface charge density will still be large enough due to the adsorption of the surfactant molecules, hence, ensuring the stability of the macroscopic system.

To determine the proper surfactant (SDS) concentration we investigated the stability of the pNIPAm-co-AAc nanobeads as a function of SDS concentration. This was achieved by monitoring the hydrodynamic diameter of the nanobeads of gel by dynamic light scattering at 35 °C (just above the VPT of the uncharged polymer network) at a given surfactant concentration (the ionic strength of the solution was set to 0.1 mol/dm³, which was characteristic for the later applied pH oscillator). At the beginning of the experiment the pH of the solution was relatively high (pH \sim 5.0), then it was decreased to pH 3.0 with the addition of a calculated amount of concentrated hydrochloric acid (Figure 2a,b). As is indicated by the figure at low surfactant concentration on the addition of the acid the individual nanogel beads first collapse, then they start to aggregate. The larger the

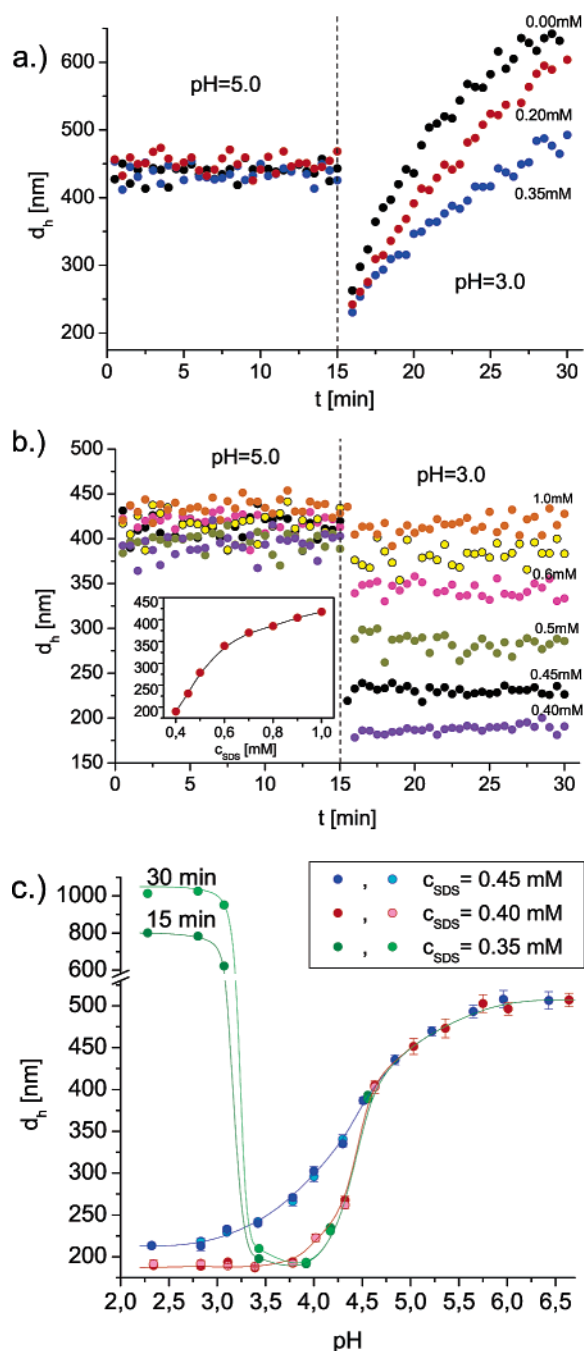


Figure 2. Hydrodynamic diameter of the pNIPAm-co-AAc nanobeads measured by dynamic light scattering at 35 °C. Panels a and b indicate the size as a function of time. At the beginning the pH of the medium (0.1 M KCl + varying amount of SDS) was 5.0, which was adjusted to 3.0 by the addition of 1.0 M HCl after 15 min. The SDS content of the medium varied between 0.0 and 1.0 mmol/dm³ as is indicated in the figure. The inset of panel b depicts the hydrodynamic size in the function of SDS concentration in the acidic media and characterizes the SDS binding to the uncharged nanogel beads. Panel c indicates the size of the nanobeads measured in the function of pH in the presence of 0.1 M KCl and varying amount of SDS. The solid and the open symbols represents data measured after 15 and 30 min in the 35 °C bath, respectively.

surfactant concentration is the slower aggregation takes place due to the increasing surface charge of the collapsed nanoparticles. When the surfactant concentration reaches 0.4 mmol/dm³ the collapsed nanogel beads become stable. However, as the surfactant concentration further increases, the size of the collapsed particles also increases and at 1.0 mmol/dm³ SDS

concentration the hydrodynamic diameter of the nanogel beads is practically identical at low and at high pH.

This behavior can be understood in terms of the characteristic features of the macromolecule/surfactant systems. It is well-established in the literature that ionic surfactants do not bind to similarly charged polyelectrolytes. However, neutral polymers can bind ionic surfactants in a cooperative interaction. This means that the surfactant molecule does not bind to the polymer up to a well-defined surfactant concentration called the critical aggregation concentration (cac). At the cac the surfactant starts to bind to the polymer in the form of micelle-like surfactant aggregates. It has also been shown in the literature²¹ that the uncharged pNIPAm nanogels bind SDS in two consecutive cooperative steps. In the first step the surfactant starts to bind in the outer loose shell of the microgel particles, then in a second step binding takes place in the cross-linked core of the nanogels.

In light of the described surfactant binding mechanism our experimental results can be interpreted as follows. At high pH where the pNIPAm-co-AAc nanobeads are negatively charged the negatively charged surfactant ions do not bind to the polymer chains. At low pH, where the polymer network charge diminishes, two characteristic SDS concentration ranges can be distinguished. At low surfactant concentrations (below the cac) the surfactant molecules adsorb at the surface of the collapsed nanogel particles providing them an increasing surface charge density, which is reflected by the decreasing aggregation rate of the collapsed particles. At high SDS concentration (above the cac) the uncharged (protonated) polymer network binds the surfactant in the form small micelle-like surfactant aggregates, which leads to the recharging of the nanogel beads in their whole volume and consequently to the reswelling of the nanobeads. This swelling is depicted in the inset of Figure 2b as a function of the surfactant concentration. In the intermediate surfactant concentration range ($c \approx 0.4$ mmol/dm³) the collapsed particles are stabilized either by the surfactant molecules adsorbed on their surface or by the cooperative binding of the surfactant in the outer shell of the microgels.

We have also investigated the pH dependence of the hydrodynamic size of the nanogels at a few surfactant concentrations around the cac (Figure 2c). These results provide additional support for our previous interpretation. In the presence of 0.35 mmol/dm³ SDS (below cac), the nanogel particles collapse with decreasing pH giving rise to a stable system around pH 4. In this pH range the stability of the nanobeads is provided on one hand by the adsorbed surfactant molecules and on the other hand by the still deprotonated carboxylic groups (at pH 4 approximately 10–15% of the carboxylic groups is charged). However, as the pH further decreases the remaining carboxylic groups become protonated and the nanobeads start to aggregate on the time scale of the experiment. In the presence of 0.40 mmol/dm³ SDS a sufficient amount of surfactant is bound after the collapse of the nanogels to stabilize them even around pH 2. Finally, when the SDS is present in 0.45 mmol/dm³ concentration (above cac) the surfactant starts to bind in the nanogel beads in the form of micelle-like aggregates resulting in the less pronounced "collapse" of the nanogels. At last, it could be concluded that the most robust response could be expected in the presence of 0.40 mmol/dm³ SDS in the case of the applied nanogel beads.

To construct an autonomous chemomechanical system, the oscillations of soft nanogel beads were driven by a sustained oscillatory reaction in an open reactor, where there is a continuous input of the reagents and an output of the bulk solution to keep the volume constant. Using an open reactor

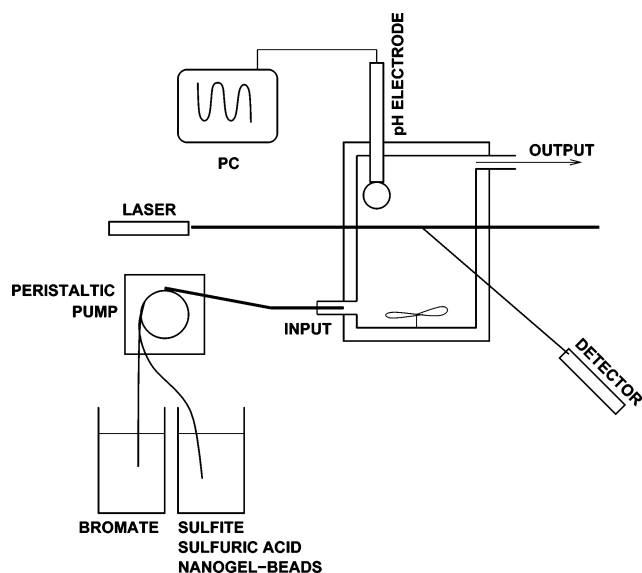
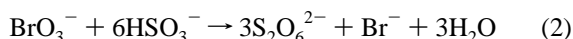
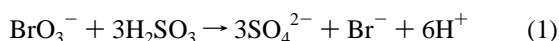


Figure 3. Sketch of the experimental setup.

allowed us to maintain the oscillations with constant amplitude and frequency as long as necessary. Since not only the chemical reagents but also the nanogel beads are continuously fed, there is a constant population of the nanoparticles in the reactor. This aspect can be important in potential applications. The applied experimental setup is depicted in Figure 3.

The “fuel” of the system is the chemical oscillator. We used the bromate–sulfite pH-oscillator,²⁴ because it shows oscillations in the appropriate pH range (between 3 and 7), the mixture is colorless, and there is no precipitate or gas formation during the reaction. Again, the period time of the pH oscillations must be long enough to perform the dynamic light scattering measurements to follow the volume oscillations of the nanobeads. Generally a pH-oscillator consists of an autocatalytic reactions for protons (positive feedback loop) and a proton consuming reaction (negative feedback loop) with appropriate time scale separation. These processes can be simply represented in the bromate–sulfite system by the next reactions:



In Figure 4a, the pH oscillations in the reactor are plotted together with the simultaneously measured hydrodynamic size of the nanogel beads. The change of the hydrodynamic size of the nanogels promptly follows the pH change of the oscillating reaction. As is indicated by Figure 2c, the size of the nanogel beads is practically constant below pH 4.0 and above pH 6.0. According to this the nanogels are either in their fully swollen state or in their collapsed state during the reaction, since the applied reaction oscillates between pH 4.0 and 6.0. It should be noted that no signs of aggregation could be observed during the reaction, indicating the success of the applied approach.

The pH dependence of the hydrodynamic size of the nanobeads measured in the presence of 0.35 mmol/dm³ SDS also implies that it is possible to construct such an oscillating system, in which a pH-regulated aggregate formation of the nanogel particles takes place. This can be accomplished if the pH of the reactor increases sufficiently quickly in an initially colloidally unstable system to avoid large extent coagulation. Such a system is demonstrated in Figure 4b. As is indicated by the figure, when the pH of the reaction mixture falls to the acidic

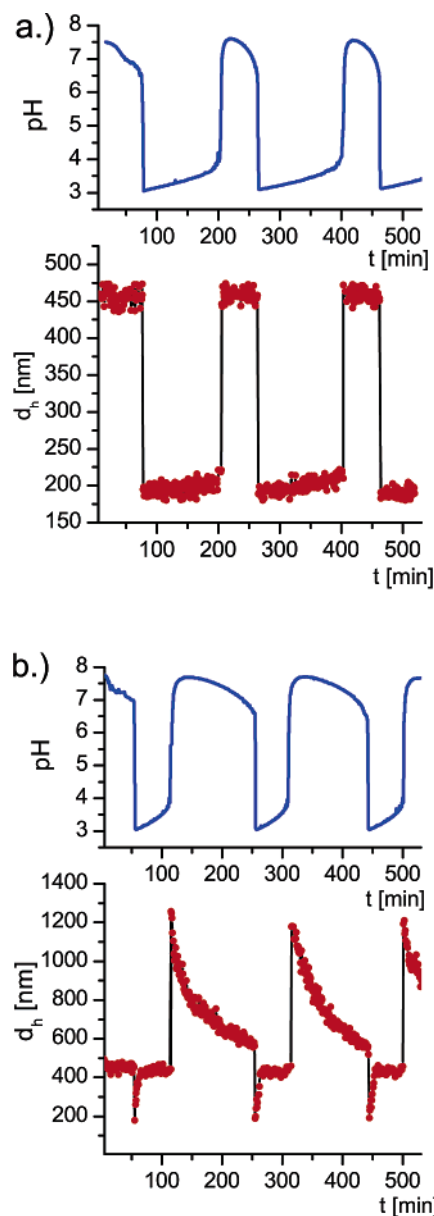


Figure 4. The pH and the hydrodynamic size of the nanogel beads as a function of time in the oscillating system. The concentrations in the input flow after mixing and prior to any reaction are $[\text{BrO}_3^-]_0 = 0.05 \text{ mol/dm}^3$, $[\text{SO}_3^{2-}]_0 = 0.05 \text{ mol/dm}^3$: (a) $[\text{H}_2\text{SO}_4]_0 = 0.0016 \text{ mol/dm}^3$, $[\text{SDS}]_0 = 0.4 \text{ mmol/dm}^3$; (b) $[\text{H}_2\text{SO}_4]_0 = 0.0010 \text{ mol/dm}^3$, $[\text{SDS}]_0 = 0.35 \text{ mmol/dm}^3$.

range the nanogel beads collapse and start to coagulate. However, as the pH of the system increases the surface charge density of the particles increases due to the deprotonation of the carboxylic groups. When the pH becomes large enough sufficient charge can accumulate on the nanogels to avoid further aggregation. The developed nanogel aggregates remain intact while the pH of the reaction mixture does not change to the basic range. When this happens the nanogel aggregates swell as a whole and then start to desaggregate.

Conclusions

In a summary, we have shown how chemoresponsive nanobeads of gel, which are capable of providing robust response, can be used for the development of a stable chemomechanical system. Since the collapsed nanogel beads can trap molecules, they can be used as nanocapsules to deliver reagents and control

their release in the reaction mixture. It should also be noted that the pH controlled aggregation of the nanogel beads might be used for the controlled multilayer deposition of solid surfaces with pH and temperature responsive nanoparticles that could lead to the development of, e.g., new optical nanodevices. This may open novel fields of application for oscillating chemical reactions.

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