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Chemical Systems for Life Science

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Abstract. The use of dynamic, adaptive materials with feedback control is a tendency of the past decade. Life sciences and medicine require materials with the controlled and responsive assembly of various components on the scales from molecular to macroscopic and even robotics. The main idea of this review is the use of synthetic systems as regulatory networks that facilitate the integration of chemical and biological materials. The synthetic systems, which are inspired by biochemical regulatory networks, help synthetic material to adapt to environmentand to interact with living matter cooperatively. The first step in realizing this concept is designing simple model systems. The simplicity means that the system should contain a minimal number of components but should be robust and sustainable to perform the required functions through logic operations and feedback loops. Here we suggest specific examples of robust systems for the selected functionality: compartmentalized signaling cascades, computation with light-induced chemical gradients andadvanced biomimetic mixed organic-inorganic materials, and self-regulation in chemical-biological systems. The main challenges for the given examples are discussed, and future prospects of logic operation with chemical systems are provided.

1. INTRODUCTION

Because of evolution and natural selection, living organisms developed elaborate structures on scales from molecular to macroscopic to effectively perform a broad range of functions. In recent years, significant progress has been made in developing bioinspired construction materials [1,2], providing exclusive stiffness [3], toughness [4,5], and strength [6]. In the 21st century, priorities shifted from finding new construction materials to problems of increasing life expectancy and finding effective ways of processing information [7]. New areas of experimental chemistry, such as "Infochemistry"—an experimental area of chemistry that deals with information storage and processing on a molecular level—were started [3,8,9]. The theoretical focus in chemistry also goes to mathematical chemistry [10], chemoinformatics [11], chemometrics [12], etc.

Nature is undoubtedly the primary source of inspiration in these endeavors. Biological tissues are simultaneously structural and information processing materials. Bioinformatics is the theoretical area of science [13]. Experimentally, biologists suggest various robust model biological objects: *in vitro* cell models [14], biofilms [15], algae [16], yeast [17], seeds [18], etc. It is interesting that the synthetic materials have programmable capabilities of biological objects: biomimetic information processing [19,20].

In this review we focus on the following aspects of biomimetic information processing in synthetic materials: (i) what types of materials [21,22] and chemistries are suitable for communication with biology; (ii) how two-way communication (information processed by synthetic chemical network as well as living entity) [23] may be organized; (iii) how to affect a cell with chemistry and how synthetic chemistry can response to living cells [24].

In the first chapter, we describe modern architectures for the synthetic cell. We discuss such aspects of

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synthetic cells as the formation of capsule based on polyelectrolyte molecules: layer-by-layer capsules, replication of vesicles, and advanced chemically synthesized materials.

The second chapter reviews the advanced materials that have multiple stimuli-responsive properties. We discuss materials that are responsive to pH, temperature, and irradiation of metal-organic, organic-organic interfaces, and robotics. We use Boolean logic to explain how systems integrate multiple of these stimuli to generate a different response. We use the concept of reaction networks to describe signal transformations during the generation of the response. We discuss how developments in microfabrication, particularly in microfluidic, helps to create modern stimuli-responsive materials.

In the third chapter, we discuss biomimetic and self-assembled functional materials. We look to the interaction of these materials with bacterial colonies, which are among the simplest organisms.

In the fourth chapter, we provide examples of communication of bacteria with synthetic chemical signals through solution chemistry: requirements for the chemistry, information processing by synthetic chemical reaction networks, and mechanisms to interact with bacteria through small molecules. We believe that knowledge is needed to integrated devices of stretchable electronics, electronic skin, and even robotics.

Thus, the present review connects recent advances in materials design and analytical techniques with challenges of designing complex biointerfaces. Such an approach will allow obtaining novel functional chemical systems and materials and, in the long run, operate chemical and biological systems integrated into the computing unit.

2. FROM CAPSULE TO SYNTHETIC CELL

The design of artificial cells is a challenging task for modern science [25-27]. It is interesting from the fundamental point of view concerning the life origin problem [28] as well as from the engineering of therapeutic agents [29] of a new generation medicine [30]. Generally, cell mimicking material should match several criteria such as being compartmentalized, able to adapt to the changing environmental conditions, grow and divide, process information, and transduce energy [31-33]. Creating autonomous artificial cells is still a challenge, whereas synthetic capsules that possess some of the above-listed properties have already been engineered (Fig. 1).

In recent years, scientific interest turns towards encapsulation of reaction cascades [34,35]. One capsule could serve both as a cage for the target molecule and an isolated reagent. In Fig. 1a, we highlight the typical release of the active chemical (A) from a capsule over time. The reaction-diffusion equation (1) describes the release of component A from the synthetic capsule.

$$\frac{\partial A}{\partial t} = F(A) + D_A \frac{\partial^2 A}{\partial x^2}, \quad (1)$$

where t is time, D_A is the diffusion coefficient for component A, F(A) - kinetic function for component A. One of the examples of systems described with Eq. (1) is the mesoporous-SiO_2/(polyethyleneimine/polystyrenesulfonate)$_2$ shell (meso-SiO_2/PEI/PSS)$_2$) capsule (Fig. 1c). These capsules demonstrate 2-(benzothiazol-2-ylsulfanyl)-succinic acid release at different pH values [36]. Besides "free-standing" capsules [31], surface nanostructuring is suggested for formation of "surface" capsules (Fig. 1d) [37].

pH gradient results in release of biomolecules from surface capsules [38]. Ultrasonically generated metal foam is used for encapsulation of doxorubicin. In Fig. 1e ,the pH dependent release of doxorubicin from surface capsules is shown. The release at pH 2 follows Eq. (1), simultaneously, stepwise release is seen when we change pH stepwise (from pH 4 to pH 3, to pH 2): delayed release. There is clear interest for the development of the capsules with delayed release [38]. Periodic self-regulated release of chemical from capsuleis now in focus.

Periodic release can be achieved by periodic reaction in capsule. For conducting periodic reaction in capsule, oscillatory reaction networks are required (Fig. 1b). Recently, the oscillator having structure shown in Fig. 1b (with reactions coupled to hydrolysis of triphosphates) was publishedas well as enzyme-free nucleic acid dynamical systems [39]. In Fig. 1b, active component A is placed into a synthetic cell. Inside the synthetic cell, component A participates in the autocatalytic reaction of production of B. Component B autocatalytically forms C, while C autocatalytically forms A [40]. This system of three autocatalytic reactions generates periodic oscillation of A, B, and C. Soloveichik *et al.*[41] realized this design of oscillatory network in the system based on DNA-strain displacement reactions network.Kinetic equations (2-4) describe such a complex cascade of reaction for component A which depends on the components A, B, and C.

$$\frac{\mathrm{d}A}{\mathrm{d}t} = k_1 \cdot A \cdot C, \quad (2)$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = k_2 \cdot B \cdot A, \quad (3)$$

$$\frac{\mathrm{d}C}{\mathrm{d}t} = k_3 \cdot C \cdot B, \quad (4)$$

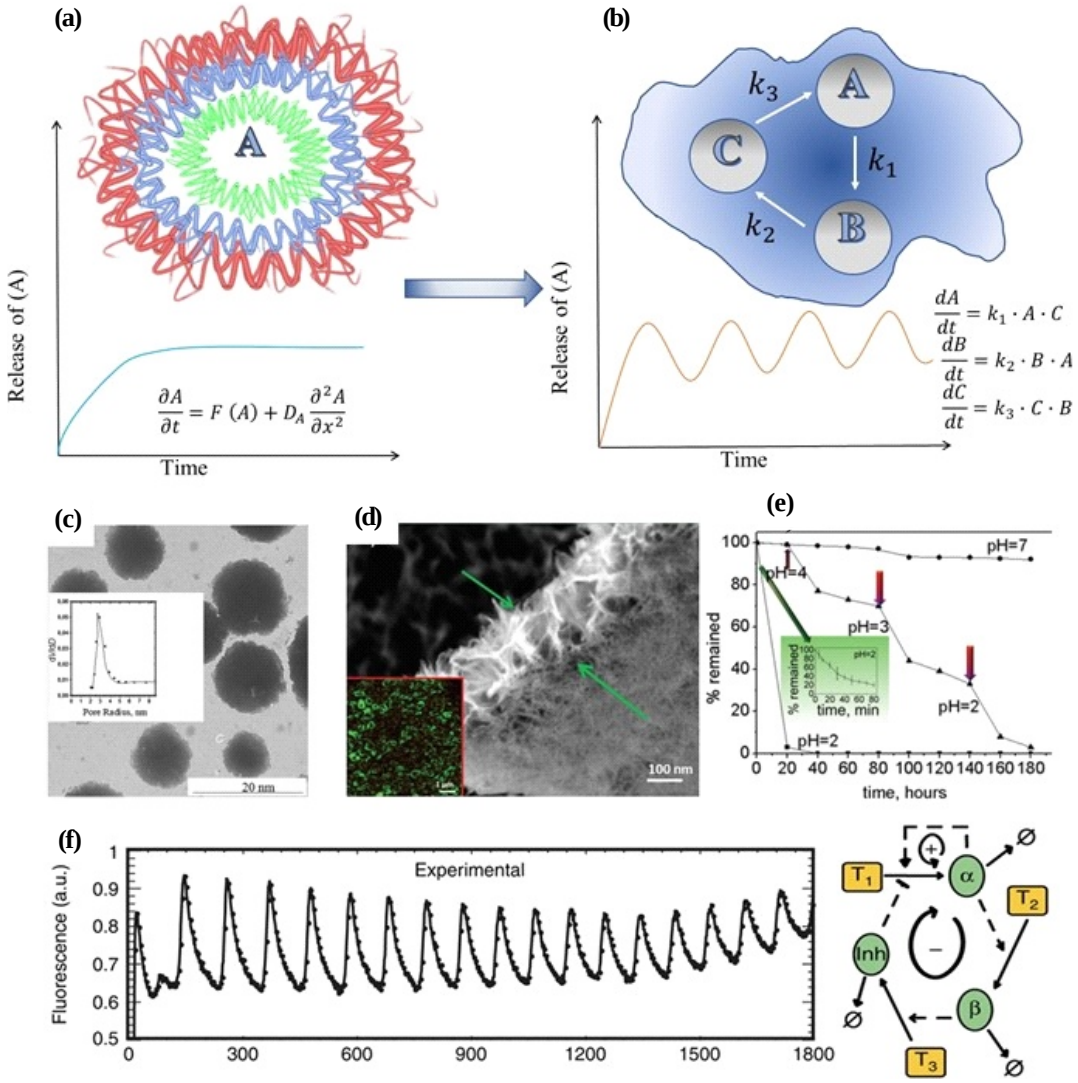

Fig. 1. (a) Polyelectrolyte capsule with the first-order reaction and (b) synthetic cell with a catalytical cascade of reaction with the assumption for the second order of the reaction. *A*, *B*, *C* are the concentrations of the components A, B, and C, respectively. K_1, K_2, K_3 are rate constants. Functions *F* and *G* are kinetic functions. (c) TEM image of the SiO_2/PEI/PSS containers (pore size distribution is in the inset; d*V*/d*D* is differential porevolume), adapted from [36].(d) SEM image of the cross-section of the ultrasound prepared aluminum sponge-like capsule layer with loaded doxorubicin. Inset: the luminescent confocal image (top view) of the surface capsules loaded with doxorubicin, adapted from [37]. (e) Doxorubicin release from Al capsules under different pH (inset shows time-resolved release at acid pH 2), adapted from [37]. (f) Example of the synthetic oscillator of the isothermal linear oligodeoxy-nucleotide amplification. Production of 30-mismatched inhibitor (Inh) is connected to the presence of complementary sequence (α). This three templates (DNA oligonucleotides of the Oligator:T1 and T3: 30 nM; T2: 5 nM) three enzymes system produces sustained fluorescent oscillations with a period of 100 min, adapted from [44].

where *A*, *B*, *C* are the component concentrations and k_1, k_2, and k_3 - kinetic function for component A. At present time, there are few experimental periodic reactions that describe biocompatible periodic reaction [39,42-46].Periodic release of biochemically active ingredient was not demonstrated.

An enzyme-based system of the isothermal linear oligodeoxy-nucleotide amplification based on the repeated extension/nicking of one strand of a short DNA duplex [44] is shown in Fig. 1f. Montagne et al. [44] describe a model of this system according to the Michaelis-Menten kinetic equations [47]. Rondelez and coworkers encapsulated this oscillatory network into microdroplets [48].

A hallmark of a living cell consists of cascade processes inside the cell, product transportation between organelles, and substance transportation from/to surrounding media. Enzymes effectively control the cas-

cade of chemical reactions within each living cell providing its viability. A shell-in-shell architecture ensures spatial separation of enzymes within a single capsule. The impermeability of the polyelectrolyte membrane to enzymes allows enzymes from separate capsule compartments to act independently on metabolites diffusing between compartments through semipermeable walls [49]. The biologically-like and biocompatible polymers that have been widely explored could be used for the reconstruction of cell membrane behavior. Biopolymer microcapsules with various architectures are assembled in aqueous media by electrostatic complexation of the oppositely charged polymers [33]. They are interesting candidates for making synthetic cells and encapsulating multicomponent chemicals for periodic reactions. Different cargos such as particles or enzymes may be encapsulated inside any other capsule to form the compartment [50].

He et al. [51] propose an opportunity for synergistic component release from different compartments. The assembly of multi-vesicle constructions with embedded pH-responsive transmembrane channels was shownby emulsion preparation of acrylic acid and acrylate of 1,2-distearoyl-rac-glycerol copolymers effect on [52]. These molecules assembled in capsules with hierarchical architecture where cargo release is controlled by a magnetic field and the temperature.

One of the examples of capsule shell is chitosan/alginate multilayered shell macrocapsules. These macrocapsules contain fluorophores and chitosan/elastin-like recombinant multilayered shell microcapsules. These microcapsules, in their turn, are also loaded by a fluorophore and magnetic nanoparticles [53]. The useof capsosomes-liposome- polymer capsules requires the introduction of liposomes into polymer multilayers [54].

Internal enzymatic reactions involving subcompartments demonstrate selective degradation of polymer subcompartments (without destroying the liposome cargos loaded by an enzyme) [55].

There are compartmentalized hydrogel capsules with subunits, selectively degradable by multiple chemical stimuli. The micrometer capsules have nanometer-scale subunits. These subunits can assemble from thiolated poly(methacrylic acid) and poly(N-vinyl pyrrolidone) [56].

Adaptive behavior also characterizes living systems. Montmorillonite (mixed silicates of alkali, alkaline earth, and boron group metals) acceleratesthe conversion of fatty acids micelles to vesicles [57]. This phenomenon helps to mimic replication and division of vesicles by embedding the montmorillonite catalyst into the vesicle membrane.The addition of charged amphiphiles into the surrounding medium demonstrates inhibition and activation of reactions inside vesicles [58].

Responsive composite capsules with microgel/SiO_2 walls also demonstrate possibility of adaptive behavoir. Microgels embedded in the membrane show transport properties [59]. Core-shell microparticles with polyacrylamide and poly(N-isopropylacrylamide) membranes are thermally responsive. These microparticles demonstrate efficiency for encapsulation and release of Rhodamine B isothiocyanate–Dextran conjugate [60].

Homopolymer capsules of 2-(dimethylamino)ethyl methacrylate and its copolymers with 2-(diethylamino)ethyl methacrylate and poly(ethylene glycol) methyl ether methacrylate carry out swelling-shrinking behavior at pH altering. The model drug encapsulated into such microparticles shows the release and triggering by pH change [61].

Semipermeable colloidosomes (the capsules fabricated by the self-assembly of colloidal particles), assembled from poly(N-isopropylacrylamide)-co-acrylic acid microgel particles expand and contract in response to temperature change [9].

The growing interest in materials that can “talk with microorganisms” should be noticed. Physical and chemical changes in these materials result in bacteria response, and bacteria response affects the materials. Such interaction becomes possible due to the fast development of multi-stimuli-responsible materials. In particular, our research focuses on inorganic/polymeric hybrids, where the inorganic part may provide the advantage of strong light absorption and photochemical stability, whereas the polymeric component provides responsiveness to light, pH, temperature or electrochemical conditions. Optical excitation of titania causes water splitting, which reduces the pH in the environment. This pH change may cause swelling of the polymer coating [62] and thus change the structure and mechanical properties that affect cells and cell behavior on surfaces [63]. In one of the examples, we have a material that “listens” to bacteria [64]. Lactic bacteria produce lactic acid that changes the pH and results in polymer coating swelling, and polymer coating pushes bacterial cells away from the surface.

A particular interest is focused on systems performing energy transfer from light to spatiotemporal chemical gradients. New materials for local delivery of different amounts and types of ions can be designed based on photocatalytic water splitting together with the formation of reactive oxygen species (ROS). Local ion gradients can perform the actuation of soft matter and biofilm manipulation. Fig. 2a demonstrates an example of light-triggered delivery of Rhodamine 6G from meso-TiO_2/$(PEI/PSS)_2$ capsule imbedded into SiO_x:ZrO_x film [65]. Under irradiation, the meso-titanium dioxide coreproduces protons which influence on the local pH changes in PEI/PSS shell. This shell is able to change

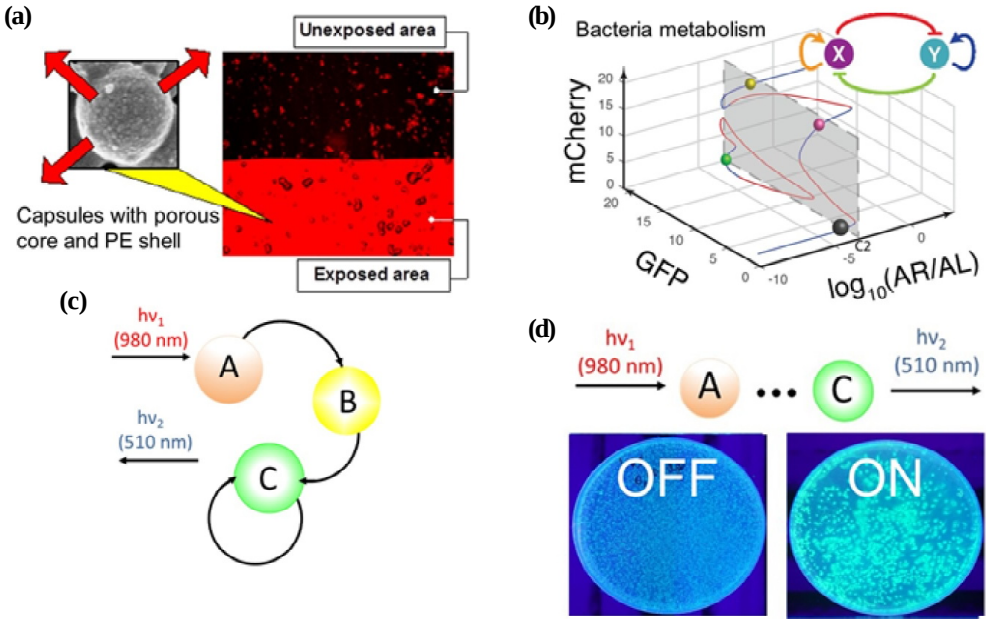

Fig. 2. An overview of polyelectrolyte capsules for biological response switching. (a) Titania capsules with a polyelectrolyte shell for local light-stimulated delivery. The confocal image proved capsules load with rhodamine 6G and entrapped in a sol-gel matrix, which releases the dye only in exposed areas, adapted from [65]. (b) Non-linear start of bacterial metabolism due to fluorescence of green fluorescent protein (GFP) in response to L-arabinose activation. AR/AL, androgen receptor fluorescence, adapted from [66]. (c, d) A block scheme of experiments where capsules (A) are nanostructured to release the required concentration of L-arabinose (B) and switch bacteria metabolism (C), a marker for switching of the fluorescence at 510 nm, which can be monitored by various methods. Petri dishes are in off and on cycles, adapted from [67].

conformation depending on pH. Polyelectrolyte shell conformation rearrangement causes the Rhodamine 6G release from this container. Example in Fig. 2a shows the possibility of loading of required reaction component into a light-triggered semiconductor/polyelectrolyte container. Fig. 2b shows the way to influence bacterial metabolism [66].

Chemical signaling for biological purposes is critical for various applications such as diagnosis, treatment, and also the modeling of complex biological systems. Nikitina et al. [67] designed polyelectrolyte capsules releasing loaded L-arabinose and switching bacterial luminescence (Figs. 2c and 2d). The release was activated by infrared illumination; as a result, bacterial fluorescence was observed. This phenomenon is an example of complex chemical and biological network integration. Delayed switching and light up conversion can be realized with this approach.

The construction of a synthetic cell requires a rigorous description of complex networks of physical-chemical interactions. Although the modeling of certain existing complex systems is a relatively straightforward task, the bottom-up construction of a de-novo system, such as a synthetic cell, requires a system of rules that help to stack individual elements in a functional system. Yet, because of nonlinearity of many chemical processes, the discovery of rules that are simple enough for straightforward application by scientists and engineers is unlikely. The computer assisted design, which will combine elements of rule-based design and evolutionary optimization, is the most likely solution for the challenge of designing synthetic cells [68,69].

3. FROM STIMULI RESPONSE TO THE LOGIC ELEMENT

Stimuli-responsive (smart or intelligent) materials are defined as materials that can behave in some specific and predetermined manner in response to external conditions. As a rapidly developing area of modern material science, the class of stimuli-responsive materials is continuously increasing and replenishing by new representatives. Such materials can be affected by various driving motives and can respond in diverse ways. These materials are fundamental for a variety of applications, such as drug delivery [70-72], tissue engineering [31,73-75], biosensors [76-80], coatings that are capable of responding to the environment [32,81,82] and composite materials [63,83,84]converting chemical, biochemical and physical signals into responses.

Much effort has recently been made to systematize and classify responsive systems adapting to the surrounding environment. The next step is moving to logic elements performing “fuzzy” logic (a form of many-val-

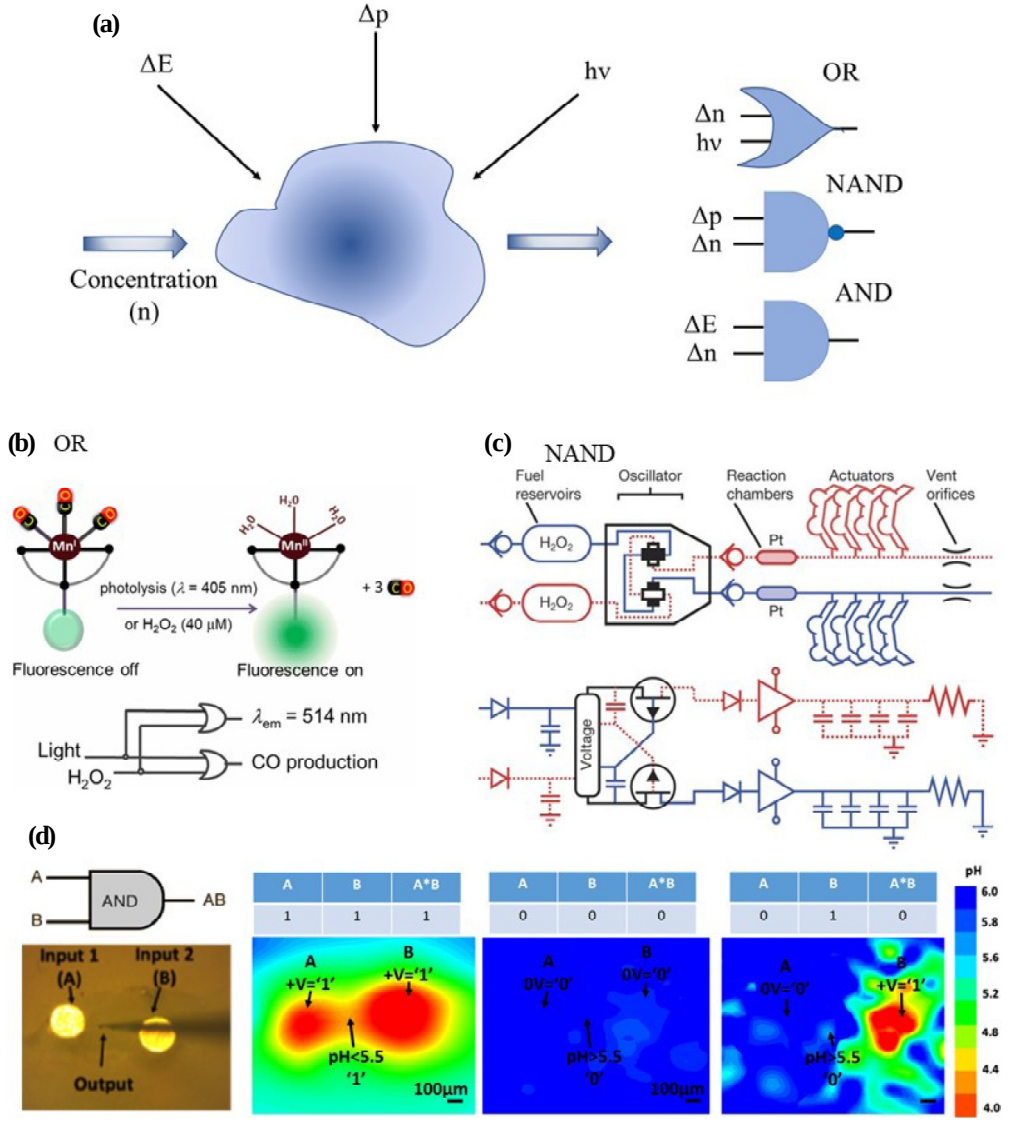

Fig. 3. (a) The stimuli-response materials are of physicochemical nature, and therefore its response associates with electric potential (*E*), pressure (*p*), concentration (*n*), and other parameters (e.g., irradiation *hν*). (b) CO-releasing molecule as Mn(I) tricarbonyl complex with the ligand 5-(dimethylamino)-N, N-bis(pyridin-2-ylmethyl) naphthalene-1-sulfonamide [87] forms OR logic. (c) A schematic (top) and qualitative electrical analogy (bottom) of the octobot system; check valves, fuel tanks, oscillator, reaction chambers, actuators and vent orifices are akin to diodes, supply capacitors, electrical oscillator, amplifiers, capacitors and pull-down resistors, respectively, adapted from [89]. (d) Basic AND logic gate and a system of two working electrodes (WEs) embedded in epoxy holder for AND logic operation. Truth tables and 2D pH-maps via scanning ion-selective electrode technique (SIET) of two input electrodes in hydroquinone solution during polarization of electrodes in different regimes and interpretation in terms of logic gates; positive polarization +V is determined as input "1," no polarization 0V as input "0," pH >5.0 is determined as output "0" and pH<5.0 as output "1," positive potential applied to both electrodes "1," resulting proton wave reaches output area giving output "1", no potential applied, both inputs are "0," as a result, no pH drop – output "0," positive potential is applied to the right electrode "1," left one is not polarized "0," resulting pH drop localized on right electrode and does not propagate to output area "0"(bottom), adapted from [97].

ued logic in which the truth values of variables may be any real number between 0 and 1 both inclusive) (Fig. 3a). This logic can include both concentrations of ions (*n*), and other thermochemical parameters that influence chemical reaction (e.g., temperature (*T*), pressure (*p*), electric potential (*E*), or irradiation (*hν*)). Therefore, there is the possibility to mix some of these parameters as an input in a logic gate to form one of the Boolean logic elements [85,86]. The logic elements AND and OR represent logical conjunction and disjunction. The NOR and NAND arealternative denial and joint denial logic elements, that can be combined to generate any other

logical function.The irradiation ($h\nu$) and concentration (n) as input demonstrate OR logic gate in case of carbon monoxide (CO)-releasing Mn(I) tricarbonyl complex with the ligand 5-(dimethylamino)-N, N-bis(pyridin-2-ylmethyl) naphthalene-1-sulfonamide [87]. CO release can be triggered by irradiation at 405 nm as well as by hydrogen peroxide in aqueous phosphate buffer (Fig. 3b). Mn(I) tricarbonyl complex behaves as a logic "OR" gate via co-registering the inputs of photolysis ($h\nu$) *or* hydrogen peroxide addition (component concentration) into the concomitant outputs both fluorescence of organic molecule (light) and CO releasing (matter) [87]. Microfluidic logic circuits and control strategies have been developed that can lead to the decoding serial instructions sent to the microfluidic circuit [88].

A combination of the microfluidic control (pressure) and concentration of reagent (n) leads to the formation of mechanochemical logic gates, for example, NAND. The applied pressure in the microfluidic system bends the actuators and exhausts to the atmosphere through the vent orifice [89] (Fig. 3c). A NAND gate can be built by align two channels near one another. If any inputs are located, they will increase the size of the output droplet. If only one input droplet is placed, the output droplet will grow in size but will not overlap with the inlets of the second channel. However, if there are droplets located on both inputs, the output droplet will grow large enough to overlap with the inlet of the second channel. The output droplet will then be pumped away through the secondary channel, leaving an output of 0. The NAND gate can be operated as a NOR gate by increasing the size of the priming output droplet or the input droplet. Therefore, for robust actuation and timely venting, a balance must be reached between supply gas flow, actuation pressure, and exhaust rate [90].

Ion fluxes are the basis of cellular information processing. A simple model electrochemical system with electric potential switching (ΔE) allows running local ion flows on demand. It has been shown that ion flows are capable of performing calculations in terms of logic gates (Fig. 3d).Three situations are possible in this case: both electrodes produce ionic current; one electrode produces ionic current; none of these electrodes produces ionic current. All these pathways and their combinations can be described by AND gate. In Fig. 3d, the two inputs are shown positive and zero-applied voltage. System of two working electrodes (WEs) was embedded in epoxy holder for AND logic operation. The two input electrodes were polarized in hydroquinone solution in different regimes. 2D pH-maps of this system were plotted from scanning ion-selective electrode technique (SIET).Inputs and outputs of this logic gate were defined as following: positive polarization +V is determined as input "1," no polarization 0V as input "0," pH >5.0 is determined as output "0" and pH<5.0 as output "1". Four situations are possible in this system: positive potential applied to both electrodes "1," resulting proton wave reaches output area giving output "1", no potential applied, both inputs are "0," as a result, no pH drop – output "0," positive potential is applied to the right electrode "1," left one is not polarized "0," resulting pH drop localized on right electrode and does not propagate to output area "0".

Synthetic composites made of polymer ion exchangers (polyelectrolytes) and lipids can mimic ion pumping in living cells.Important classes of smart materials include inorganic piezoelectric materials producing voltage under mechanical stress and vice versa [91,92], thermoelectric materials [93] converting temperature difference into electricity, shape memory alloys [94], photovoltaic materials [95]. These materials are structural elements of living systems or their mimics. They open broad perspectives for smart material implementation in biomedicine, development of human-computer interfaces, and novel bioinspired approaches to information storage and processing. Here and elsewhere we discuss the development of these smart materials, their description in terms of information theory and discuss future trends of physicochemical systems performing logical operations and chemical computing.

3.1.Stimuli-responsive materials

3.1.1. pH-sensitivity

All chemical and biological processes depend on the pH of the surrounding media. Therefore, pH-sensitive systems draw the most attention in developing smart materials and several ways to regulate pH in bulk as well as locally [96]. Proton coupled electron transfer is widely used for electrochemical generation of pH gradient [97]. Chemical and a biocompatible way to get pH gradient in solution may involve immobilized enzymesthat catalyze formation of an acid or acid-producing bacteria that are attached to a surface (Fig. 4a). Acidic and basic functional groups result in pH-sensitivity in molecules. The polymer molecules, in which multiple acidic or basic functional groups are presented simultaneously, on the same backbone, are called polyelectrolytes. In relevance to pH values, these groups ionize and acquire a positive and negative charge. Electrostatic interaction between charges in one or different molecules causes drastic changes in a system [98]. These molecules are able to form pH-sensitive supramolecular assemblies on demand. Such assembly process is reversible [99,100]. Swelling and deswelling behavior is also observed due to pH change [101]. The pH-responsive polymers un-

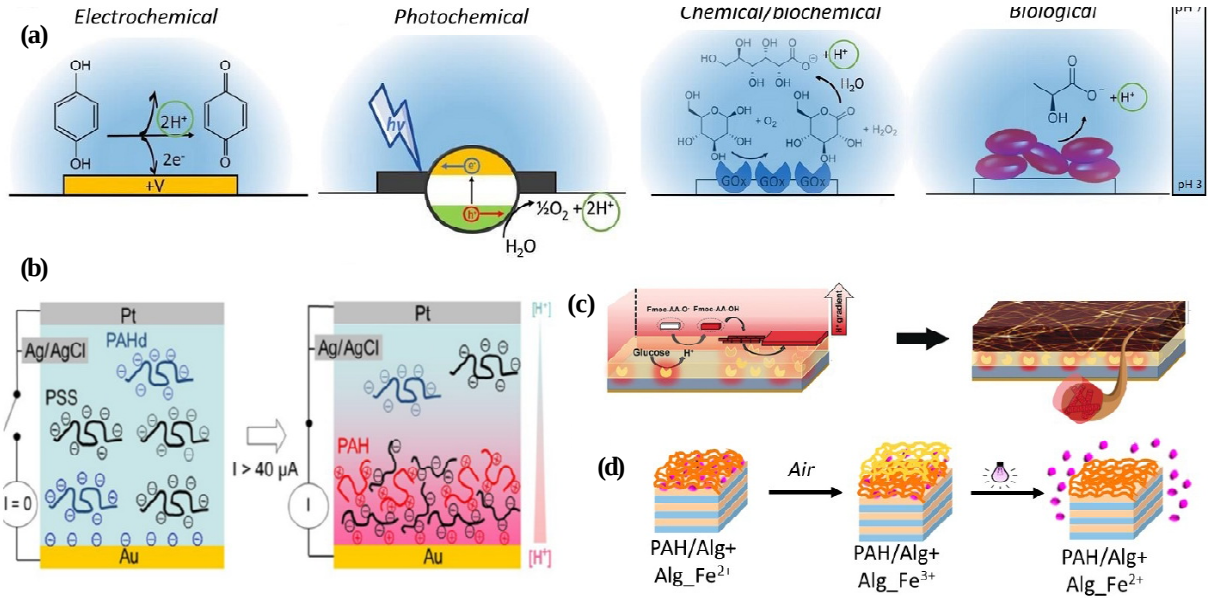

Fig. 4. (a) Various approaches to generation of local pH gradient: electrochemical hydroquinone oxidation, photoelectrochemical water splitting, chemical reaction yielding H^+ release, H^+ release during bacteria lifecycle, adapted from [96], (b) electrochemically triggered self-assembly of PAH/PSS polyelectrolyte multilayer from solution of charge-shifting polymer PAHd recharging via acidic hydrolysis and PSS, adapted from [104], (c) self-assembly of Fmoc-Ala-Ala peptide fibers in acidic media locally generated by reaction of glucose with immobilized glucose oxidase, adapted from [110], (d) light-induced release of folic acid from alginate/Fe^{3+} hydrogels due to photoreduction of "hard" Fe^{3+} to "soft" Fe^{2+} cations, leading to changes in the mechanical properties of the hydrogels related to their cross-linking behavior, adapted from [112].

dergoing sol-gel transition [102] were designed as well as gels changing their stiffness [62].

The pH-triggered assembly of polyelectrolyte complexes from H^+ sensitive polyelectrolytes with electrochemical pH-gradients was performed [103]. Nanoscale polyelectrolyte multilayers were assembled from charge-shifting polyelectrolytes with electrochemically generated protons (or hydroxide anion) on the electrode surface [104,105]. Hydrolysis of anionic dimethyl maleic-modified poly(allylamine) (PAHd) or citraconic-modified poly(allylamine) PAHc to cationic poly(allylamine) (PAH) was performed with an electrochemical proton gradient. The hydrolysis at locally produced acidic or basic pH leads to a switching PAH charge.After charge switching, PAH adsorb on the oppositely charged electrode surface. Reversed currents cause reverse PAH switching and its disruption from the electrode surface. Layer-by-layer assembly of cationic PAH with anionic PSS was demonstrated (Fig. 4b).

Payne et al. offer the electrodeposition of chitosan films using basic pH gradient to develop biosensors by co-deposition with enzymes and various inorganic compounds [106]. Another way to generate self-assembly is to use peptides that are transformed from a non-self-assembling state into a self-assembling one by a pH trigger [107]. Cameron was the first to develop such self-assembly processes, where protons are generated electrochemically, leading to localized self-assembly [108]. Peptide self-assembly processes are induced locally by enzymatic reactions [109,110] (Fig. 4c).On the one hand, enzymatic reactions influence the local pH changes. On the other hand, the self-assembly of peptides depends on the pH.

The latest approach to pH gradient generation is light-pH coupling [111]. This coupling is caused by light irradiation of inorganic semiconductors that produce a pH gradient due to water decomposition. Whereas changes in mechanical properties of hydrogels related to their cross-linking behavior via photoreduction of "hard" Fe^{3+} to "soft" Fe^{2+} cations were demonstrated (Fig. 4d) [112], assembly triggering by light-pH coupling effect is still a challenge. The challenging prospects of synthetic cell construction are 1) ion feedback mechanism in synthetic capsules [96], *in vivo* biomolecule synthesis inside synthetic cell [113]; 2) localization of biochemical processes inside capsule [97], and 3) delayed assembly of biomolecules on the surface and inside capsules.

3.1.2. Temperature

Thermally responsive materials modulating their behavior with temperature change are widespread in biomedical applications, drug delivery, tissue engineer-

ing, and soft robotics. Among the most common thermo-responsive systems are polymer mixtures or block-co-polymers which undergo aggregation and disaggregation in transition temperatures (upper or lower critical solution temperatures). The polymer structure switches from hydrophilic to hydrophobic states when a lower critical solution temperature is exceeded [114]. Recent studies also aim to reveal temperature effect on diffusion through polyelectrolyte multilayers [115]. Thermo-responsive polymer membrane (elastic polyurethane (TPU) -poly(N-isopropylacrylamide) (PNIPAM)) demonstrate switchable superhydrophilicity and superhydrophobicity with temperature changes from 25 to 45 ºC [116]. There is a method of cell manipulation using polymer surfaces, which are reversibly and repeatedly switchable between a cell-attractive and a cell-repellent state in changing surrounding temperature [117]. The synthetic approach leads to a novel class of thermoresponsive dendronized polypeptides [72]. Organic chemistry allows functionalizing polymers with functional groups that provide desired properties.

2.1.3. Light

Among the large variety of stimuli, the light draws much attention since it can be easily localized in space, tuned in terms of intensity and wavelength, as well as turned off immediately. Moreover, this approach to trigger material's response is unique and efficient for many light-sensitive parts. Azobenzene-derivatives are among the most well studied photoswitchable systems. Under irradiation, azo bonds undergo isomerization, and a molecule converts from trans to cis isomer. This process is reversible, and the lifetime of the excited cis state can range from seconds to days and be easily tuned by ortho-fluorination [118]. With varying the number and nature of substituents, the sensitivity of azobenzene derivatives to different excitation wavelengths, as well as their stability [119],can be finely tuned. Tremendous work has been done to associate the isomerization process with functional change [120]. The sol-gel transition of an inclusion complex between the α-cyclodextrins and the azobenzene moieties was demonstrated by photoirradiation. Photoisomerization followed by the separation of the azobenzene/β-CD bridging units also resulted in hydrogel exhibiting cyclic and reversible switching between high and low stiffness states on demand [121]. Reversible solid-to-liquid transitions of azobenzene-containing polymers can be induced by irradiation [122]. Conformational change related to photochemical isomerization of azobenzene was used for liquid-phase exfoliation of graphite [123].

Azo-benzene photoswitches reversibly control the folding and unfolding of peptides and proteins and thereby control their function [124]. Here [124], light-induced isomerization of azobenzene changes wettability of LbL films assembled from these photoswitchable molecules. This phenomenon is used for the regulation and control of cell adhesion [125]. Azobenzene derivative is also reported to be a light-switchable crystal growth modifier [126].

Photothermal functional nanocomposites are used in design of materials with photomechanical response. Such composites consisting of polymer or hydrogel thermo-responsive soft matrix (in most cases, poly(N-isopropylacrylamide)) with embedded metal nanoparticles or carbon nanomaterials are characterized by excellent photothermal conversion. Under illumination, such hydrogels effectively actuate as a result of reversible bending deformation and are widely used in biomimicking soft robot design [127]. The incorporation of gold nanoparticles and graphene oxide into thermally responsive hydrogels results in photoactuators demonstrating rapid, reversible bending behavior under irradiation [128-130].

Another conceptual strategy for photosensitivity is light-pH coupling [98,111]. It was previously demonstrated that significant pH-gradient might be induced on the illuminated semiconductor surface [63,131]. The pH-sensitive soft matter assembled on top of the semiconductor surface or together with nanoparticles carry out the photohealing effect [131], high amplitude actuation [62], switching the stiffness [132] and protein conformation changes [133]. This approach is especially promising because there is a large variety of materials changing their thickness, stiffness, permeability, hydrophilicity, and other properties in the changing pH conditions. The photoelectrochemical photocurrent switching effect is described for titanium dioxide modified with iron(II) complexes. This phenomenon significantly expands the area of TiO_2 utilization as a photocatalyst for stimuli-responsive systems, including logic gates and demultiplexers [134,135]. Direct photosensitization includes a direct electron transfer from iron complexes to the conduction band of TiO_2. Three different types of photoelectrochemical behavior yielding binary, ternary, or fuzzy logic circuits have been demonstrated on organotitania nanocomposites [136,137].

Electrical, magnetic, mechanical, and Red/Ox stimuli are worth mentioning. Electrowetting and external pressure manipulates the shape of a liquid droplet and hence focal length of the droplet and thereby adjust its optical properties [138]. Hydrogels responding to a target antigen may be prepared via the introduction of antigen-antibody bindings as crosslinks into the gel network [139].

Suitable stimuli-response materials mainly include functionalized polymers, polyelectrolytes, and

metalorganic composites. These materials combine the possibility of input interruption and output response.

3.2. Logic

In terms of information theory, any stimuli-responsive devices described above work like a simple Buffer logic function, it is an underlying logic gate passing its input, unchanged, to its output. A buffer has one input and one output; its output always equals its input. In other words, concerning the smart systems described earlier, positive input (presence of stimuli) leads to positive output (material's response). Along with simple, smart materials that accept a single input, multiresponsive systems also exist. By combining different blocks in single polymer molecule simultaneous sensitivity to various inputs can be achieved, for example, pH, temperature, and glucose [140,141] or Fe^{3+} ions [142]. Graphene oxidepoly(N-isopropylacrylamide) allows obtaining multiresponsive hydrogel undergoing 3D complex deformations and sensitive to temperature, pH, and ionic strength [143]. It is a combined polymer with inorganic nonmetal material. Multi-responsive (sensitive to temperature and solution composition) double-folding bilayer hydrogel sheet actuators were designed [144]. Enzyme-cleavable polyethylene glycol (PEG), a light-responsive photosensitizer pheophorbide, and a temperature-sensitive liposome were integrated into a single nanoplatform to obtain multiresponsive intelligent vesicles for drug loading and delivery [122].

Multiresponsive systems are widely exploited for performing simple logic operations. Special attention nowadays is given to the concatenation of chemical logic switches and the design of computingand memory chemical systems. Different types of logic gates (YES, NOT, AND, OR, NOR, NAND) were assembled from combinations of stimuli-responsive hydrogels changing their size being exposed to different types of stimulus. Inthe report by [144], different logic was realized by a flexible design of chemical systems, whereas the synthesis of stimuli-responsive hydrogels is well established and pretty simple [145]. A smart device implementing logic is suitable for physiological conditions because the "ON" state is only realized according to a particular logic when a specific combination of signals is present. The physiological environment has many stimuli; thus, a target is often characterized by a specific combination of signals in contrast to one unique signal. Thus, stimuli-responsive biomaterials can be useful platforms for drug delivery. Hydrazine functionalized PEO-b-PMAA block copolymer was used to attach adriamycin (ADR, anticancer drug) through the formation of hydrazide [146]. Polymer micelles of the composition above were designed for the controlled release of encapsulated drugs under the simultaneous application of pH-input and reduction [146]. Small molecules (model therapeutics) labile linked with nondegradable host hydrogel can be released in the preprogrammed way according to Boolean logic. Depending on the type of linkage, YES, OR, and AND logic elements can be realized by different types of inputs (enzymes, chemical reductants, light) and their combinations [147,148].

Micromotors sensitive to UV and NH_3 stimuli have been designed. Their moving direction can be manipulated and accelerated according to a predetermined logic [149]. Reprogrammable OR and INHIBIT (3-input AND gate with one of the inputs inverted) logic gates and logic circuits concatenated of OR, NOT, and AND logic gates can be realized by multistimuli-responsive gelatin/polypyrrole nanoparticle/catalase micromotors sensitive to H_2O_2, near-infrared light, NH_3, and their combinations [150]. Supramolecular hydrogel co-assembled from phenylalanine-based amphiphile and bis(pyridinyl) derivative with gel–sol transition in response to temperature, acid, base, and light and realizing OR and XOR logic have been obtained [151].

Electrochemical and photochemical processes give a convenient way to generate ion gradients locally at solid-liquid interfaces. Spatially organized electrodes provide a unique pattern of proton distribution in solution, which is a crucial iontronics [70].Combining different approaches to ion gradient generation with biomimetic composite material, one may simulate the natural way of ion transportation and information transfer and processing.

4. SELF-ASSEMBLY, MORPHOGENESIS, AND BIOMIMETIC MATERIALS

Even bacteria (single cells, colonies, and biofilms) — being among the most primitive biological systems— are governed by complicated networks of chemical reactions with various feedback loops. Thus, the comprehensive study of information processing in bacterial communities is of great importance for the prospective design of artificially thinking objects.

Bacteria tend to form 3D structures, known as biofilms. Bacterial biofilms demonstrate extreme resistance to antibiotics. Drescher and coauthors' work [152] mapped all individual cells in *Vibrio cholerae* biofilms at different stages of development. The critical transitions of the internal and external biofilm architectures were investigated. These transitions separate the major phases of *Vibrio cholerae* biofilm growth.

Laws of biofilm growth and its architectural changes were discovered. Ammoniacal by-products inhibited the growth of the *Bacillus subtilis* colony, and differentiat-

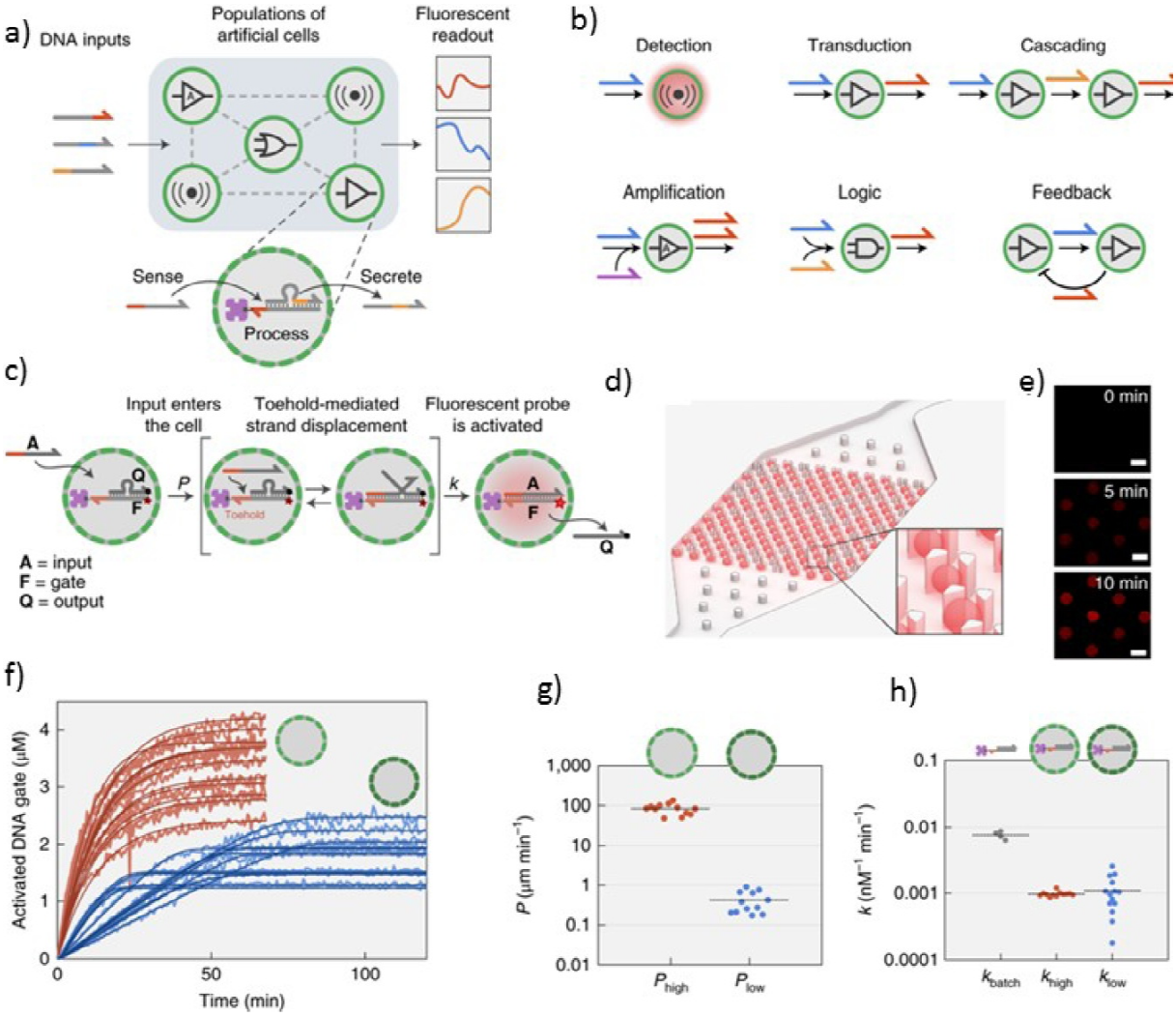

Fig. 5. (a) General strategy of the chemical-biological network platform. Protocells with encapsulated DNA gate complexes are localized on a two-dimensional (2D) spatial grid and can sense, process, and secrete short ssDNA-based signals. The system is initiated by adding ssDNA inputs, and the response dynamics associated with the compartmentalized DSD reactions for each protocell are followed by confocal microscopy. (b) Individual protocells are configured to perform various tasks ranging from signal detection to Boolean logic operations. Individual modules are combined to implement more complex population behaviors such as cascaded signaling, bidirectional communication, and distributed computing. (c) A mechanistic model for toehold-mediated DSD reactions inside protocells. The input strand A diffuses through the semipermeable membrane at a rate governed by permeability constant P (μm min^{-1}) and then activates a fluorescent (Cy5) DNA gate complex F:Q (F, fluorophore/gate; Q, quencher/output strand) via a DSD reaction described by a bimolecular rate constant k (nM^{-1} min^{-1}). (d) CAD drawing of a microfluidic protocell trap array with computer-rendered trapped protocells shown in red. (e) Confocal micrographs of eight trapped proteinosomes showing a time-dependent increase in Cy5 fluorescence associated with the activation of an encapsulated DNA gate complex. Scale bar, 50 μm. (f) Fluorescence measurements (light traces) and model fittings (dark traces) of DSD reactions in protocells with high (red) and low (blue) membrane permeability. Reactions were carried out with 100 nM of A for high-P and 1,000 nM for low-P proteinosomes. For the maintain a constant concentration inputin the medium, the input strand solution has slowly flowed through the microfluidic chamber at a rate of approximately 0.1 μl min^{-1} throughout the experiment. Concentrations of the activated DNA gate complex (F:Acomplex) are determined from time-dependent fluorescence measurements on individual protocells trapped within the microfluidic array device. (g) Estimated permeability constants for the two protocell populations. (h) Estimated bimolecular rate constants for the DSD reactions inside high-P and low-P proteinosomes compared to the estimated rate constant for a reference DSD reaction under batch conditions. Adapted from [157].

ing bacteria produced extracellular polymeric substances and formed tightly packed bacterial chains [153]. The microfluidic approach allowed a new look at electrical signaling provided by a Bacillus subtilis biofilm mediated by potassium ions [154]. Mathematical modeling and cell experiment demonstrated that potassium ion emission by bacterial cells forming biofilm able to change the membrane potential of distant cells forcing them to move. Release of ionic signals by Bacillus subtilis can also affect Pseudomonas aeruginosa behavior. Thus, it was demonstrated that the biofilm community could coordinate its behavior as well as influence the behavior of diverse bacteria [154]. The *Escherichia coli* were self-assembled into a cell-pole to cell-pole oscillating structure on the membrane to prevent divisions at the cell poles. The reconstitution of this setup on a lipid bilayer sheds light on the oscillatory mechanism of *E. coli* Min system [155]. Exploration of bacterial ion channels functionality gave fundamental insights into the mechanism of neuronal signaling. It was shown [156] that ion signaling by propagating potassium waves provides long-range communication within bacterial communities. These waves originate from a positive feedback loop of potassium release by a metabolic trigger and are followed by neighboring cells depolarization [156]. Unconventional approaches to determination of intracellular properties and manipulation by subcellular structures expand horizons for study intracellular ion concentration [127].

Autocatalytic reactions also have the ability to simulate molecular communication. For example, it was shown, in Fig. 5, that encapsulated DNA gate complexes can be localized on a two-dimensional (2D) spatial grid and can sense, process, and secrete short ssDNA-based signals [157]. Microfluidic trapping devices are able to collect protocellular communities that perform collective sensing, amplification, bidirectional communication, and distributed logic operations. As mentioned in the 2nd chapter, such systems could lead to the building complex programmed chemical systems. Such systems will be based on advanced materials with outstanding properties.

5. SYNERGY AND CHEMICAL CYBERNETICS

5.1. Communication of bacteria with synthetic chemical signals through solution chemistry

5.1.1. Requirements for the chemistry

Designing a cross-talk between biological and synthetic smart materials requires a) the development of a chemistry that will be a basis of signal exchange between these materials and b) the development of autonomous chemical computation in synthetic materials. First of all, this chemistry should be water-based. Life happens in water, and most of it prefers environments with neutral pH and mild temperatures (25 – 35 ºC). Thus, the reactions that talk to bacteria should happen in the water at neutral pH and room temperature.

Second, the chemistry should be compatible with the biochemistry of the cell. Biochemical signaling and metabolic networks consist, with some exceptions, such as calcium, of small organic molecules, proteins/enzymes, and nuclear acids. Enzymatic and nuclear acid chemistry happens in the water in mild conditions. Organic chemistry, in contrast, is not usually water-based, although many reactions (e.g., thiol conjugate addition, amide formation) were adopted to aqueous media.

Third, regarding bacteria, a chemical network should analyze information which it receives from bacteria. We thus will talk about computation and signal transformation with these three types of chemistries outside of living organisms (e.g., bacteria, cells).

5.1.2. Information processing by synthetic chemical reaction networks

The goal of this section is not to review all literature on chemical computation, but to identify basic types of computation/signal transformation and to discuss examples that belong to organic, enzymatic, and nuclear acid chemistries.

The first class is the systems that convert input signals into a single output in a nonlinear way. Three subclasses of these systems are most recognizable: (i) filters/modulators – these are networks which suppress any signal below a threshold [158-161] (ii) bistable switches – these are networks where output signal does not return to its original value when the input is changed above a threshold and then changed back [47,162-168] (iii), and chemical oscillators [44,112,168-177] Oscillators are the most complex of all. We will look to representative examples of oscillators with three types of chemistries, which were discussed above.

Fig. 6 demonstrates examples of synthetic organic, enzymatic, and DNA oscillators. From the chemistry perspective, these oscillators convert a steady supply of reactants into a signal, and one of the products is an output (Fig. 6a). Oscillations exist in a limited region of the parameter space. Thus, usually, as input rumps up, the oscillatory network first transits from steady output to oscillatory output and then back to a steady state.

Huck and coworkers recently published an enzymatic oscillator [112,178,179]. This oscillator uses trypsino-

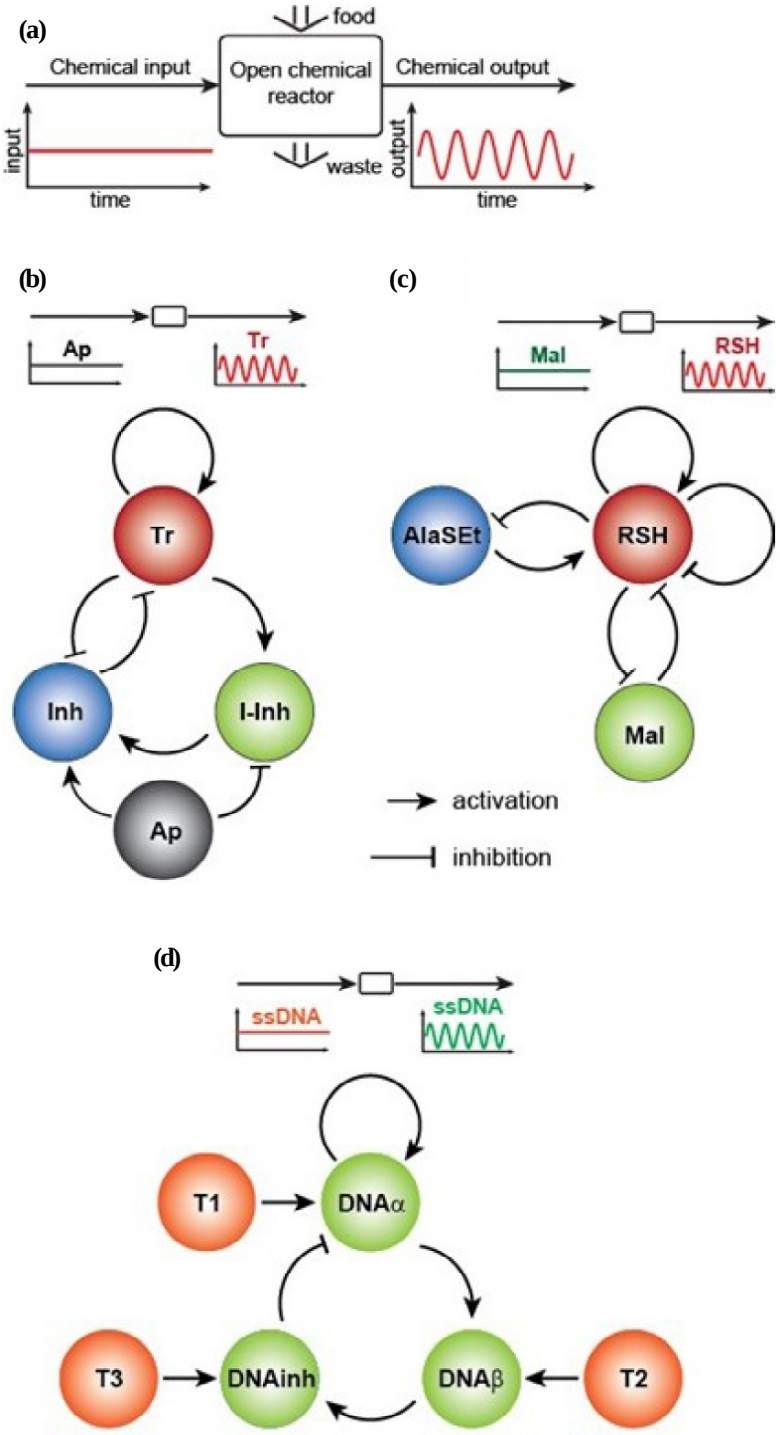

Fig. 6. Signal processing in three types of biocompatible and synthetic chemical reaction networks: enzymatic, organic, DNA based. The chemical networks transform a stationary chemical signal into an oscillatory signal. (a) A diagram showing the conversion of a stationary chemical signal into an oscillatory output in the open chemical reactor (e.g., flow reactor, diffusion fed hydrogel), which is fed with necessary food (fuel) molecules. (b) An example of an enzymatic reaction network. The cycles represent chemical species, and arrows represent the influence of one species on the production of another. The enzyme trypsin (Tr) activates its own production and its own destruction by activating the production of a precursor for Inhibitor (I-Inh). The aminopeptidase (Ap) activates the conversion of I-Inh to the active inhibitor (Inh). (c) The organic oscillatory reaction network, which consists of the autocatalytic production of organic thiols (RSH), the suppression of this production by maleimide (Mal), and depletion of the L-alanine ethyl thioester (AlaSEt). (d) The single-stranded DNA based oscillatory network consists of the autocatalytic production of DNAα coupled to delayed negative feedback loop, which involves DNAα and DNAinh. Templates T1 – T3 guides all reactions.

gen, synthetic tripeptide inhibiting trypsin, and aminopeptidase. Trypsin is autocatalytically produced from trypsinogen, and the simultaneous production of a trypsin inhibitor occurs. As indicated above, processes are positive and negative feedbacks and lead to oscillations. Aminopeptidase catalyzesthe delay step. Aminopeptidase may be considered as the input signal and trypsin as the output signal. This synthetic oscillator is a good model of microorganisms biosynthesizing an inhibitor for aminopeptidase: it responds by trypsin oscillation and thusaffects the microorganisms.

The second example is a purely organic oscillator, which was recently published by Semenov et al. [47]. It is based on the chemistry of organic thiols and has a somewhat different architecture from the trypsin oscillator (Fig. 6b). An autocatalytic production of thiols is coupled to two negative feedback loops: (i) conjugate addition of thiols to maleimide; (ii) conjugate addition of thiols to acrylamide. We can consider maleimide as input and thiols as an output. The system operates at neutral pH in a phosphate buffer; the source materials (L-alanine ethyl thioester and cystamine) are bioderived, except for maleimide and acrylamide. Thiols are important metabolites (e.g., glutathione) and signaling molecules in the cell [180-182]. Therefore, to interface this system with microorganisms, the chemistry of negative feedback loops, which involves maleimide and acrylamide, should be modified.

The lastexample, probably the closest to interface with bacteria, are single-stranded DNA (ssDNA) based oscillators presented by the Rondelez's group [44]. Its architecture is close to the trypsin system (Fig. 6c). The self-activated production of ssDNAα is coupled to its delayed destruction. The inputs and outputs in this system are all ssDNA. An advantage of this system is programmability because the thermodynamics and kinetics of interaction between ssDNA are predictable [163]. This system still requires a few enzymes to function. Winfree and coworker designed a ssDNA oscillator, which does not require any enzymes [174]. Because various RNA molecules are instrumental in cellular regulatory systems, inputs, and outputs of ssDNA are compatible with biochemistry if we find ways to regulate the transport of ssDNA through the cellular membrane.

The second class of systems performs logic operations with multiple input signals. Single-stage logic gates are easy to design (e.g., any bimolecular reaction is an AND gate because it requires the presence of both reactants to produce a product), but not functional. More interesting are cascadable designs that were developed on DNA chemistry. Notable examples of these cascades were developed by Winfree [182,183], Soloveichik [184], Benenson [185], and others. They constructed up to four levels of deep DNA strand displacement cascades [182].

5.1.3. Mechanisms to interact with bacteria through small molecules

Although enzymes and RNA provide a very versatile way to send messages to microorganisms, they require strategies to pass the membrane. We, therefore, focus on communication through small molecules. We discuss three strategies that could be used by synthetic systems to communicate with microorganism through small molecules: (i) communication through small organic molecules that are used in quorum sensing [186];(ii) extra reactions for metabolism by supplying synthetic substrates or catalysts [187-190]; (iii) creating artificial connections in the signaling pathways [191,192].

Quorum sensing is the best-known example of bacterial communication. The derivatives of homoserine lactone are principle messengers. Bacteria produce and sense the same messenger molecule detecting in this way, the density of bacteria in a colony (Fig. 7a). The synthetic system should produce an active homoserine lactone as an output signal to communicate through the same channel [186]. As an example, N-(3-hydroxybutanoyl) homoserine lactone can be masked by converting the hydroxyl to the ester group. If removal of this ester group is a part of the synthetic reaction network, the network will talk to a microorganism.

Balskus and others showed an exciting way to combine small molecule organic chemistry with bacterial metabolism. The synthetic substrates and catalysts supplement metabolic transformations to access biochemically inaccessible products [187-189]. Although this work is mostly about synthesis, the concept is applicable to communication. Thus, the synthetic chemical network that produces iron polyphthalocyanine would communicate with an organism by forcing the production of a new metabolite.

Finally, the synthetic signaling molecule can create a new link in the cellular metabolic/signaling network. Margulis and coworkers demonstrated (in vivo and in vitro) this concept by creating a link between naturally unrelated proteins: platelet-derived growth factor (PDGF) and glutathione-S-transferase (GST) [191,192]. Specifically, they designed PDGF aptamer – GST inhibitor conjugate (chemical transducer). In the absence of PDGF, GST is inhibited by the chemical transducer, but in the presence of PDGF, the chemical transducer is not an inhibitor to GST because it is bonded to PDGF.

In conclusion, the challenge is to interface chemical switches, oscillators, and computing cascades with bacterial signaling and metabolism.

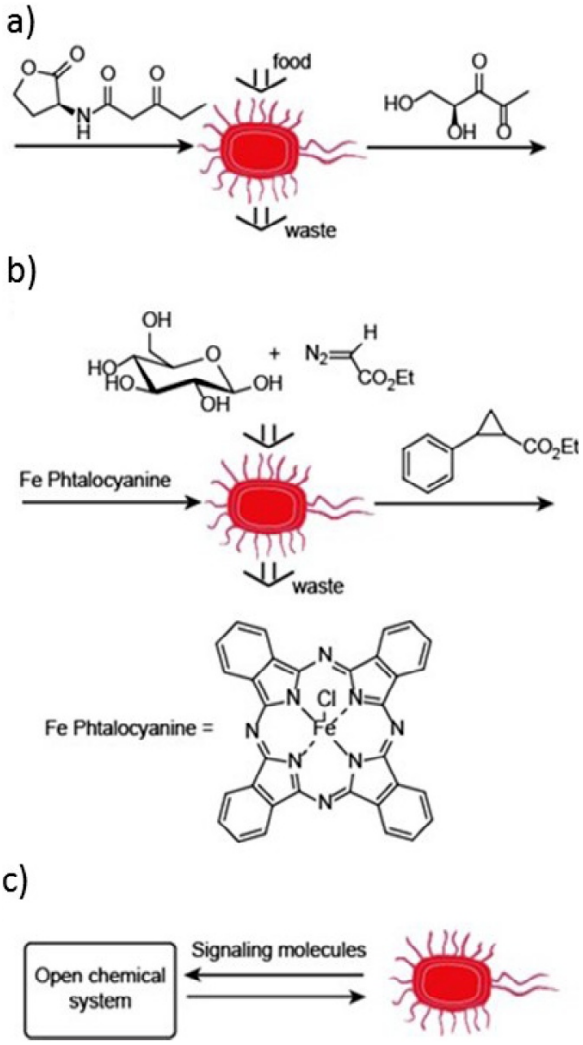

Fig. 7. Communication with bacteria through small organic molecules. (a) Communication through natural signaling molecules which are part of quorum sensing. (b) Possible communication with bacteria through interfering with the bacterial metabolic network. Here iron phthalocyanine catalyst activates a pathway that produces organic cyclopropanes. (c) Communication between the synthetic chemical system and bacteria through the exchange of common signaling molecules. Adapted from [189].

5.2. Soft robotics

Development of biomimetic chemical systems is not limited only by modeling live on a cellular scale. Significant progress is achieved in tissue engineering and designing composite materials with hierarchical architecture performing functions of individual living tissues, organs, and whole living entities (Figs. 8a and 8b).

Soft materials changing living tissues upon stimuli are extensively employed in biomedicine and soft robotics. Cao et al. [193] presented polyester inspired by covalent–noncovalent networks.

The prediction and control of biomimetic chemical systems is a challenging problem because of interaction complexity. These systems demonstrate the similarity of behavior with living cells, especially in terms of catalysis and self-organization. It was shown that 3D-shaped structures could perform clutching, swaying, open-close behavior, lifting, and transferring of different objects. Henson and coauthors [194] suggested a novel approach to understand complex chemical systems using a droplet maker to control composition and size of droplets as well as their position in a predetermined chemical environment. The system was considered as the programmable entity performing the processing of information.

A swimming biohybrid device following the light beam was designed (Fig. 8c). The musculoskeletal system was constructed from a three-dimensional elastomer (polydimethylsiloxane) body and a gold skeleton with an additional interstitial elastomer layer and rat cardiomyocytes microcontact printed from fibronectin. Light-responsive cells provide reproducible and controllable locomotion under pulsed irradiation [195].The architecture of the composite, body was inspired by batoid fish [196]. The gold skeleton replicates fish morphology, and a rubber body was powered by rat heart muscle cells [197,198]. Studying ways of information transfer in aqueous solutions helps to understand communication in a living matter [199]. Much attention is drawn nowadays to the explanation of communication between programmable functional materials and bio objects (Fig. 8a). Sustainable ways to control tissue and cell growth [75], control autocatalytic processes [199], develop bionic devices with bioinspired response and communicate with bacteria colonies [67] are being developed. There is a photocatalytic water splitting reaction in nanoparticles for the formation of reactive oxygen species that affect biological cascades in a bacterium (Fig. 8b) [201].

The behavior of the bacterial community can be operated by photoreactions occurring on surfaces of nanostructured semiconductors. The coupling of biofilm behavior with oscillating K^+ concentration was previously demonstrated [202]. Photosensitive materials releasing hydrogen or potassium ions on-demand enables one to alter biofilm growth regime and response of particular cells. Thus, bacterial cells and their communities can follow the desired spatiotemporal program predetermined by the photoresponse of light-sensitive material.

High-amplitude oscillations of block copolymer films wasusedfor controlling cell behavior [62,131].Previously, block copolymer brushes revealed useful self-cleaning properties. This effects employed to perform lactic bacteria repulsion from the surface. This type of bacteria

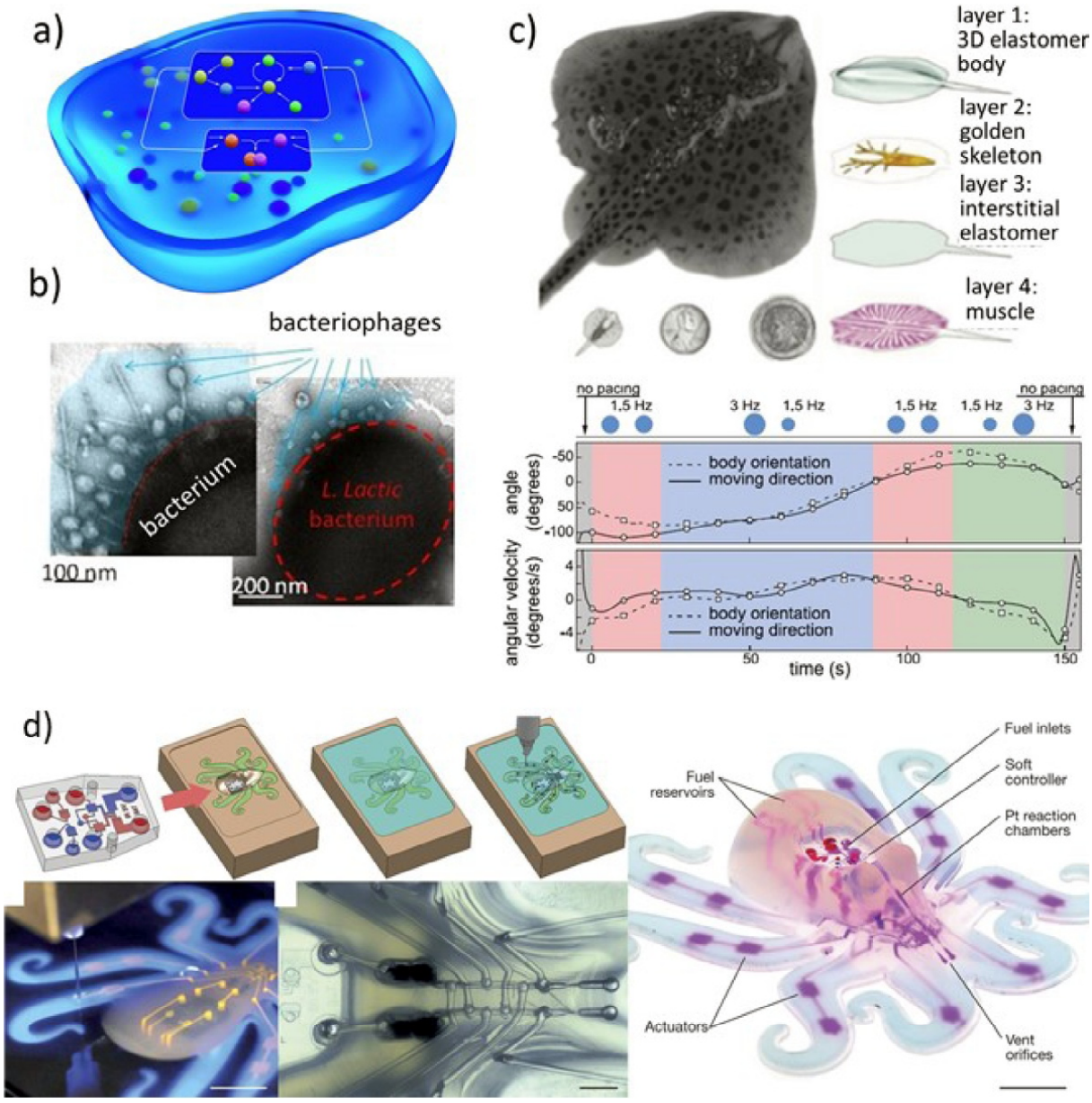

Fig. 8. (a) Scheme of networks in the natural or synthetic cell. (b) A system where light activates titania to generate reactive oxygen species that activate cascade in bacterium cell and initiate generation of bacteriophage released from the cell. Transmission electron microscopy image of the stained cell in the moment of bacteriophage release, adapted from [201]. (c) Example of nanoengineering implant, a robot for targeting light-sensitive muscle cells with the possibility of external control for the produced "cyborg", adapted from [195]. (d) The octopus is removed from the mould and inverted to reveal a fully soft, autonomous robot that is controlled via the embedded microfluidic soft controller and powered by monopropellant decomposition. Scale bar, 10 mm. Fluorescent dyes have been added in e and g to assist in visualization of internal features, adapted from [90].

produces lactic acid followed by a pH drop of surrounding media and block copolymer activation. Thus, their thickness increase, and bacteria are released from the surface [64,203].

The autonomous operation of pneumatically actuated systems can be obtained bya combination of monopropellant fuels and microfluidic logic [89]. Oxygen gas from the water decomposition on the Pt electrodes inflates fluidic networks downstream of the reaction sites, resulting in actuation (Fig. 8d) [89]. This programmable assembly of multiple materials provides completely soft, autonomous robots.

6. CONCLUSION

In this review, we highlighted the gap in information processing capabilities between biological and synthetic materials. The following directions were discussed in

the review: i) from capsules to a synthetic cell, ii) from stimuli-response to the logic element, iii) from biomaterial to chemical-biological networks, and iv) synergy and chemical cybernetics. The directions are aiming to narrow the gap between biological and synthetic systems, responsive and information processing materials, autonomous materials and robotics. Examples which we provide in this review prove the importance of interface engineering and spatial and temporal control of chemical processes. A key challenge in designing interfaces between chemical and biological systems is making synthetic materials that respond to biological metabolites and release chemical cues (molecules and ions) which effect biological systems. In addition to biological metabolites, advanced materials should react to temperature, light, etc. Because of the variety of biological metabolites and environmental conditions, synthetic advanced materials should be able to recognize the complex patterns of physico-chemical signals. For recognition of the complex pattern, synthetic systems and materials should process physico-chemical information. In solution and soft materials, physico-chemical information is processed by chemical networks. Living and non-living interfaces are ubiquitous in physico-chemical and biological systems and are manifested at different scales ranging from molecules to robots.

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