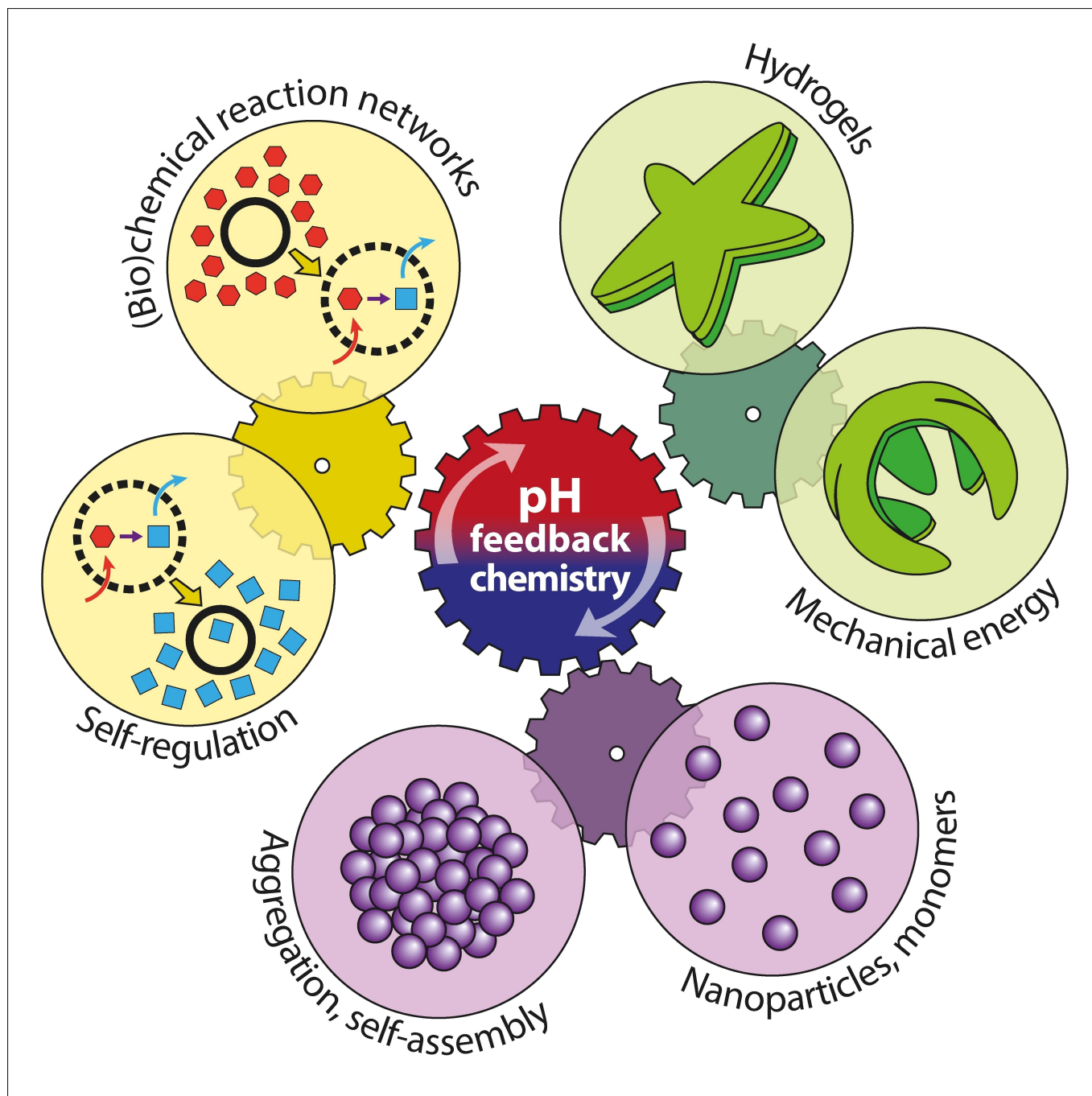


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Functional Rhythmic Chemical Systems Governed by pH-Driven Kinetic Feedback

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Hydrogen ion autocatalytic reactions, especially in combination with an appropriate negative feedback process, show a wide range of dynamical phenomena, like clock behavior, bistability, oscillations, waves, and stationary patterns. The temporal or spatial variation of pH caused by these reactions is often significant enough to control the actual state (geometry, conformation, reactivity) or drive the mechanical motion of coupled pH-sensitive physico-chemical systems. These autonomous operating systems provide nonlinear chemistry's most

reliable applications, where the hydrogen ion autocatalytic reactions act as engines. This review briefly summarizes the nonlinear dynamics of these reactions and the different approaches developed to properly couple the pH-sensitive units (e.g., pH-sensitive equilibria, gels, molecular machines, colloids). We also emphasize the feedback of the coupled processes on the dynamics of the hydrogen ion autocatalytic reactions since the way of coupling is a critical operational issue.

1. Introduction

The rational design of an artificial autonomous system that mimics some fundamental functions of the living systems is at the forefront of systems chemistry.^[1,2] Out-of-equilibrium complex reaction networks, including positive and negative feedback, are apparent building blocks of such systems. It is essential to notice that relatively simple chemical reactions, mostly inorganic redox processes, can produce various dynamical behavior, such as multistability, oscillations, chaos, and pattern formation.^[3,4] Organic chemistry-based systems with similar capabilities are less known, but there are interesting developments in this direction.^[5,6] As important biological functions, like switches and clocks, are operated by bistable and self-oscillatory processes, these dynamic behaviors are essential in adaptation, regulation, and morphogenesis. The periodic temporal and spatial variation of concentrations of chemicals can induce and drive linked physico-chemical processes in artificial systems to mimic the operation of natural ones. The linked process can be an additional reaction, like complex formation or polymerization,^[7,8] a molecular motion,^[9] gel deformation,^[10,11] structure changes of supramolecular systems,^[12] self-regulation,^[13] drug delivery,^[14] and dynamic changes of nanomaterials.^[15]

Among the hundreds of known oscillatory reactions, the Belousov-Zhabotinsky (BZ) reaction^[16,17] is the most recognized

and used for theoretical studies and applications. The long-lasting batch oscillatory capability is one of the main advantages of the BZ systems. The applications are mainly based on the periodic concentration changes of intermediate radicals (e.g., BrO_2^{\cdot}),^[8] and the catalyst (e.g., ferriin or $\text{Ru}(\text{bpy})_3^{2+}$).^[10] In their pioneering works, Yoshida and coworkers coupled the BZ reaction and a gel with a polymerized catalyst, demonstrating the chemomechanical energy conversion to mechanical work in a "self-oscillating" polymer.^[18] During the past decades, this original system has been developed in many directions, e.g., to create self-walking and self-swimming gels, ciliary motion soft actuator, and periodic motion on a surface.^[10] A critical species of coupling between the BZ chemistry and the responsive material is the catalyst. Therefore the change in the oxidation state of the catalyst, which goes, e.g., from +2 to +3, limits the effect stimuli. Different theoretical approaches, based on the lattice spring model and the combination of the macroscopic transport equations for mixtures, elasticity theory, and local equilibrium have been developed to understand these phenomena.^[19–21]

A crucial advantage of pH-oscillators is the significant amplitude variation of pH, which may cause an intense change in any coupled system (Figure 1). The protonation and deprotonation


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 An invited contribution to a Special Collection on Autocatalysis.

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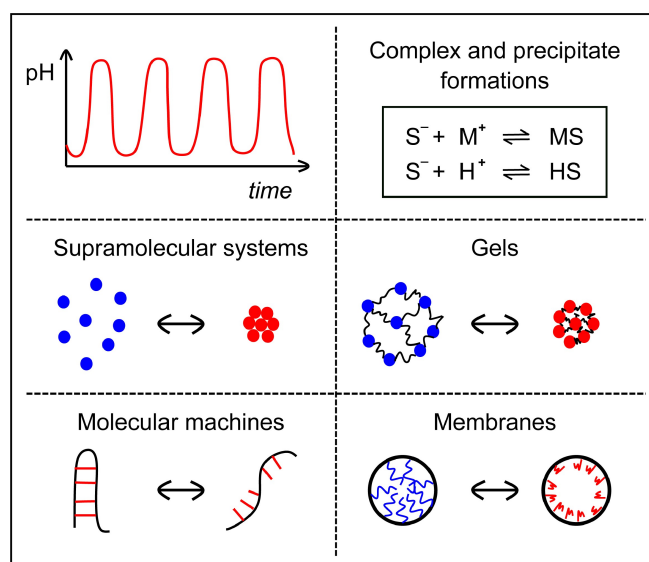


Figure 1. Different approaches have been developed to couple a pH-oscillator and a pH-sensitive unit to create an autonomous functioning system.

nation reactions are fundamental as they determine the reactivity and the geometry of molecules and the behavior of supramolecular structures. The importance of the acid-base reactions and the availability of easy-to-use pH oscillators resulted in a fruitful synergy in the past decades. The regulation of simple protonation/deprotonation equilibria, molecular machines, supramolecular systems, gels, and porous materials have been operated this way. Notably, a pH-oscillator was also used in one of the first reports on coupling responsive gels and oscillatory reactions.^[22] In this review, we aim to summarize the operation of pH-oscillators, highlight the coupling problem, and present the diverse applications.

2. Discussion

2.1. Driving systems: H⁺/OH⁻ autocatalytic reactions and pH-oscillators

The chemistry, the general aspects of the mechanism and the dynamics of H⁺/OH⁻ autocatalytic reactions and pH-oscillators have been reviewed in detail.^[23–26] The core part of these reactions is a positive feedback process, either driven by H⁺ or OH⁻ ions and can be described by the following overall reactions (R1 and R2) and rate equations (v_1 and v_2):^[25,26]



$$v_1 = (k_1 + k'_1[\text{H}^+])[\text{HA}][\text{B}] \quad (1)$$



$$v_2 = (k_2 + k'_2[\text{OH}^-])[\text{O}] \quad (2)$$

Here, HA, B, O, S, and P denote a protonated form of weak acid (e.g., HSO₃⁻), an oxidant (e.g., BrO₃⁻, IO₃⁻, H₂O₂), a hydrated aldehyde (e.g., methylene glycol), an adduct-forming compound (e.g., SO₃²⁻) and different products, respectively. An auspicious way, namely the use of a bell-shaped rate-pH curve of the OH⁻-producing urea-urease enzyme reaction to create a positive feedback mechanism, has been recently demonstrated.^[27] This results in similar pH-clock behavior to the reactions presented above.

The positive feedback might result in clock behavior in a batch reactor (Figure 2A). The abrupt change in pH appears after a well-defined lag period. This sort of kinetics can be effectively used in time-programming of supramolecular^[28] and nanoscopic assemblies and dynamic hydrogels.^[29]

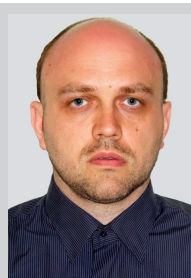
Autonomous oscillations require the presence of a delayed negative feedback process that drives back the system by removal of the autocatalytic species. A chemical reaction can make the removal, but a transport process can also play this role. The latter case opens a way to build a self-oscillatory system where the mutual coupling between the chemical reaction and the volume change of hydrogel results in oscillations.^[30] In some cases, the complex reaction of the main chemicals includes both the positive and the negative feedback pathways; therefore, oscillation appears without adding any other chemicals (e.g., BrO₃⁻-SO₃²⁻ reaction).^[31] A large variety of pH-oscillators have been designed by adding a proper negative feedback reaction to the above mentioned autocatalytic ones.^[23] In Table 1, we summarize the characteristics and dynamics of the reactions preferably used to create coupled systems. In these reactions, transient oscillations may develop in the presence of continuous feeding of at least one of the reagents. In contrast, sustained oscillations appear only in a continuous-stirred-tank-reactor (CSTR). In a closed two-compartment or a semi-batch reactor (Figure 2B and 2C) to get transient



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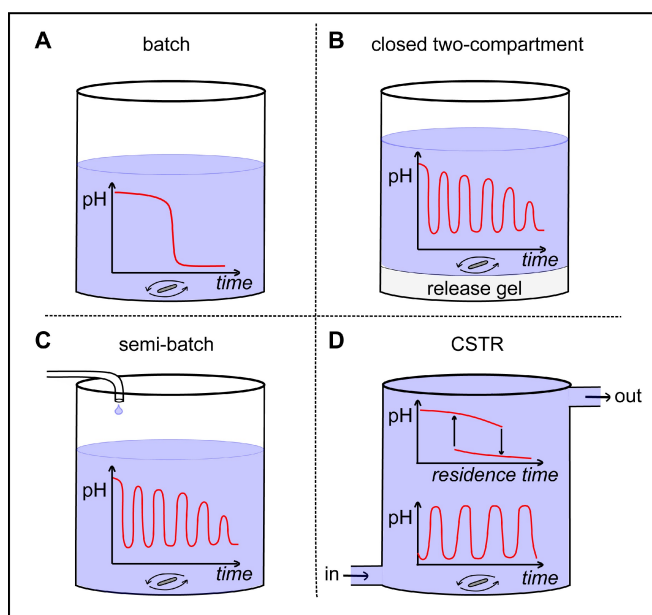


Figure 2. Operational modes and the corresponding dynamics of pH-oscillators: clock behavior in batch (A), transient oscillations in closed two-compartment (B) and in semi-batch (C) and bistability and sustained oscillations in CSTR (D).

oscillations, one reagent (e.g., HA) is continuously fed by dissolution from a precipitate,^[40] by release from a gel compartment^[33] or by inflow into a mixture of the other chemicals (e.g., the oxidant and the reactant induces the removal reaction). An interesting observation was made in a closed system that contains a release gel compartment and a pH-responsive oil droplet. The system shows continuous oscillations due to the asymmetric diffusive flux around a moving droplet.^[46] In a CSTR (Figure 2D), quite rich dynamics, bistability, oscillations, chaos, and excitability can be easily obtained.^[23] These reactions also show interesting spatiotempo-

ral phenomena, formation of pH-fronts, waves, and Turing-patterns.^[24]

The known mechanism, the corresponding simple models, and the several operational modes (batch/closed/semi-batch/continuous) of these reactions make them ideal for creating coupled functioning systems (Table 2.).

2.2. Coupling

In the past decades, enormous efforts have been devoted to designing oscillatory systems by coupling equilibrium chemical systems (having originally non-oscillatory behavior) to systems exhibiting autonomous pH variations (e.g., pH-clock reactions, pH-oscillators). These systems are of fundamental importance because they might contribute to the design of new stimuli-responsive materials, drug delivery tools, pH-driven synthesis methods, and self-assembly techniques. The chief idea in most of these applications is that the coupled systems are pH-responsive, and the pH variation triggers the change in their physical and/or chemical characteristics, which manifest in the change in the concentration of the chemical species, turbidity, etc. Two types of strategies have been introduced, the primary-driven (Figure 3A) and the peer-to-peer coupling (Figure 3B).^[47–50] In the first case, the originally non-oscillatory (driven) system does not significantly interfere with and does not change the main characteristics of the driving pH-oscillatory (primary) system. In the latter case, this interference is significant, and the driven system dominantly determines the characteristics of the driving systems (time period, clock time, amplitude of the oscillations). In this concept, there are three important chemical species. The coupling species is always the H^+ ion because it is involved in both chemical systems. The control species is the chemical species whose concentration can be varied to investigate the coupling strength between the two chemical systems. The target species (or phenomenon such as aggregation/disaggregation and swelling/shrinkage) is the

Table 1. Characteristics of the H^+/OH^- autocatalytic reactions and pH-oscillators most often used to create coupled systems.

Reaction	Dynamical behavior			Typical pH range	Refs.
	Batch/closed	Semibatch	CSTR		
$BrO_3^- - SO_3^{2-}$	clock/osc.	osc.	bist./osc.	4–7	[31,32]
$BrO_3^- - SO_3^{2-} - Fe(CN)_6^{4-}$	clock/osc.	osc.	bist./osc.	4–7	[33]
$BrO_3^- - SO_3^{2-} - Mn(II)$	clock/osc.	osc.	bist./osc.	3–7	[33]
$BrO_3^- - SO_3^{2-} - marble$	clock	osc.	bist./osc.	3.5–7.5	[34]
$BrO_3^- - SO_3^{2-} - HCO_3^-$	clock	osc.	bist./osc.	3–7.5	[35]
$IO_3^- - SO_3^{2-}$	clock	not reported	bist.	2.5–7	[36]
$IO_3^- - SO_3^{2-} - Fe(CN)_6^{4-}$	clock/osc.	osc.	bist./osc.	4–7.5	[33,36]
$IO_3^- - SO_3^{2-} - S_2O_3^{2-}$	clock	osc.	bist./osc.	5–7	[37]
$H_2O_2 - SO_3^{2-}$	clock	not reported	bist.	5–8	[38]
$H_2O_2 - S_2O_3^{2-}$	clock	not reported	bist./osc.	3.5–8	[39]
$H_2O_2 - CaSO_3 - NaHCO_3$	clock/osc.		bist./osc.*	5–7	[40]
$H_2O_2 - SO_3^{2-} - Fe(CN)_6^{4-}$	clock	not reported	bist./osc.*	5–8	[38]
methylene glycol- SO_3^{2-}	clock	not reported	bist./osc.	7–9	[41]
methylene glycol- SO_3^{2-} -gluconolactone	clock	not reported	bist./osc.	7–11	[42]
$ClO_2^- - S_4O_6^{2-}$	clock	not reported	bist.	2–9	[43,44]
urea-urease	clock	not reported	bist.	4–9	[27]

*The $H_2O_2 - SO_3^{2-} - HCO_3^-$ system shows CSTR oscillations.^[45]

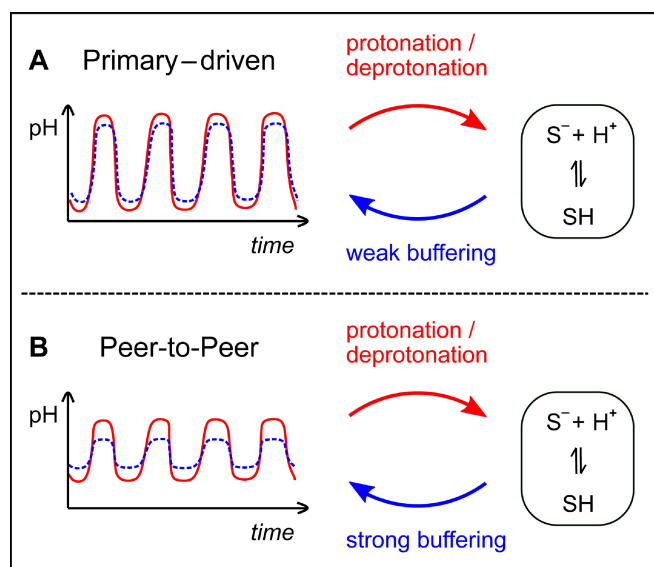


Figure 3. General coupling modes of pH-oscillators and pH-sensitive units. Primary-driven (A) and peer-to-peer (B) coupling. Red color shows the pH-oscillator, blue indicates the periodic changes in the coupled system.

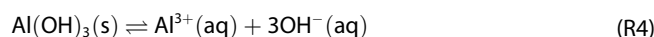
chemical species (phenomena) whose oscillatory behavior is wanted to be monitored. The coupling strength can be varied and controlled by the concentration of a control species. It reacts with H^+ ions and affects its concentration in the system. At a low concentration of the control species, the feedback from the driven system to the driving one can be weak but the concentration oscillation of the target species/phenomenon can be sufficiently strong to be measured and detected. This can be called a primary-driven coupling. The peer-to-peer coupling should be considered when the feedback from the driven system to the primary one results in significant changes in the characteristics of the primary system. It should be noted that there is no strict boundary between the primary-driven and peer-to-peer coupling because the transition between them is continuous that can be controlled by changing the concentration of the coupling species. In a one-compartment system, a pure primary-driven coupling cannot be established simply because the coupling species is incorporated in both systems thus affecting their kinetics. Especially, it is true if this species is directly involved in the autocatalytic pathway of the pH oscillator.

2.3. Complex and precipitate formations

At the beginning, the conscious design of new chemical oscillators was limited to compounds of certain elements, e.g., halogens, sulfur, and a few transition metals, because the required kinetic feedback steps were achieved by transitions between the oxidation states of the central species. The new approach of primary-driven coupling of a stable core oscillator and a non-redox reaction (complex or precipitate formation equilibrium) was proposed by Orbán and coworkers to over-

come this limitation and create concentration oscillations of several ions having only one stable oxidation state, e.g., Ca^{2+} , Al^{3+} , and F^- .^[7]

The core system was typically a pH oscillator (e.g., $BrO_3^- - SO_3^{2-} - Fe(CN)_6^{4-}$) having a large pH amplitude of at least 3 pH units. The driven system was a fast, pH-dependent equilibrium between different forms of the target ion, e.g., free hydrated ion and a complex or precipitate, see Eqs. (R3) and (R4).



Ideally, the pH oscillator periodically shifted the coupled equilibrium between its extremes. The key aspects were to match the pH range of the core oscillator and the pH-dependent stability constants of the equilibrium (the latter one depends on the protonable ligand/counterion), and to minimize the effect of the driven system on the primary one.^[76] To this end, the total concentration of the target ion was typically around 0.5–3.0 mM. In the coupled system operated in a CSTR, the fraction of the free target ion changed from >99% to <1% with the frequency of the core pH oscillations, while the pH amplitude remained almost the same as in the pure pH oscillator. Using the combination of complexation and precipitation reactions, oscillating anionic pulses (F^-) have also been created.^[79] More complex equilibria between metal ions and amino acids were also coupled to pH oscillators.^[63,64] In these, periodic changes in the distribution of the different complex forms were detected. The Ni^{2+} -histidine reaction being coupled to the $BrO_3^- - SO_3^{2-}$ pH oscillator significantly decreased the period of the core oscillations, indicating a peer-to-peer coupling.^[64] In the $BrO_3^- - SO_3^{2-} - Co^{2+}$ -histidine system, the coupling had an additional ingredient besides the pH-dependent equilibria, namely a redox reaction between the core pH oscillator and the linked equilibrium.^[63] This goes beyond the original approach to minimize the effect of the linked system on the core pH oscillator, and led to more complex synergistic phenomena, i.e., oscillations in the oxidation state of the Co^{2+}/Co^{3+} central ion.

The coupling of pH oscillators to pH-dependent reversible reactions allows us to orchestrate autonomously oscillating physical/optical properties (color, turbidity) in bulk (Table 2). We can also induce sustained periodic chemical signals of a large variety of cations, anions, and neutral compounds, since pH-dependent equilibria are ubiquitous in (bio)chemistry. Based on the temporal oscillations of Ca^{2+} ions, abiotic spatiotemporal Ca^{2+} -waves have been created as analogues of signaling processes in living systems.^[83] It is proven that even a complex equilibrium can be coupled to a pH oscillator, not only as a driven system but also as a synergistic ingredient, which might promote further biocompatible applications.

Table 2. Coupled systems operated by a pH-oscillator.

Oscillatory reaction	Driven systems	Rhythmic process	Refs.
$\text{IO}_3^- - \text{SO}_3^{2-} - \text{Fe}(\text{CN})_6^{4-}$	block copolymer	self-assembly	[49]
	protein hydrogel	swelling/deformation	[51]
	DNA machines	conformation	[52]
	nanochannel	self-gating	[53]
$\text{IO}_3^- - \text{SO}_3^{2-} - \text{S}_2\text{O}_3^{2-}$	DNA	conformation	[9]
	pseudorotaxane	shuttling	[54]
	membrane	permeability	[55]
$\text{BrO}_3^- - \text{SO}_3^{2-}$	two-compartment system	color change	[48]
	giant vesicles	assembly	[56,57]
	nanogel particles	swelling	[58]
	hydrogel	shape deformation	[59]
$\text{H}_2\text{O}_2 - \text{S}_2\text{O}_3^{2-}$	hydrogel blocks	assembly	[60]
	dynamic covalent bond formation	fluorescence	[61,62]
	complex formation	color change	[63,64]
	functionalized membrane	pore size change	[65]
$\text{BrO}_3^- - \text{SO}_3^{2-} - \text{Fe}(\text{CN})_6^{4-}$	hydrogel	swelling	[66]
	nanofiber gel	shape deformation	[67]
	photonic crystal hydrogel	color change	[68]
	cryogel	swelling	[69]
	hydrogel	swelling	[70]
	polymeric multilayer	swelling	[71]
	polyelectrolyte brushes	swelling	[72]
	artificial nanochannel	self-gating	[73,74]
	block copolymer	assembly	[75]
	complex formation and precipitation	color change/precipitate formation	[7,76]
	hydrogel	swelling	[77]
	gold nanoparticles	aggregation	[78]
	complex formation and precipitation	color change/precipitate formation	[79]
	oil droplet	motion	[46]
oleic acid	vesicle/micelle formation	[12]	
gold nanoparticles	aggregation	[80]	
$\text{H}_2\text{O}_2 - \text{CaSO}_3 - \text{NaHCO}_3$	hydrogel surface	adsorption/desorption	[81]
	hydrogel	swelling	[22]
$\text{BrO}_3^- - \text{SO}_3^{2-} - \text{marble}$	membrane	permeability	[82]
$\text{BrO}_3^- - \text{SO}_3^{2-} - \text{HCO}_3^-$	peptide	conformation	[50]

2.4. Supramolecular systems: self-assembly

After the seminal paper by Orbán and coworkers, the interest of the scientific community turned in the direction of designing chemical oscillators of higher complexity with the ability to drive and control the self-assembly of various building blocks (such as DNA strands, metal nanoparticles, block copolymers).^[84] The design strategy to create such chemical systems was that the building block should be pH-sensitive via protonation and deprotonation in the pH range where the oscillators operate (i.e., the pK_a of the corresponding ligand(s) should fall into this pH window). The ratio of the protonated and deprotonated ligands in the building blocks determines their global behavior and drives the assembly processes.

The first successful demonstration was the development of a bio-related DNA oscillator, in which a variant of the Landolt reaction oscillating between pH 5 and 7 was coupled to drive the conformational change of a cytosine-rich DNA strand (having pK_a of 4.45) between the random coil conformation and folded i-motif structure.^[85] At lower pH, where cytosines are more protonated, the i-motif conformation is a dominant structure. However, at higher pH, the cytosines are deprotonated and the DNA strand forms a random coil conformation. To follow the conformational transition, the DNA molecules were labeled with a pH-insensitive fluorophore.

Investigation and understanding of the self-assembly of various nanoparticles into nanostructured materials are the key challenges in nanoscience and nanotechnology. From this point of perspective, autonomously driven nanosystems might play a central role in various branches of science. It was demonstrated that methylene glycol- SO_3^{2-} -gluconolactone and $\text{BrO}_3^- - \text{SO}_3^{2-}$ pH oscillators were used to drive the periodic aggregation and disaggregation of gold nanoparticles decorated with 2-fluoro-*para*-mercaptophenol and mercaptododecanoic acid, respectively (Figure 4A).^[80,86] The key feature of these systems is that the pK_a of the ligands on the surface of NPs falls within the pH range of the oscillators. At a low-pH state, most of the ligands are protonated, therefore, the electrostatic repulsions between the nanoparticles are weak and the interaction is directed by the attractive van der Waals interaction which causes the aggregation of nanoparticles. At a high-pH state, the ligands are deprotonated, thus the electrostatic repulsion between the nanoparticles overcomes the attractive van der Waals interaction creating a dispersion of free nanoparticles. This periodic change in the aggregation and disaggregation of the nanoparticles manifests in pronounced periodic color changes (from red to purple/blue) that are due to the surface plasmon resonance. Using a similar principle, a plasmonic oscillator was designed coupling gold nanoparticles decorated by carboxyl group terminated poly(*N*-isopropylacrylamide) to the

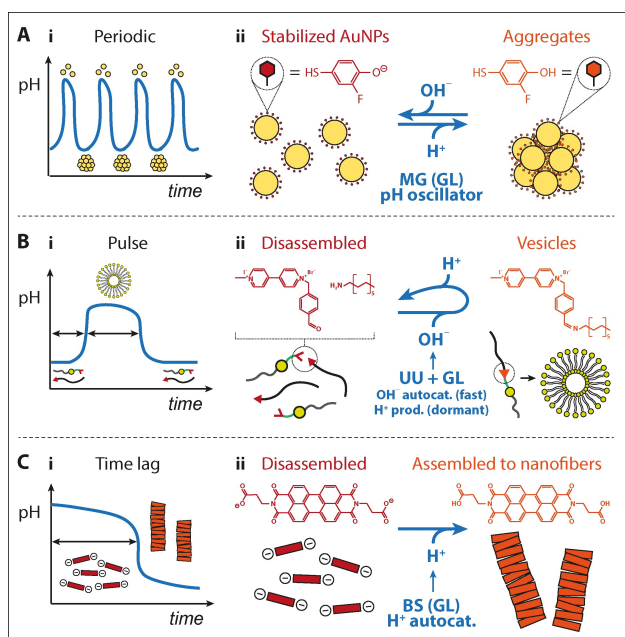


Figure 4. Routes to choreograph self-assembly by pH-feedback systems. Periodic self-assembly of gold nanoparticles (AuNPs) (A),^[80] time-programmed micelle-vesicle transition (B),^[88] and nanofiber formation of perylene diimide with time-lag (C).^[28] Abbreviations: MG: methylene glycol, GL: δ -gluconolactone, UU: urea-urease, BS: BrO₃⁻-SO₃²⁻. Figures adapted with permission. Copyright 2010 WILEY-VCH Verlag GmbH & Co. KGaA (A), Copyright 2019 Royal Society of Chemistry (B), Reproduced under terms of the CC-BY license.^[28] Copyright 2020, The Authors, published by the Royal Society of Chemistry (C).

BrO₃⁻-SO₃²⁻-Mn(II) pH oscillator.^[78] Imitating the fireflies' dissipative bioluminescent behavior, autonomous periodic aggregation-induced fluorescence was shown in pH-responsive (amino-functionalized) tetraphenylethene molecules by using the H₂O₂-S₂O₃²⁻ CSTR oscillator.^[87]

The periodic self-assembly of amphiphilic block copolymers (having polyethylene glycol and polyacrylic acid segments) was driven by the BrO₃⁻-SO₃²⁻-Fe(CN)₆⁴⁻ oscillator.^[75] The self-assembly of the block copolymers was followed by detecting the light scattering due to the Tyndall effect. At a low-pH state (pH ~3.5), the scattering was significant due to the formation of vesicle-like aggregates. Once the oscillator reached the high-pH state, the intensity of the scattered light decreased and the

solution in the reactor turned clear. This occurred due to the disintegration of the aggregates. This approach was later improved to drive the self-assembly of dual responsive (pH- and iodine-responsive) copolymer using the IO₃⁻-SO₃²⁻-Fe(CN)₆⁴⁻ oscillator.^[49]

Similarly, the methylene glycol-SO₃²⁻-gluconolactone pH oscillator, operating between neutral and alkaline states, was used to periodically control the conversion of oleic acid molecules from vesicles to micelles and vice versa. The oscillation manifested in the periodic change of the turbidity of the solution in the CSTR.^[12] The construction of a transient supramolecular peptide amphiphile and its vesicular aggregates was demonstrated using a pH-responsive imine bond formation driven by the urea-urease clock reaction coupled to gluconolactone hydrolysis (Figure 4B).^[88]

A higher complexity of engineering of the usage of pH oscillators was presented in the work by Perez-Mercader and coworkers.^[56] They showed that radicals produced by the semi-batch BrO₃⁻-SO₃²⁻ oscillator can initiate the synthesis of amphiphilic block copolymers. These block copolymers were self-assembled into nano-sized micelles, which were transformed into submicron and then giant vesicles (~10 μ m) controlled by the pH oscillator. In the follow-up paper, the authors reported that BrO₃⁻-SO₃²⁻ oscillator can also destabilize the formed vesicles due to the protonation of the hydrophobic block.^[57] Later these building blocks can be activated due to the deprotonation driven by the increase of the pH generated by the oscillator. This event induces the repetitive self-assembly of the building blocks.

Recently, it was presented that not only the pH oscillators but a chemical clock can be used to drive the assembly of supramolecular and nanoscopic building blocks (Table 3). The assembly of the perylene diimide nanofibers was time-programmed by using the BrO₃⁻-SO₃²⁻ clock^[28] (Figure 4C) and driven transiently by using the methylene glycol-SO₃²⁻ clock^[89] mediated by the hydrolysis of cyclic esters. At alkaline pH, perylene diimide molecules are deprotonated having negative charges, and the electrostatic repulsion can overcome the π - π attractive interaction between the perylene cores causing the building blocks to separate. At the acidic range, the protonated molecules form supramolecular aggregates due to π - π stacking. A similar idea was used to drive the aggregation and disaggregation of gold nanoparticles functionalized by mercaptododecanoic acid.^[90] In addition to this, it was shown that the

Table 3. Coupled systems operated by a H⁺/OH⁻ autocatalytic (non-oscillatory) reaction.

Clock reaction	Driven systems	Rhythmic process	Refs.
BrO ₃ ⁻ -SO ₃ ²⁻	macrogel nanofibers	swelling/deformation self-assembly	[92] [28]
ClO ₂ ⁻ -S ₄ O ₆ ²⁻	macrogel	swelling/deformation	[93]
IO ₃ ⁻ -SO ₃ ²⁻	macrogel	swelling/deformation	[94]
H ₂ O ₂ -SO ₃ ²⁻	macrogel	swelling/deformation	[95]
methylene glycol-SO ₃ ²⁻	macrogel nanoparticles nanofibers	swelling/deformation self-assembly self-assembly	[96] [90] [89]
urea-urease	ZIF-8 framework polymerization/ nanoparticles	synthesis self-assembly	[91] [29,97–102]

methylene glycol-SO₃²⁻ chemical clock can be successfully used in material design. This reaction was utilized to drive the synthesis of the zeolitic imidazole framework-8 (ZIF-8) in an autonomous and time-programmed manner.^[91] In the induction period of the chemical clock, the slightly acidic state does not allow the generation of ZIF-8 crystals due to the protonation state of the methylimidazole molecules. The synthesis starts when the pH reaches a slightly alkaline state. The start of the synthesis can be controlled by the concentrations of reagents and experimental conditions.

2.5. Molecular machines

Here we discuss molecular machines, i.e., molecular components capable of quasi-mechanical movements in response to an autonomous periodic pH-stimuli. Such constructions are crucial to perform tasks in cellular mechanisms and can be used for computational tasks, to solve energy storage problems and to construct smart materials.^[103] A pH-driven molecular switch or shuttle performs back and forth motion due to a reversible pH-sensitive conformational change. Examples are the transition of a cytosine-rich DNA strand between its random conformation and the so-called i-motif,^[9] or the relative displacement of interlocked molecular units due to a change in the intermolecular interactions.^[52,54] The movement should be directed in order to exploit the mechanical energy of the machine and take a step towards molecular motors. Directionality has been provided by immobilizing the motifs on a solid substrate in case of molecular switches,^[9,72] or by using mechanically interlocked molecular architectures in molecular shuttles.^[52,54] The pH oscillator serves as an integrated nonlinear dynamical unit, which autonomously drives the system back and forth between the two conformational states, and for a sustained operation we need only cheap inorganic chemicals.

Autonomously oscillating (swelling and collapse) immobilized brush layers have been created using DNA motifs and polyelectrolyte strands being immersed in continuously renewed pH oscillatory solutions. The Simmel group immobilized thiol-modified, fluorescently labeled DNA strands on a gold/glass substrate in a CSTR, which was fed by the IO₃⁻-SO₃²⁻-S₂O₃²⁻ pH oscillator.^[9] At pH < 6.5, the DNA switches were in a closed i-motif form and the fluorophore on the 3' end was in proximity to the surface and was thus quenched. At pH > 6.5, the DNA strands adopted a random single-stranded conformation and the signal of the fluorophore was detectable. The Willner group used this switch to control autonomously the interfacial electron transfer at an electrode.^[52] Zhang and coworkers monitored the pH-oscillator-induced structural changes in the immobilized layer of poly(acrylic acid) (PAA) using a quartz crystal microbalance with dissipation (QCM-D).^[72] The flow-through QCM-D chamber served as a CSTR for the BrO₃⁻-SO₃²⁻-Fe(CN)₆⁴⁻ pH oscillator and allowed the precise monitoring of the thickness, viscosity, and elastic modulus at the solid/liquid interface in real time. They also fabricated a layer-by-layer acrylic acid-based film that exhibited similar periodic swelling and shrinkage.^[71]

pH-sensitive molecular shuttles made of interlocked molecules were fueled by pH clocks and oscillators to produce autonomous time-programmed and sustained back-and-forth movement on the molecular scale. A pH-driven switchable DNA pendulum and an autonomously opening-closing DNA tweezers were constructed using an i-motif (Figure 5), and were operated periodically using a pH oscillator in a CSTR.^[52] At higher pH, the straightened (dissociated) form of the DNA strand of interest (green) hybridized with the complementary strands and created a type I secondary structure (Figure 5A(i) and 5B(i)), while at lower pH, it released the complementary strand and formed an i-motif, allowing a type II secondary structure (Figure 5A(ii) and 5B(ii)). The time-programmed shuttling dictated by a pH clock reaction was demonstrated using the cucurbit[7]uril-BODIPY pseudorotaxane.^[54] At higher pH, the cucurbit[7]uril "wheel" preferred the bipyridinium dication-substituted site (ion-dipole interactions), while at lower pH it moved to the protonated carboxylic terminus of the rigid "axle". Theoretically, a sustained periodic shuttling could also be possible by using pH oscillators in a CSTR. The structural changes were followed by coupled fluorescent switches both in case of the DNA and cucurbit[7]uril machines.

2.6. Membranes

Designing and controlling the periodic drug release is one of the most challenging issues in medicine.^[104] In the work of Misra and Siegel, it was presented that the BrO₃⁻-SO₃²⁻ oscillator can be used to control the periodic accumulation of benzoic acid through a lipophilic membrane.^[82] In a two-compartment setup, the two reservoirs were separated by the membrane. The

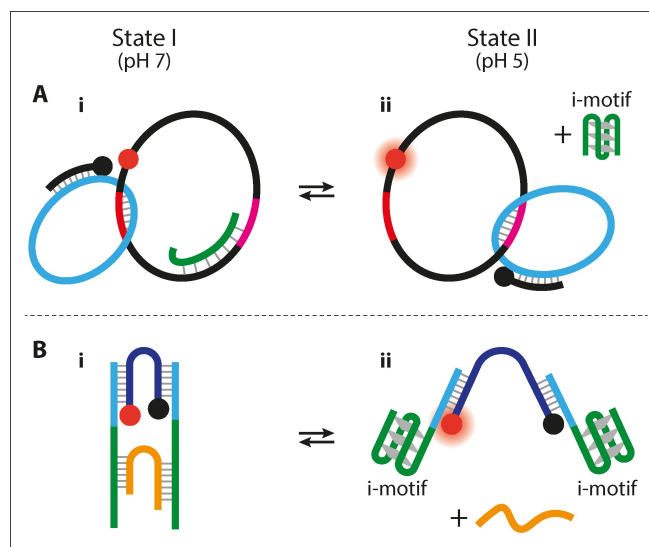


Figure 5. Autonomous back and forth motion of molecular DNA machines fueled by pH oscillators. Two-ring catenane DNA pendulum (A), opening and closing DNA tweezers (B) in their higher pH state (i) and lower pH state (ii). Orange and black balls indicate a fluorophore and a quencher, respectively. Figures adapted with permission. Copyright 2013 American Chemical Society.^[52]

“donor side”, where the pH oscillation occurred, contained the benzoic acid. At a high pH state (pH \sim 7) the benzoic acid molecules were deprotonated ($pK_a=4.2$) and could not penetrate the hydrophobic membrane. Once the oscillator reached the low pH state (pH \sim 3.5), the majority of the benzoic acid molecules became protonated having the ability to diffuse through the membrane. This sequence of events generated the periodic accumulation of the benzoic acid in the “receptor side”. The accumulation of the benzoic acid was followed by UV-Vis spectroscopy. Previously a similar approach was reported to drive the periodic flux of benzoic acid and nicotine through a lipophilic membrane using the semi-batch IO_3^- - SO_3^{2-} - $\text{Fe}(\text{CN})_6^{4-}$ oscillatory system.^[55,82,105]

Zhang and coworkers built a nanofluidic system driven by a pH oscillator where the functionalized nanochannels open and close periodically.^[53,73,74] As pH-oscillator, the BrO_3^- - SO_3^{2-} - $\text{Fe}(\text{CN})_6^{4-}$ reaction was used in a CSTR, and the IO_3^- - SO_3^{2-} - $\text{Fe}(\text{CN})_6^{4-}$ was used in a closed two-compartment configuration. The applied polyethylene terephthalate membranes had bullet-shaped nanochannels with a radius of the base side around 90 nm, while the tip was around 14 nm. The channels were chemically modified by carboxyl groups (pK_a of 3.8) or C4 DNA molecules. The C4 DNA shows conformational transitions between random coil structures and i-motif. The channels opened at high and closed at low pH, resulting in ionic current oscillations. Transporting Rhodamine B and $\text{Ru}(\text{bpy})_3^{2+}$ through the channels also demonstrated the possibility of periodic cargo delivery.

Quemener and coworkers pointed out the importance of chemomechanical feedback on the pH-oscillator dynamics in a self-oscillating filtration membrane system.^[65] They used an alumina membrane functionalized with poly(methacrylic acid) (PMAA) and ended with a catechol. At low pH, the PMAA chains adopted a globular conformation, and the membrane pores were then in an “open” state. At high pH, the polymer chains took a stretched conformation and the pores were in a “close” state. The BrO_3^- - SO_3^{2-} - $\text{Fe}(\text{CN})_6^{4-}$ reaction was performed in the filtration cell under pressure. The mechanical effect of the pore size changed the flux through the membrane, and consequently, the residence time in the filtration cell supported the appearance of pH oscillations. This peer-to-peer type coupling resulted in a chemically powered autonomous pulsating flow.

2.7. Gels

The groundbreaking work of Tanaka and coworkers revealed that hydrogels, under certain conditions, undergo a discrete transition in equilibrium volume, e.g., when the pH within the gel changes.^[106] In 1995, Yoshida presented experiments on the swelling and deswelling of millimeter-sized hydrogels (a copolymer of N-isopropylacrylamide (NIPAAm) and acrylic acid (AAc)) by coupling to a pH-oscillator.^[22] Later on, Crook improved this original idea by using a gel made by polymerizing methacrylic acid (MAA) and getting a more significant volume change,^[70] and measured a peak power of 20 mW kg^{-1} during the oscillations of the gel.^[66]

The general aim of coupling pH-sensitive gels and pH-oscillators is to convert chemical energy to mechanical work efficiently and thus create soft actuators (Figure 1). Efficiently means fast response and large swelling ratio, and robust operation. The first step to optimizing the swelling ratio is to match the working conditions, the pH range, the temperature and the ionic strength of the oscillatory reaction, and the volume-phase transition of the gel. The typical pH amplitude of the oscillators (Table 1) is large enough to get this match by appropriate tuning of the gel composition. The time-scale of swelling strongly determines the response time because the solvent must diffuse into the gel. Using macro-porous hydrogels is a promising way to improve the response time.^[69,77] The main parameter affecting the operation's robustness is the degradation of the gel. Some of the strong oxidants (e.g., BrO_3^-) used in the pH-oscillators may attack the gel and result in a fast degradation.

In terms of potential applications, several promising new directions have appeared in the past years, which go beyond the simple volume-phase transition phenomena: using color-oscillating,^[68,107] and protein hydrogels,^[51] designing anisotropic and heterogenous hydrogels to get the desired type of motion for actuators (e.g., bending and stretching, bilayers, grippers),^[59,67] and driving of periodic dynamic covalent bond formation between phenylboronic acid moieties and 1,2- or 1,3-diol moieties.^[60–62] Recently, Novakovic and Isakova invented a patent on oscillatory gels driven by an oscillatory reaction within the gel.^[108] They suggest using a palladium-catalyzed oxidative carbonylation reaction that shows oscillations in pH between 2 and 5.^[109]

The pulsation of micro- or nanogels can also be driven by pH-oscillators. Compared to the case of macrogels, a new aspect is the control of the colloid stability in a wide range of experimental parameters without significant interference with the swelling characteristics of the gel particles. The problem is that the surface charge density of the gel particles must be high enough even at low pH, which can be achieved by adding an anionic surfactant to the system.^[58] The nanometer-scale periodic changes of a polymeric multilayer's thickness^[71] and the periodic alteration of a micropatterned hydrogel's surface morphology and hydrophobic properties^[81] have also been successfully demonstrated.

Microgels containing covalently linked urease and fueled by acidic urea solution can show an interesting “breathing” phenomena. The microgel (containing aminic functions) is initially collapsed in a basic environment. Then, by adding acidic urea, the gel is brought to a swollen nonequilibrium state, where the urea-urease clock increases the $[\text{OH}^-]$ after an intrinsically coded time-lag. With the increase of the pH, the microgel goes back to the initial collapsed state. Repeated addition of the fuel allows to create multiple cycles, but this system is not autonomously oscillatory.^[110] Based on this concept, self-regulated polymersome nanoreactors have been constructed.^[100]

A unique approach was proposed to get oscillating macrogels by De Kepper and coworkers, which does not require the presence of a pH-oscillator.^[93] This approach is based on the

mutual interaction of autocatalytic kinetics, diffusion, and volume changes of the responsive gel (Figure 6). The gel was immersed in a CSTR where a pH-autocatalytic reaction was performed. The CSTR content showed bistability between a high pH (low extent of reaction) and a low pH (high extent of reaction) state (Figure 6A). In this approach, the CSTR content must have been kept in a high pH (low extent of reaction) state to get periodic swelling and deswelling of the gel. As the gel was immersed into the CSTR, the unreacted chemicals diffused into the gel. At the swollen state of the gel, supported by the high pH of the CSTR content, the diffusion time-scale was long enough to let the autocatalytic reaction start in the depth of the gel. As the autocatalytic reaction lowered the pH inside the gel, it started to shrink. The diffusion time-scale shortened as the gel shrank, which resulted in the termination of the autocatalytic process inside the gel. After it, the gel started to swell, and the cycle restarted. This approach has been supported both theoretically,^[30,111,112] and experimentally.^[92,94–96] Table 3 summarizes the experimental observations made with different pH autocatalytic reactions. The same idea, to use chemomechanical feedback to control a chemical reaction, was also used by the Siegel group to produce pH oscillations in a system where a negative feedback loop is provided by pH-driven changes in membrane permeability.^[113]

Transient or permanent gelation processes were induced by pH-feedback systems in a homogeneous phase^[29,114] and also in a spatiotemporally programmed manner.^[115] The urea-urease reaction as a pH-signal generator was successfully used to create bio-inspired autonomous, adaptive materials systems.^[29,97–102] This reaction does not show oscillations but generate a pH-jump, where the lag (induction) period can easily be controlled by adjusting the concentration of urease and

urea, and by the adjustment of the initial pH.^[116] Its advantages are its mild operation conditions and the ability to be combined with various counter-triggers. The urea-urease system was the delayed deactivation step resetting the initial alkaline conditions after a fast acidic activation to induce the time-programmed temporary gelation of a small peptide.^[29] In other applications, it played the role of the primary autocatalytic clock signal to trigger base-induced gelation, e.g., crosslinker formation via base-catalyzed Michael addition of a water-soluble thiol to a polyethylene glycol diacrylate (PEGDA).^[115] Also, the pH-jump was used to create temporally programmed dynamic materials, which showed autonomous behavior when coupled with a second chemical reaction that decreased the pH and thus created a pH cycle (Figure 6).^[117] A unique example of such a system is where the antagonistic process is an enzyme reaction (acetate-esterase) having a bell-shaped rate-pH curve: its power was demonstrated by dictating the temporary gelation of DNA hydrogels.^[114] The urea-urease autocatalytic system is also capable of controlling a gelation process and mediating the rheological properties of a non-Newtonian fluid, switching between shear thickening and shear thinning behaviors.^[118]

3. Summary and Outlook

The study of chemical oscillations and pattern formation has been motivated from the beginning by the similarities between the dynamics of chemical and biological systems. In the case of pH-oscillators, their application to create a functioning system was also a concept from their early discovery. The significant pH change during the clock behavior, between the stationary states in the domain of bistability and along the oscillations, can be utilized to drive physico-chemical changes, molecular motion, conformational changes, volume-phase transitions, and changes in supramolecular structures in a coupled system. The aim of this review is to highlight the application potentials of the pH-feedback nonlinear chemical reactions. To this end, first we summarized the chemical principles and the dynamical phenomena in different reactor types, and then we categorized the most prominent applications from the perspective of the coupled systems. The coupling between pH-driven reactions and pH-sensitive units have been realized from the molecular size up to the centimeter scale. The protonation and deprotonation of molecules change their reactivity and geometry and even can drive their motion. The molecular-level changes may induce supramolecular level processes, self-assembly and aggregation, and eventually macro-level changes like the deformation of gels.

The numerous known pH-responsive nano- and macro-molecular systems combined with autonomous pH fuel systems are ideal to construct smart materials systems. A straightforward approach to design time-programmed behavior is to temporally separate two reactive events (promotion and delayed deactivation) that trigger opposite pH variation.^[119] However, using simple kinetics, the resulting phenomena is moderately autonomous because the restart of the cycle requires external

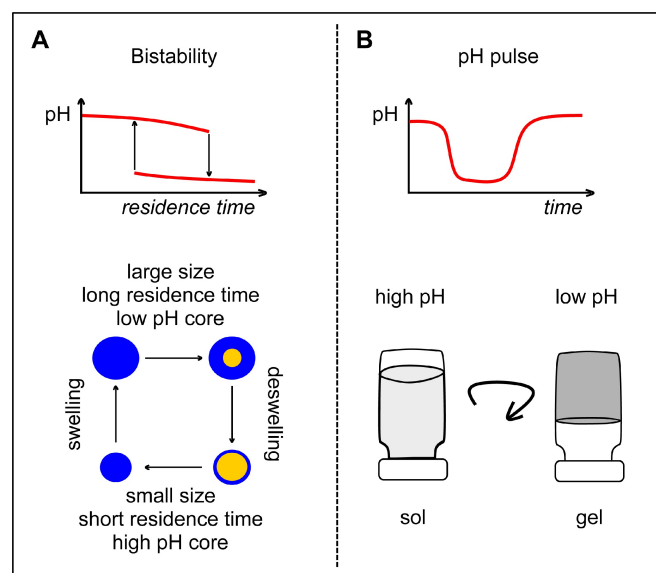


Figure 6. Dynamic hydrogel systems driven by non-oscillatory pH-feedback reactions: chemomechanical oscillations due to coupling a bistable chemical reaction and negative feedback caused by the change of the timescale of diffusive transport in a pH-responsive gel (A) and dynamic spatiotemporally programmed gelation driven by a pH-pulse (B).

stimulus again and again. Even if we place the system to a CSTR, the lack of dormant period (lag-time) of the promotion step hinders the autonomous oscillations. High level of programmability and self-oscillatory systems cannot be created without proper nonlinearities in the chemical kinetics, this makes the pH-autocatalytic clock reactions (inorganic or enzymatic)^[114] of crucial importance. Nevertheless, the invention and coupling of the perfectly matching pH clocks and oscillators to the desired functional pH-responsive entities is always a challenge due to the system-specific optimization. This challenge has been addressed by creating new oscillatory reactions (e.g., with milder operation conditions), and by developing the functionalisation in the coupled systems.

A critical but often overlooked problem is the feedback of the coupled system to the dynamics of the pH-driven chemical reaction. The pH-driven chemical reaction drives the other system without any significant feedback in primary-driven coupling. It is the case, e.g., when a small piece of gel is immersed into a large volume CSTR. However, the feedback of the driven system is more often relevant, leading to peer-to-peer coupling. A further step in synergistic interaction is when the periodic operation results from the mutual coupling between the dynamics of the chemical reaction and the driven unit. The oscillatory motion of gels in a bistable reacting system is an excellent example.

In almost all the pH-driven smart systems, the functional units are dispersed in or immersed into the solution of the fueling pH-feedback reaction. A step towards new materials systems or soft autonomous motor constructions is to integrate the above coupling strategies into bulk hydrogels.^[120] However, since the pH oscillators typically require continuous supply of fresh reactants, new configurations (hierarchical approaches, device geometries) are needed. We predict great importance of reaction-diffusion processes and chemo-mechanical feedback steps in future solutions. By all means, the already discovered broad spectrum of functions and the several untapped directions of pH-sensitive structural changes make the pH-driven operating chemical systems one of the most relevant examples of systems chemistry.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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