



Self-regulation in chemical and bio-engineering materials for intelligent systems

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Zhongyuan Huang^{1,2}, Kewei Lei^{1,3}, Dan He^{1,4}, Yanbin Xu⁵, Jacob Williams^{6,7}, Liu Hu^{8,9}, Macy McNeil¹, Juan M. Ruso¹⁰, Zhen Liu⁶, Zhanhu Guo⁸ ✉, Zhe Wang¹ ✉

¹Chemistry Department, Xavier University of Louisiana, New Orleans, LA 70125, USA

²College of Chemistry and Chemical Engineering, Xinyang Normal University, Xinyang 464000, Henan, People's Republic of China

³Materials Science and Chemical Engineering, Ningbo University, Ningbo 315211, People's Republic of China

⁴Department of Pharmaceutical Analysis, Chongqing Medical University, Chongqing 400016, People's Republic of China

⁵School of Chemistry and Materials Science, Ludong University, Yantai 264025, Shandong, People's Republic of China

⁶Department of Physics and Engineering, Frostburg State University, Frostburg, MD 21532, USA

⁷Department of Mechanical Engineering, University of Maryland, College Park, MD 20742, USA

⁸Integrated Composites Laboratory (ICL), Department of Chemical & Biomolecular Engineering, University of Tennessee, Knoxville, TN 37996, USA

⁹National Engineering Research Center for Advanced Polymer Processing Technology, Zhengzhou University, Zhengzhou 450002, People's Republic of China

¹⁰Soft Matter and Molecular Biophysics Group, Department of Applied Physics, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain

✉ E-mail: zguo10@utk.edu; zwang@xula.edu

Abstract: Herein, the authors review the self-regulation system secured by well-designed hybrid materials, composites, and complex system. As a broad concept, the self-regulated material/system has been defined in a wide research field and proven to be of great interest for use in a biomedical system, mechanical system, physical system, as the fact of something such as an organisation regulating itself without intervention from external perturbation. Here, they focus on the most recent discoveries of self-regulation phenomenon and progress in utilising the self-regulation design. This paper concludes by examining various practical applications of the remarkable materials and systems including manipulation of the oil/water interface, cell out-layer structure, radical activity, electron energy level, and mechanical structure of nanomaterials. From material science to bioengineering, self-regulation proves to be not only viable, but increasingly useful in many applications. As part of intelligent engineering, self-regulatory materials are expected to be more used as integrated intelligent components.

1 Introduction

Various methods have been used to regulate characteristics of materials in both the chemical and chemical engineering industries in recent years [1–6], which regulate the hydrophobic [7–10], antibiotic [11–15], radical polymerisation [16–20], electrical conductivity [21–23], thermal conductivity [23, 24], and mechanochemical properties [25–31] within porous, biological, polymer, and photoelectric materials. The materials, which have the ability to regulate above characteristics, could be allowed to be utilised in many different and innovative applications [32–34]. Moreover, these applications will have very positive impacts and change their respective industries [35–38].

Taking porous materials as an example, their structure could be altered so that the materials can accept and filter substances from liquid [39–41]. Typically, porous hydrophobic/oleophilic material (PHOM), the original polymer sponges (PSs), has the potential to change the environmental engineering industry [42]. Coating with a hydrophobic material, the polymers will become hydrophobic PSs (HPSs) and can be used for particular applications. By using PHOMs along with applied suction, oil may be cleaned out of the water more quickly and efficiently through capillary action.

In medical apparatuses and instruments field, self-regulation is also found in certain polymers that are used to clean medical devices [43–45]. Depending on the bacteria in the surrounding, these polymers adjust and release disinfectant. By using the disinfectant released by this kind of polymers, people can regulate

how much antibiotic is released on a site, and know the level of antibiotic resistance. It is not only applicable to medical instruments, but also to the cleaning of actual wounds. The polymer will only release antibiotic when surrounded by certain bacteria, so it can be accepted better if they are incorporated into wound dressing and among other things. Moreover, self-regulation is common in the controlled radical polymerisation. Through a new approach and controlled radical polymerisation, monomers can be polymerised without spontaneous initiation.

Self-regulation is found in the regulation of charge in, especially transition-metal (TM) compounds [46–48]. The charge of photoelectric materials may be regulated through various oxidation and reduction processes, which can regulate the concentration of charge carriers and then defect formation, and affect the photovoltaic properties of the material.

Moreover, self-regulation may be proved to be particularly useful in the biological field [49–51]. It is well known that organisms can adjust to their surroundings through chemo-mechanochemical feedback loops, in which regulation is widely existing [52–54]. Through self-regulated mechanochemical adaptively reconfigurable tunable system (SMARTS), we can study the chemomechanical events, and give us the way to know the regulation of chemical reactions due to mechanical actions. This can be applied to various regulating processes such as pH levels, heat, light, glucose formation, and so on. A particular application is using a material composed of microstructures to form a reaction that can be turned on or off. When the catalyst is coated on the tips of the microstructures in a liquid bilayer of nutrient and reactant layer,

the system switches on or off with the microstructures being straight or bent.

Clearly, self-regulation can be applied in various fields and has been shown to be very versatile in its application. Moreover, it has the potential to change the fields, in which it has been applied, and it is already having a positive impact on those fields. From material engineering to chemical engineering industries, self-regulation proves to be not only viable, but also increasingly useful in many applications. In view of the artificial intelligence operation mode, we can forecast intelligent computing and intelligent control will be an important part of the future intelligent engineering. The intelligent materials with automatic control performance would be accurate to accept and regulate the work instructions of the intelligent distributed computing centre.

In the following sections (from Sections 2 to 7), we will review the six major research areas which directly related to the self-regulation behaviours in chemical and bio-engineering materials for intelligent systems, mainly focus on the porous materials, biomaterials, polymeric materials, photoelectric materials, mechanochemical systems, and energy materials. In conclusions and perspectives part, our review will not only summarise the current research highlights, but also offer the research perspective to project the future development and designing the self-regulation system and their interactions throughout interdisciplinary subjects.

2 Physical self-regulation based on porous materials

Porous materials are of great interest because of their ability to interact with atoms, ions, and molecules not only at their surfaces, but also

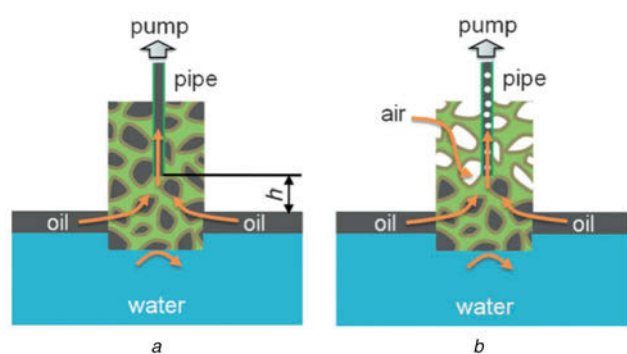


Fig. 1 Capillary pressure at the oil/air interface transportation mechanisms with the HPS fully filled with oil, and with an air channel created in the HPS, respectively [42]. Reprinted with permission from Ref. [35]. Copyright 2014 John Wiley and Sons
a water
b oil

throughout the bulk of the material [55–57]. Applications of porous materials mainly involve ion exchange, adsorption (for separation), and catalysis [57, 58]. On the basis of the multi-channel capillary pressures of PHOMs at oil/air and oil/water interfaces, PHOMs can spontaneously regulate using applied suction power [42]. It can prevent air and water permeating into the PHOMs to absorb floating oil. When the oil flows along the pipes to the collecting tank, PHOMs can regulate the oil present [42].

For example, Yu *et al.* reported the continuous collection of oil spills in situ from the water surface with high speed and efficiency [42]. This self-controlled oil collection system could collect oil spills easier and faster using a smaller amount of PHOM material. HPSs, which were obtained by modifying commercially available PSs with a hydrophobic silicon dioxide nanoparticle/polydimethylsiloxane coating through a facial dip coating method, were chosen as typical PHOMs. Capillary action at the oil/air and oil/water interfaces of HPS mainly contributed to the self-regulating properties of the system. As shown in Fig. 1, first the capillary pressure at the oil/air interface made the floating oil to be absorbed throughout the macropores of the HPS. However, after imposing a suction force to the HPS, because of the inverse relationship between the capillary pressure and the radius of curvature of the interfaces, the capillary pressure at the oil/air and oil/water interfaces increased subsequently due to the decrease of curvature radius of the interfaces to reach a new equilibrium with decreased pressure at the nozzle of the pipe. It would break the equilibrium between the pressure at oil surface and at the nozzle of the pipe, then the oil penetrated into the HPS through its surface. Then, the flow rate of oil decreased because the floating oil on the water surface vanished, which further caused the pressure at the pipe nozzle decreased. Then, the pressure at the oil/air interface was not able to keep such suction force that the oil above the pipe nozzle was pumped further away until an air channel formed in the HPS. Furthermore, this technique also could be applied to the separation of the organic-water phase, or kitchen waste oil material, or chemical production in the collection tank.

Kawano *et al.* [40] prepared honeycomb scaffolds for cell culturing by using ‘breath figure’ method, and they found that photo-cross-linking poly (1,2-butadiene) (PB) honeycomb cell culture substrates can modulate their deformation behaviour. They demonstrated that the regulation on a scale of several micrometres could affect the cell morphology and focal adhesion formation. In the cross-linked honeycomb scaffold, where the cells adhered tightly, as shown in Fig. 2, and did not have any deformation. On the contrary, the honeycomb structure was deformed and elongated against the cell edges in the non-cross-linked honeycomb scaffold. The microtopography effect is one of the important factors for this regulation of honeycomb scaffolds, because cells in vivo usually grow on various regulated surroundings provided by other cells and extracellular matrices. Furthermore, the topological regulation of the cells is a biologically non-invasive strategy without the

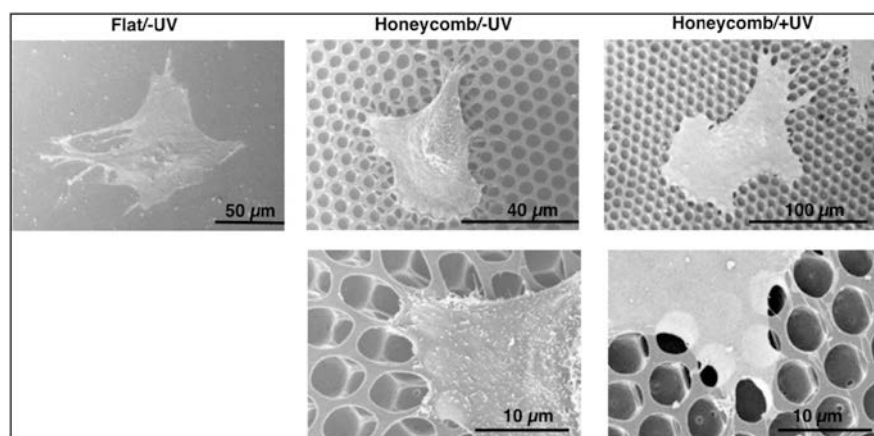


Fig. 2 Scanning electron microscopy (SEM) images of fibroblasts on a flat substrate, a non-cross-linked honeycomb substrate, and a photo-cross-linked honeycomb substrate [40]. Reprinted from Ref. [33]. Copyright 2013 American Chemical Society

chemical factors. The microtopography effect of honeycomb scaffolds provides us a new method to understand the interaction between cells and material interface and scaffolds. On the basis of the multi-channel capillary pressures and cross-linked honeycomb scaffold, it can work together to construct an intelligent and efficient oil/water-controlled separation system.

3 Material based biological self-regulation systems

Self-adjusting sterilisation system based on the principle that system could release fungicide to disinfect due to their responses to biochemistry reactions caused by outside bacteria is a new research field in recent years [59–61]. Current research about this system is mainly focused on medical apparatuses and wound disinfection. For example, Nielsen *et al.* reported a self-adjusting poly(ethylene glycol) (PEG) for medical instrument disinfection [60]. As shown in Fig. 3, extracellular bacterial lipases are particularly abundant at sites of infection. When active or proactive compounds attached to polymeric surfaces using lipase-sensitive linkages such as fatty acid esters or anhydrides, fungicide may be released in response to infection. The key point of this system is that the precursor can be hydrolysed in bacterial media by extracellular lipases in the presence of a cleavable anhydride bond. When the accumulation of bacteria on the surface at the stage of early biofilm formation, the lipase is eventually provided and many compounds with a diverse range of biological activities such as compounds that will either stimulate or block quorum sensing (QB), may in principle be released to sensitise bacteria to the action of the immune system and antibiotics subsequently. This self-regulating system not only

provides the basis for the development of device relevant polymeric materials, but also solves some of the key challenges for the treatment of bacterial infectious disease including both the mode of delivery, dosage of antibiotics at the site of infection, and development of antibiotic resistance (Fig. 4).

The treatment of wound infection is one of the most serious threat in health care due to the increasing number of bacterial resistances and the difficulty of timely infection detection. For example, Tegl *et al.* reported a smart antimicrobial system that is activated in the case of infection based on elevated lysozyme activities [63]. First, *N*-acetyl chitosan (degree of *N*-acetylation: 40%) was synthesised and hydrolysis by lysozyme in artificial wound fluid to prepare *N*-acetylated chito-oligosaccharides (COSs) with a degree of polymerisation of 2–5 units. Then, the COS were used as substrate for cellobiose dehydrogenase (CDH) to produce antimicrobial hydrogen peroxide (H_2O_2). This approach represents the first self-regulating system for the infection responsive inhibition of bacterial growth in response to lysozyme as infection biomarker. The results of simulated experiments in artificial wound showed that the system had a good work ability to generate up to 1 mM H_2O_2 at physiological conditions. This system by combining lysozyme responsive *N*-acetyl chitosan and CDH could facilitate or be used for the potential treatment of bacterial wound. Potentially, the above self-regulated antibacterial model could be a role as an important part in intelligent medical treatment engineering (Fig. 5).

4 Self-regulated polymerisation

Recently, the development of controlled radical polymerisation has attracted much attention [64–67]. For example, Steenbock *et al.*

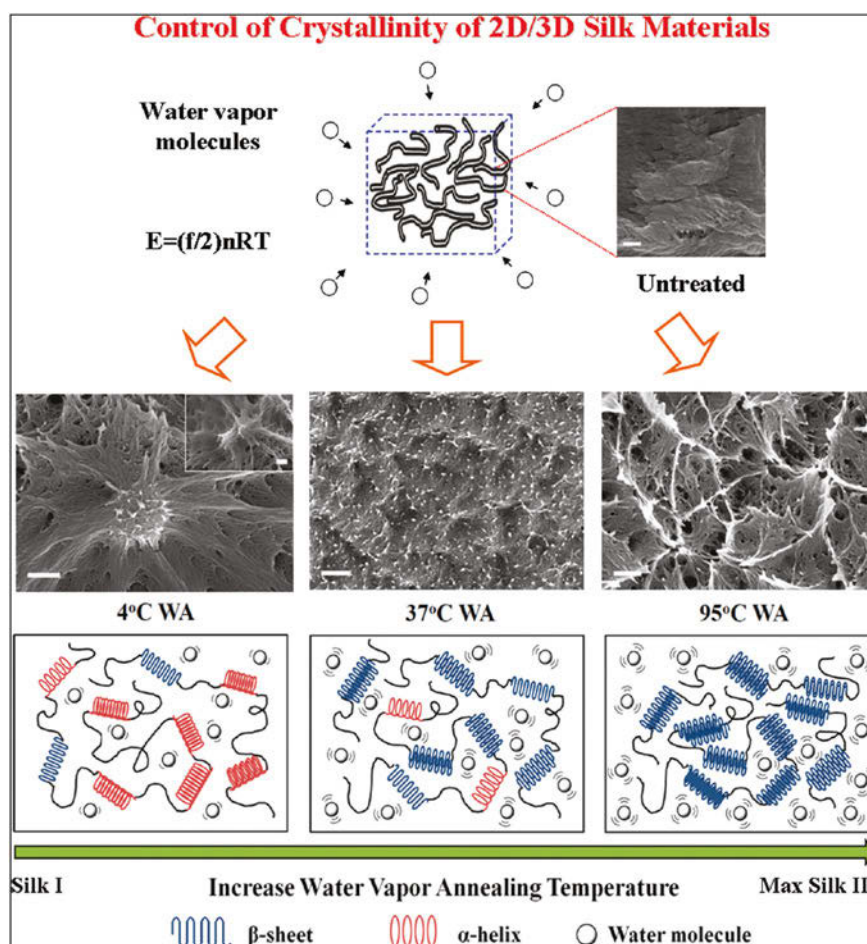


Fig. 3 Mechanisms of temperature-controlled water annealing to silk fibroin proteins. Through the variation of vapour temperature, the structure of silk materials can be fully controlled from an R-helix-dominated silk I structure to the maximum β -sheet silk II structure. (Bar length in SEM images: 200 nm) [62]. Reprinted from Ref. [62]. Copyright 2011 American Chemical Society

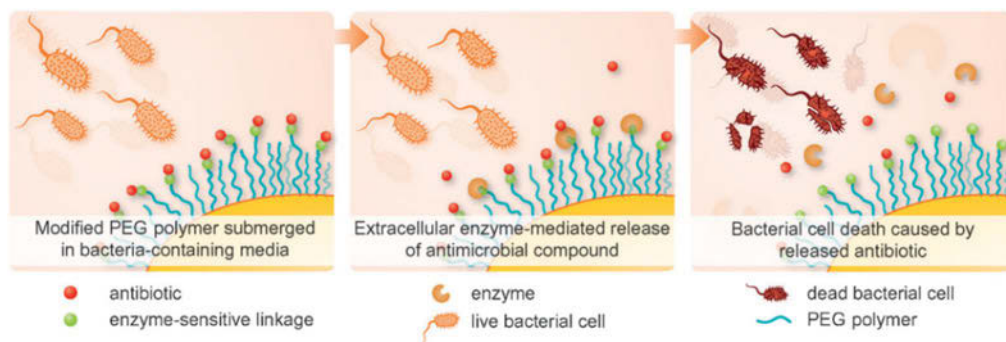


Fig. 4 Concept of bacteria-triggered enzymatic release of antibiotics from chemically modified PEG [60]. Reprinted with permission from Ref. [60]. Copyright 2014 John Wiley and Sons

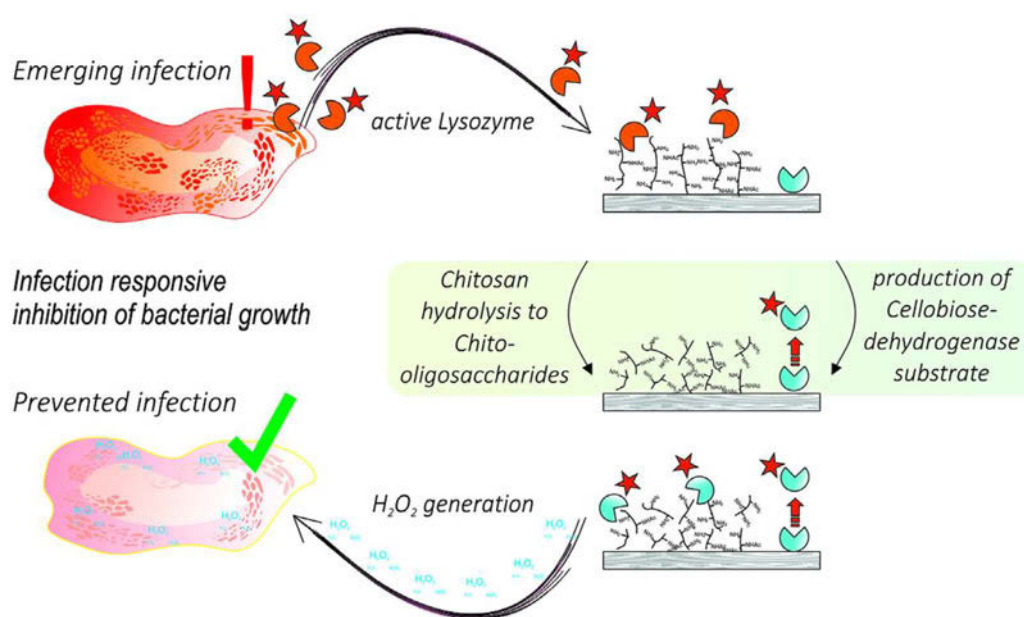


Fig. 5 General scheme of the mode of action of the intelligent antimicrobial system. *N*-acetyl chitosan (NAC - CTS) is hydrolysed to COS in the presence of lysozyme. The produced COSs act as substrate for CDH that generates the antimicrobial agent H_2O_2 [63]. Reprinted with permission from Ref. [63]. Copyright 2017 John Wiley and Sons

[68] reported the decomposition of stable free radicals as self-regulation' in controlled radical polymerisation of styrene. The polymerisation reaction stops could be catalysed by irreversible side reactions of the free radicals, the amount of dead polymer chains, and, consequently, the concentration of stable free radicals increases during the polymerisation reaction. They found that triazolinyl four radicals could reduce its own free concentration in solution, and therefore to establish a self-regulating reaction cycle. They provided two possible reasons for radical four to prevent the increase of free radical concentration in solution. First, it slows the thermal reinitiation of the monomer and second it can decompose to new initiating radicals to control its free concentration in solution. The triazolinyl four controlled polymerisation of styrene is a self-regulating mechanism instead of the slow thermal initiation of styrene (Fig. 6).

Xu *et al.* reported the fluorescence in a responsive polymer system was autonomously regulated based on the reversible formation of dynamic covalent bonds by utilising a chemical oscillating reaction as a periodical driving source [69]. Yao *et al.* found that the conformation of polyaniline (PANI) molecules changed from a compacted coil to an expanded coil when they prepared pure PANI films with different molecular chain packing states by simply tuning the *m*-cresol content in the solvent [70]. This phenomenon is due to enhancement of the delocalisation of *p*-polarons along the polymer chain caused by chemical interactions between PANI and *m*-cresol. Furthermore, with

increasing the *m*-cresol content, the ordered regions in PANI molecular structures were enhanced because *m*-cresol could decrease the hopping barrier and increase the carrier mobility. Especially, the electrical conductivity increased from 4.7 to 220 S cm^{-1} when the *m*-cresol content changed from 0 to 100%.

Hu *et al.* [62] used a simple and effective method to obtain refined control of the molecular structure of porous silk biomaterials through physical temperature-controlled water vapour annealing (TCWVA). The crystallinity of silk materials can be controlled from a low content using conditions at 4°C (R-helix-dominated silk I structure), to the highest content of $\sim 60\%$ crystallinity at 100°C (β -sheet dominated silk II structure). This new approach to control crystallisation also provides an entirely new green approach without using organic solvents. The method using water to control chain interactions described here may be suitable for silk proteins and many other structural proteins. Controlled radical polymerisation and TCWVA method can be applied to intelligent synthesis, both of them provide a self-regulating reaction synthetic method for polymer materials with special properties.

5 Photoelectric self-regulation

Classic inorganic chemistry of TM coordination compounds and semiconductors tacitly assumes that the total charge of the

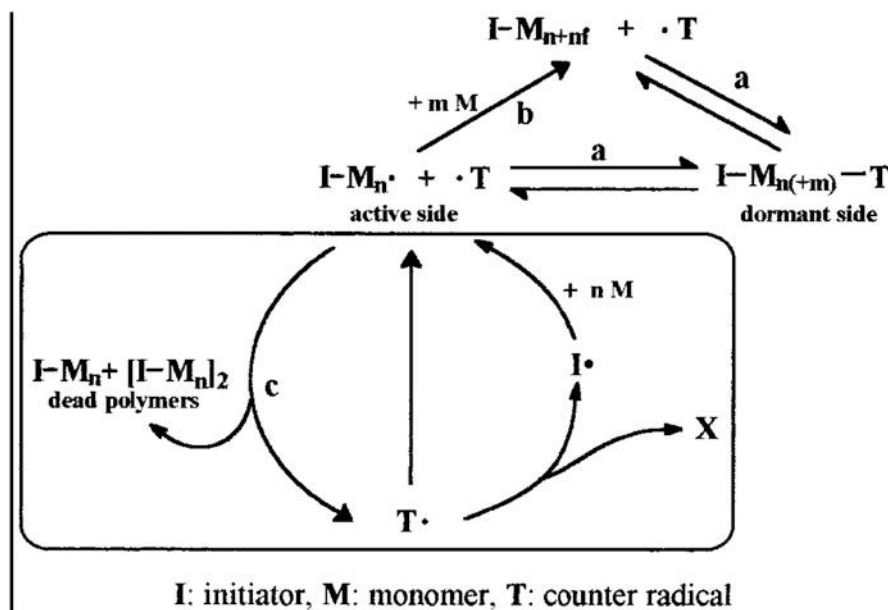


Fig. 6 Controlled radical polymerisation in the presence of triazolynyl 4 [68]. Reprinted from Ref. [68]. Copyright 1998 American Chemical Society

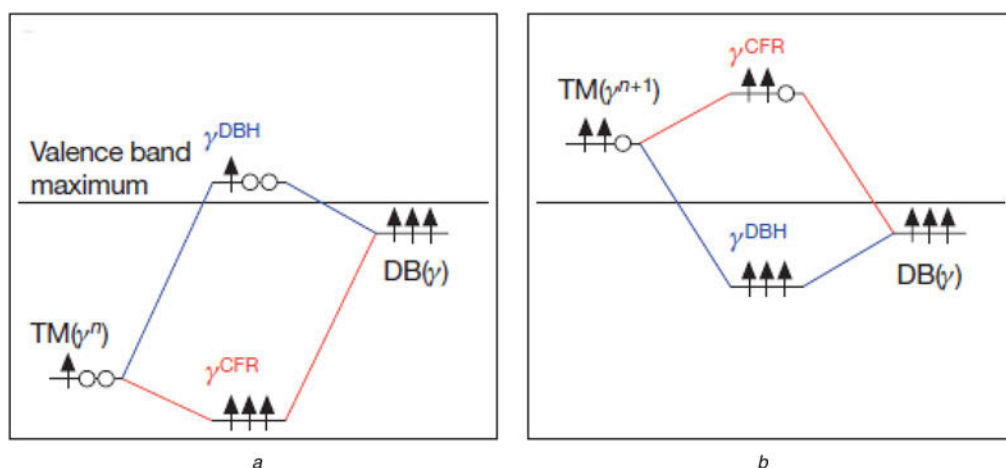


Fig. 7 Energy-level diagrams for TM–host interaction

a System charge, q

b System charge. In each panel, the free-TM-atom orbital with irreducible representation (left-hand side) interacts with a host dangling bond level with the same representation (right-hand side), forming two hybrid levels (centre), namely the CFR level CFR and a DBH level DBH. The arrows indicate spin-up electrons occupying the level, and the circles indicate unoccupied states [72]. Reprinted by permission from Macmillan Publishers Ltd: Nature [59], copyright (2008)

compound will be mainly accomplished by the changes in the charge of TM ions [71, 72]. However, in some cases, this change of charge is considered to be physical entities or capable of physical interactions. Raebiger *et al.* [72] studied multiple-charge configurations of isolated TM atoms in representative host materials including the archetypal ionic magnesium oxide, and covalent compounds gallium arsenide and an intermediate case involving d electrons-Cu₂O. Fig. 7 shows the negative charge feedback in their work. Here, n electrons occupied the isolated TM (d) orbitals to split into crystal field levels. If the system with q charge in Fig. 7a is doped with an electron, the system charge becomes to $q-1$ in Fig. 7b. Then, the level occupancy of the TM-induced hybrid states increases, the relative weight of the bonding levels shifts toward the ligands and such charge doping consequently causes the bonding and anti-bonding hybrid levels to shift up in energy by means of a negative feedback. Typically, when the energy of the TM(γ) level is lower than that of the DB(γ) level, as shown in Fig. 7a, the bonding level occurs as a crystal field resonance (CFR) with a strong TM character and the anti-bonding level occurs as a dangling bond hybrid (DBH)

formed mostly of the ligand orbitals. In addition, to counterbalance the increase in the anti-bonding gap-level charge, this negative feedback causes a reduction of TM charge in the bonding states. In other words, this self-regulated response could keep the net local charge at the TM site approximately constant. In this model, the change of charge in TM coordination compounds and semiconductors reflect the occupancy of the respective crystal field levels rather than the local charge at the TM site [60].

Zhou *et al.* reported the preparation of titanium dioxide (TiO₂) composite nanofibres by solvent volatilisation during the electrospinning process. Their results showed that the surface area to volume of the obtained TiO₂ nanofibres was enlarged with the increased weight fraction of tetrahydrofuran in the hybrid solvent. The structure and the surface area to volume ratio of the fibres could be adjusted by regulating the weight ratio of the solvent in the mixture and even by calcinations [73]. Lu *et al.* found that tunable emission from green to red and the inverse tuning from red to green in α -L-(Ca,Sr)₂SiO₄:Eu²⁺ phosphors were demonstrated magically by varying the incorporation content of Eu²⁺ and Sr²⁺ ions [74]. The change of emitting centres from

ten- to eight-coordinated sites caused by the increase of Eu^{2+} incorporation concentration was the reason for the red-shifting from 546 to 638 nm in $\alpha'_L\text{-(Ca,Sr)}_2\text{SiO}_4\text{:Eu}^{2+}$ phosphors. Moreover, the lattice expansion induced crystal field splitting decrease resulted in the blue-shifting from 638 to 540 nm in $\alpha'_L\text{Ca}_{1.6-y}\text{Sr}_y\text{SiO}_4\text{:Eu}^{2+}$ phosphors along with the change of the Sr^{2+} incorporation content. Self-regulated occupancy of the charge in TM coordination compounds, self-regulated change of emitting centres, and self-regulated synthesis of photoelectric materials will greatly promote the rapid application of intelligent semiconductor devices.

6 Self-regulated mechanochemical system

Biochemical reactions involved with SMARTS can control innumerable sophisticated, environmentally friendly, enzymatic, or other biological activities useful for self-regulating medical implants such as biomolecule detection, separation, and signal amplification [25]. He *et al.* [25] demonstrated precise control of biochemical signal transduction using a model system composed of reconfiguration of the gel to microstructure tips, catalysing the oxidation of luciferin in an oscillatory fashion. The self-regulated reaction in this work is SMARTS, which can be tailored to a broad range of coupled chemomechanical and mechanochemical events. They applied fluoresce into the microstructure tips and observed the on/off states of fluoresce in quenching by potassium iodide in the nutrient layer. The SMARTS device could be compatible with delicate biological constraints and capable of accommodating enzymatic reactions for signal transduction. The potential variety of switchable biochemical reactions that could be accommodated by this $\text{C1} \rightarrow \text{M} \rightarrow \text{C2}$ cascade (as shown in Fig. 8) is complemented by the customisability of the hydrogel response, which can, in turn, be tailored to a wide range of stimuli such as pH, heat, light, glucose, or other metabolic compounds, as well as the vast varieties of outputs such as gas generation, colour change, DNA polymerisation, and proteolysis, thus improving the combinatorial diversity of coupled effects. In the future work, they anticipated using of SMARTS to maintain a stable temperature

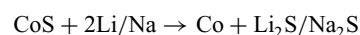
could be used in autonomous self-sustained thermostats with applications ranging from medical implants.

Mzyk *et al.* [75] reported chemo-mechano-regulation of endothelial cell response based on polyelectrolyte multilayer film modification. In this system, multilayer polyelectrolyte films (PEMs) are able to simulate the structure and functions of the extracellular matrix. The bioactive PEM was investigated as a supportive system for efficient endothelialisation of cardiovascular implants. The results showed that the PEM rigidity was regulated by the cross-linking chemistry as well as nanoparticle incorporation. Bionic biological monitoring and sensing is an important node of intelligent engineering, and the self-regulating system with biological detection, separation, and signal amplification can even be expected to use for autonomous self-sustained thermostats. This makes the intelligent materials more broad application prospect in the field of intelligent engineering.

7 Self-regulated energy materials

Recently, lithium-ion batteries (LIBs) and sodium-ion batteries (SIBs) are considered the high-efficiency and environment-friendly energy storage systems, due to their outstanding features which include high-energy density, high-power density, and high-cycle life [76–78]. Many alternative power materials have been explored as potential anodes for LIBs and SIBs such as carbon materials, metal oxides, TM chalcogenides, and alloy materials [79–81]. Self-regulated energy materials with hollow structure and carbon modification have been used to improve their electrochemical performances.

Li *et al.* reported mesoporous CoS@alveolus -like carbon yolk-shell microsphere for alkali cations storage. In this unique yolk-shell microsphere, the alveolus-like carbon shells provide a highly self-regulated void space to guarantee the integrity of mesoporous CoS during the below cycling process:



Without self-regulated structure, the volume expansion of CoS will not be controlled in process of discharging and result in the

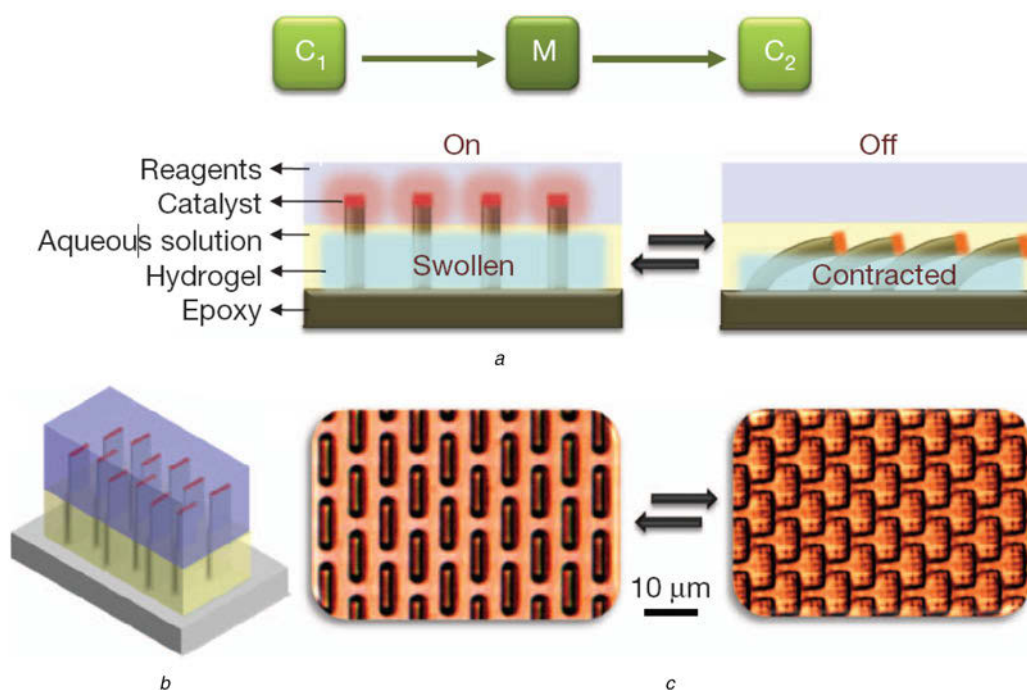


Fig. 8 General design of SMARTS

a Cross-section schematic representation

b Three-dimensional schematic representation [25]. Reprinted by permission from Macmillan Publishers Ltd: Nature [25], copyright (2012)

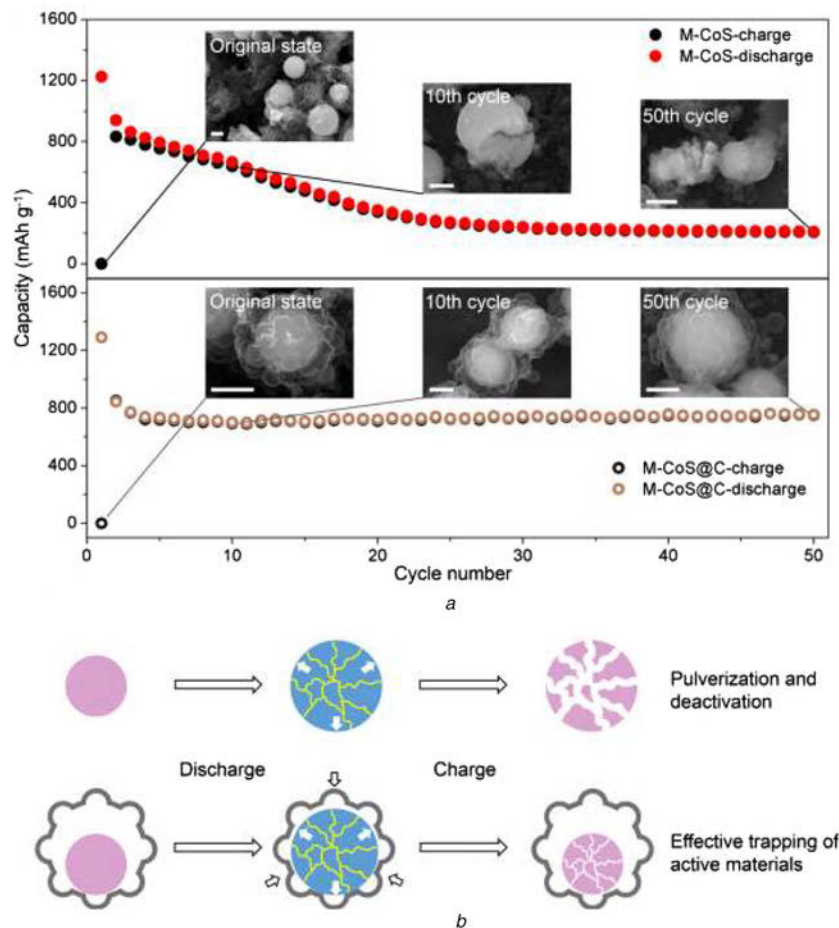


Fig. 9 Morphological changes of the M-CoS and yolk-shell M-CoS@C during the cycling process
a SEM images of the M-CoS and yolk-shell M-CoS@C at 0, 10th, and 50th cycles (full charge state), and their corresponding cycling performances at 1 A g⁻¹. Scale bar, 1 μm
b Schematic representation of the morphological changes during the discharge/charge process. Reprinted from [81]. Copyright 2017 Elsevier

fracture of the particle. During the charging process, the fragments of CoS materials shrink and separate from each other, causing the electrode to be crushed and inactivated. Once constructing the unique self-regulated structure of the yolk-shell, similar to the expansion of alveoli in the process of respiration, the carbon shell with alveolar function limited the volume expansion of sulphide cobalt particles during the discharge process. These phenomena show that the unique alveolar carbon shell can effectively bear the huge volume changes of the active electrode material and greatly improve the circulation stability. It is similar to the important role of temperature self-sustaining system in intelligent engineering, self-regulated energy materials could be anticipated to supply a constant energy in the complex and variable environment (Fig. 9).

8 Conclusions and perspectives

Self-regulation is proved to widely exist in many well-designed materials/environment systems. For example, porous materials can self-regulate their structure such as pore size and density, according to the changes in their environment. Biological materials need to adapt the living body through self-regulation of biological reactions. The self-regulation of stable free radicals in controlled radical polymerisation could be used to control the polymerisation processes. The photoelectric materials are sensitive to the environment due to a series of self-regulation processes. Biochemical reactions involved with SMARTS can control innumerable sophisticated, environmentally friendly, enzymatic, or other biological activities. On the basis of the theory of self-regulation, the self-regulated materials are in prospect for the application not only in self-regulation industry, but also in the

biological field such as emotional self-regulation and homeostasis of a living body, and self-control in sociology/psychology and self-learning of animals and human beings. Even the assembly of parts with different self-regulating characteristics will form a complex intelligent system, which will play a larger role in the future intelligent society.

For future development, the knowledge bases regarding for examples, designing the self-regulation system and their interactions throughout the medical; mechanical properties, energy control, and their influences on the interface are still incomplete. These materials science aspects still need further investigation. Meanwhile, the characterisation and designing strategy vary from system to system, and standards need to be established to ensure better quality control. Furthermore, relative theoretical instruction tailoring for new systems need to be stored. In summary, the outlook on discovering the self-regulated system and utilising self-regulation method on material and medical appliances, formed by current methods, as a smart interface to aid the functional process, is favourable. Future developments that revolve around process/material control in order to predetermine the precise regulation and exact function will assure agreeable future results. In fact, in addition to materials, self-regulation could be found in almost all of the living bodies. The breakthroughs in self-regulated materials and bio-self-regulation are expected to archive in the near future. However, the basic theory of self-regulation is still not impeccable.

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