Recent Progress in Enzyme-Driven Micro/Nanoswimmers: from Fundamentals to Potential Applications

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Abstract

Recent progress in the field of enzyme-powered micro/nanoswimmers is summarized and discussed, covering different theoretical and mechanistic aspects, as well as potential applications. This is motivated by the increasing number of reports focusing on the design of biocompatible systems, able to move in complex environments and their potential use for biomedical applications. Motion is achieved by enzymatic reactions, enabling bubble-propulsion and self-diffusiophoretic or self-electrophoretic displacement. Single- and multiple-enzyme-powered micro/nanoswimmers are presented as interesting and original systems for cargo delivery, the detection of various analytes and the biodegradation of complex organic molecules.

Keywords: microswimmers, enzymes, biocompatibility, biomimetic systems

1. Introduction

Smart biological systems in living organisms can transform chemical energy into mechanical action, and hence carry out precise tasks in confined spaces [1,2]. Inspired by such natural motors, artificial biomimetic systems that can transform different types of energy into mechanical motion, have been developed. These so-called micro/nanoswimmers have gained considerable attention due to their numerous potential applications, e.g., for sensing, cargo delivery, and environmental remediation. However, these artificial devices often suffer from the toxicity of their components (e.g. Al, Ga, Cu) or the employed fuels (e.g. acidic or alkaline solutions, H_2O_2), thus partially preventing

their use for biomedical applications, such as biorecognition, biosensing, imaging and nano-surgery. In order to circumvent these limitations, more recent studies suggested miniaturized engines based on enzymatic catalysts, providing unique characteristics such as biocompatibility of the swimmers and fuels, as well as adaptability to different environments. Such self-propelled enzymatic micro/nanoswimmers, powered by different enzymes, have been proposed for exciting potential applications e.g. active targeted drug delivery [3] or blood-brain barrier crossing [4], which might be important for transporting pharmaceutical compounds toward localized areas inside organs. The rational design of these swimmers, incorporating various enzymes, is a critical factor concerning their performance, in particular the efficiency of their motion in complex environments. Hence, swimmers with different shapes (spherical or tubular) and sizes (from 200 nm to 5 mm), decorated with single or multiple enzymes, have been developed [5•]. Among the different enzymes used to power motion of micro- and nano swimmers, two different enzymatic processes are mostly used. The first category is based on redox reactions like it is the case for glucose oxidase, catalase, bilirubin oxidase or peroxidase, whereas a second category employs hydrolysis reactions e.g. urease and lipase (Table 1). The present review aims to discuss the recent advances concerning the mechanisms of propulsion and the potential applications of single- and multiple-enzyme powered micro/nanoswimmers. In addition, this report especially focuses on devices where motion is achieved by enzymatic process based on redox reactions or fully triggered by electrochemical processes.

Table 1. Representative enzymatic reactions used for the propulsion of micro and nanoswimmers.

Enzymatic processes using redox reactions	
Enzyme	Reaction
Glucose oxidase (GOx)	β-D-Glucose $+O_2 + H_2O \rightarrow H_2O_2 +$ D-glucono-1,5-lactone
Catalase	$H_2O_2 \rightarrow 2H_2O + O_2$

Bilirubin oxidase (BOD)	$½O_2 + 2H^+ + 2e^- \rightarrow 2H_2O$
Peroxidase	$H_2O_2 + AH_2 \rightarrow 2H_2O + A$
Enzymatic processes using hydrolysis reactions	
Urease	$(NH_2)_2CO + H_2O \rightarrow CO_2 + 2NH_3$
Lipase	triglyceride $+3H_2O \rightarrow$glycerol +fatty acids

2. Single-enzyme-powered micro/nanoswimmers

In the majority of the literature examples, the motion of single-enzyme-powered swimmers is achieved via bubble-propulsion or self-diffusiophoretic mechanisms. Self-propulsion allows decreasing mass transport limitations and enabling selective directional motion towards specific locations. These swimmers are mostly built by immobilizing various enzymes, such as urease [3,6-8], acetylcholinesterase, glucose oxidase, aldolase [9], catalase [10-12], and lipase [13,14] on a large variety of miniaturized objects with different architectures, by covalent binding, encapsulation, adsorption or drop-casting. For example, Schmidt, et al. designed hybrid Ti/Au-catalase micro-tubes, where motion is based on the enzymatic decomposition of H_2O_2 into water and oxygen (Figure 1a) [15•]. These devices move faster, and with higher efficiency at low H_2O_2 concentrations compared to those comprising a Pt catalyst. Recently, pH-responsive biocatalytic microswimmers were designed by assembling catalase and succinylated β-lactoglobulin in a zeolitic imidazolate framework-L (ZIF-L) (Figure 1b) [16•]. Motion control is achieved due to the pH-induced reversible gelation process of β-lactoglobulin. At neutral pH, β-lactoglobulin is permeable, enabling H_2O_2 to reach the enzymatic sites, causing motion due to a bubble propulsion mechanism. However, at slightly acidic pH, gelation occurs, blocking the access of fuel and stopping the motion. A similar principle was used to produce submarine-like microswimmers that use buoyancy forces to control vertical motion. In this case poly-(2-

diisopropylamino)-ethyl methacrylate (PDPA) and catalase were incorporated into the ZIF-L structure [17]. At neutral pH, the oxygen generated by the enzymatic reaction binds to the hydrophobic PDPA, leading to an ascending motion. In contrast, at slightly acidic pH, PDPA becomes hydrophilic, causing the release of oxygen, and consequently a sinking of the device. In a recent work, protein micro-tubes, functionalized with urease, exhibit self-propulsion in the presence of urea, due to a concentration gradient established by the enzymatic reaction in the inner part of the tube [18] Motion of dissymmetric magnetic microparticles, asymmetrically modified with multilayers of biotinylated urease, has also been reported [19]. Most importantly, these devices move at physiological urea concentrations (10 mM) and in liquids with viscosities four times higher than the viscosity of water, which is important for future *in vivo* applications. Ma et al. synthesized hollow mesoporous SiO_2 microspheres functionalized with urease at the sphere surface [20]. The resulting propulsion is due to the intrinsic asymmetry of the SiO_2 spheres, generating ionic self-diffusiophoresis caused by the enzymatic decomposition of urea. An interesting alternative is the design of systems that can be triggered by different stimuli, thus facilitating motion in complex fluids. For example, lipase-modified dendritic silica/carbon/Pt dissymmetric nanoparticles can move either via self-diffusiophoresis or bubble propulsion, as well as self-thermophoresis (Figure 1c) [21]. In these devices, the Pt nanoparticles catalyze the disproportionation reaction of H_2O_2, the asymmetric photothermal effect of the carbon part causes a thermal gradient when irradiated with near-infrared light, and lipase, loaded in the pores of the dendritic structure, decomposes a triglyceride, causing concentration gradients. Finally, Arnaboldi et al. developed hybrid bioelectrochemical swimmers, for which motion is achieved when coupling the spontaneous reduction of oxygen by bilirubin oxidase (BOD) with the enantioselective

oxidation of 3,4-dihydroxyphenylalanine (L- or D-DOPA) by inherently chiral oligomers ((R)- or (S)-2,2′-bis[2-(5,2′-bithienyl)]-3,3′-bithianaphthene (oligo-BT_2T_4)) (Figure 1d) [22••]. Both, BOD and the enantiopure oligomers are immobilized on opposite extremities of a freestanding miniaturized polypyrrole film, thus allowing electron transfer between the cathodic and anodic sites. This electron transfer across the microswimmer is accompanied by a proton flux, resulting in self-electrophoretic propulsion.

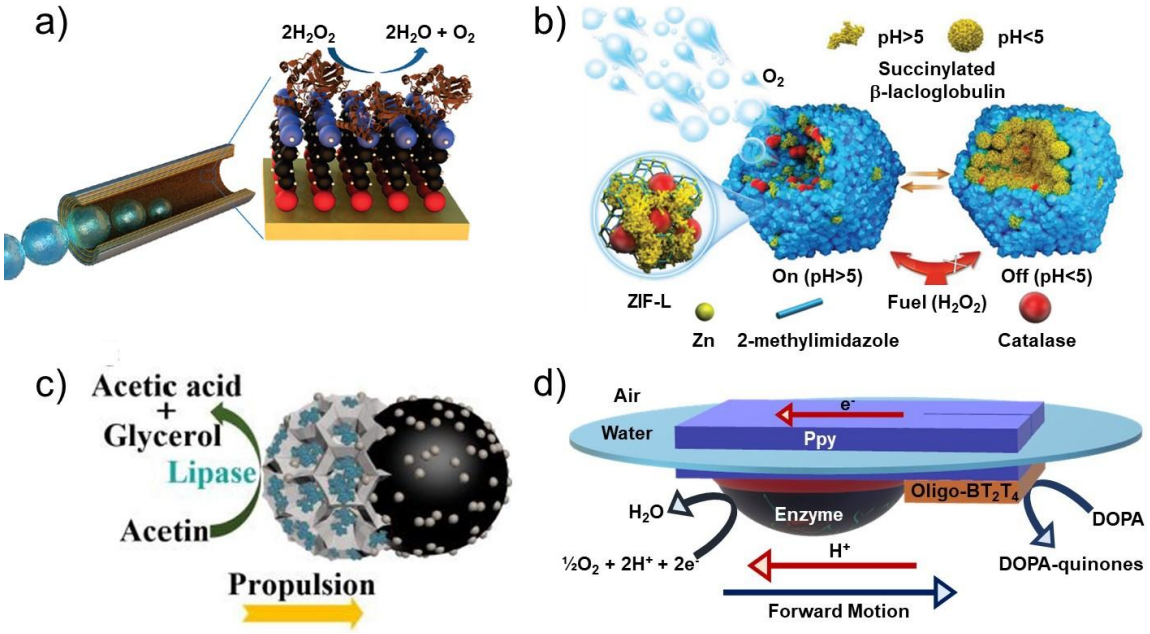


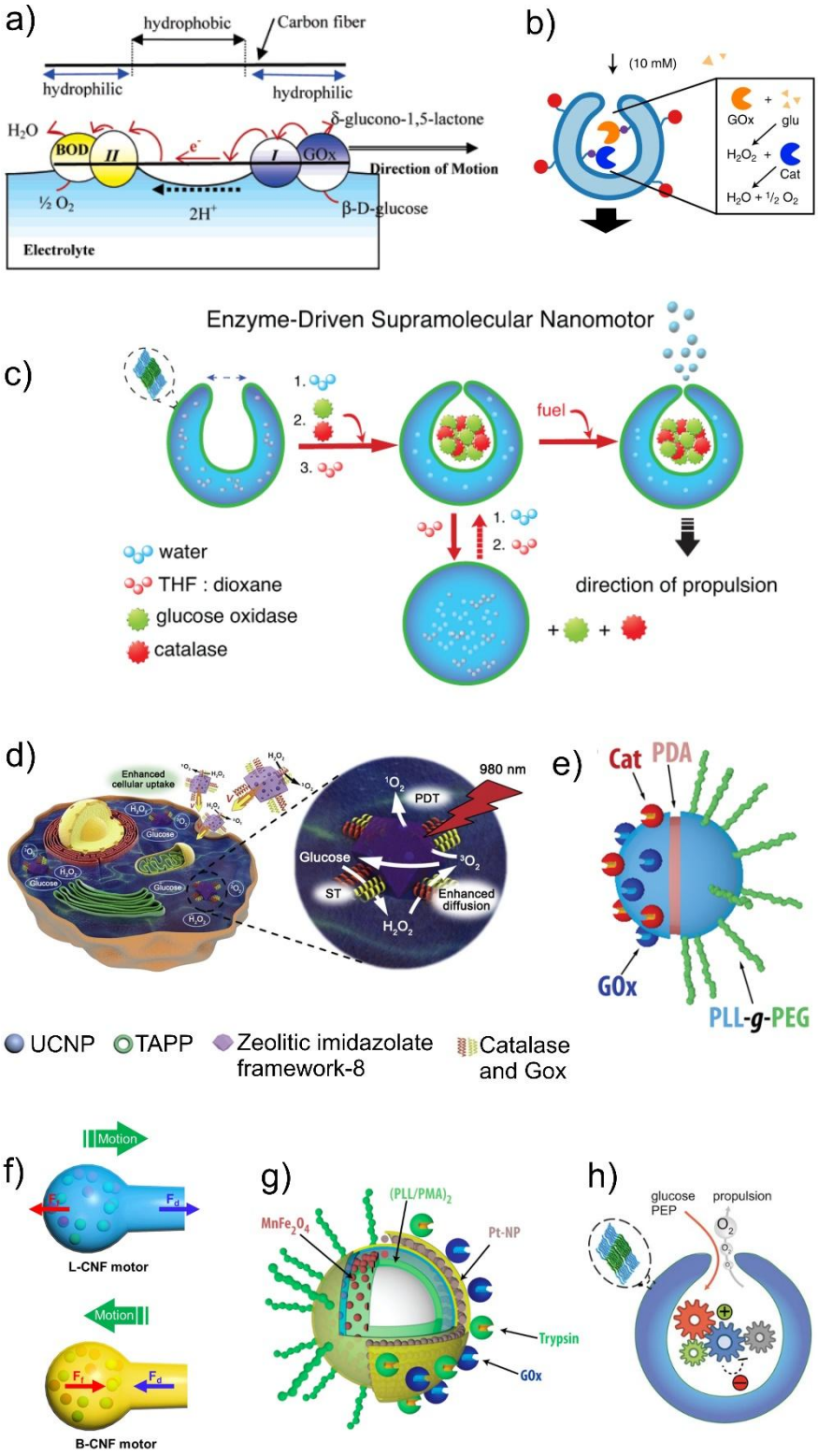
Figure 1. Schematic illustrations of different single-enzyme-powered micro/nanoswimmers. a) Open view of a hybrid biocatalytic micro-tube (left), and surface modification of the inner Au layer allowing the enzymatic decomposition of H_2O_2. Adapted from reference [15•]. b) Structure and propulsion mechanism of a biocatalytic microswimmer with pH-responsive on/off motion. Adapted from reference [16•]. c) Motion of a lipase-modified dendritic silica/carbon/Pt nanoparticles Janus-type swimmer, based on self-diffusiophoresis. Adapted from reference [21] d) Design of a hybrid

bioelectrochemical swimmer in an upside-down configuration at the air/water interface together with a representation of the mechanism of selective motion induced by proton flux. Adapted from reference [22••].

3. Multiple-enzyme-powered micro/nanoswimmers

Multiple-enzyme-powered micro/nanoswimmers have been introduced (i) to achieve higher velocities via combining multiple propulsion mechanisms; (ii) to avoid toxic fuels, particularly H_2O_2; (iii) to facilitate the adaption to different environments; and (iv) to generate more functionalities. Hence, swimmers modified with different enzymes, promoting enzymatic domino reactions have been developed. [23•-28]. From a more historical point of view, Mano et al. decorated a carbon fiber with GOx/redox polymer I (RPI) as a glucose oxidizing microanode at one extremity, and BOD/RPII as an O_2 reducing microcathode at the other end (Figure 2a). In the presence of glucose, the electron flow Glucose → GOx → RPI → fiber → RPII → BOD → O_2 is accompanied by an ion flow along the carbon fiber, resulting in its propulsion at the water/oxygen interface [29••]. Feringa, et al. designed swimmers based on multi-wall carbon nanotubes (MWCNTs), decorated with GOx and catalase to transform glucose into H_2O_2 and then to water and oxygen, respectively. Such domino reactions avoid the addition of H_2O_2 and hence lower the biotoxicity [30]. Following a similar elegant principle, Wilson et al. proposed bowl-shaped polymeric systems with a narrow opening containing GOx and catalase enzymes (Figure 2b) [31•]. These systems not only prevent the hydrolysis of the protected enzymes, but also allows generating motion of the biocompatible swimmers in the presence of physiological amounts of glucose (Figures 2b-c) [32]. In another example, Ma et al. assembled a core-shell nanoswimmer utilizing metal-organic frameworks to promote

129 photodynamic therapy (PDT) and starvation therapy (ST) (Figure 2d). In the involved
130 domino reaction, GOx initially catalyzes the decomposition of intracellular glucose to
131 promote cell starvation and H_2O_2 generation, whereas catalase decomposes the generated
132 H_2O_2, thus triggering motion and oxygen production, which promotes PDT [33]. An analog
133 enzymatic system was employed by Städler et al., based on Janus microswimmers
134 decorated by enzymes only on one hemisphere (Figure 2e). The diffusion of these
135 biocompatible swimmers is enhanced in the presence of glucose [34]. In a more recent
136 study, He et al. elaborated a nanoswimmer powered by GOx and catalase, trapped in a
137 carbonaceous nanoflask (CNF), moving in a glucose solution via a domino reaction
138 mechanism[35], similar to previous studies (Figure 2f)[30-34]. In this work, it was
139 demonstrated that changes in surface wettability (hydrophobicity or hydrophilicity) of the
140 nanoswimmer can dictate the direction of motion [35]. In another study, a dissymmetric
141 microparticle was proposed where one side included two enzymes, GOx and trypsin, which
142 were working as independent engines using different fuels, namely glucose and
143 bis(benzyloxycarbonyl-L-arginine amide) (Figure 2g). Both enzymes contribute to the
144 enhanced diffusion of swimmers using biocompatible fuels [36]. Finally, Van Hest et al.
145 reported swimmers with a shape similar to the one of Figure 2b, containing multiple
146 enzymes, promoting several feedforward loops using various substrates to produce kinetic
147 energy as the output of the enzymatic network (Figure 2h) [37••].



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149 **Figure 2**. Schematic illustrations of dual/multiple-enzyme-powered micro/nanoswimmers.

150 a) The structure and propulsion of a carbon fiber decorated with GOx and BOD. Adapted

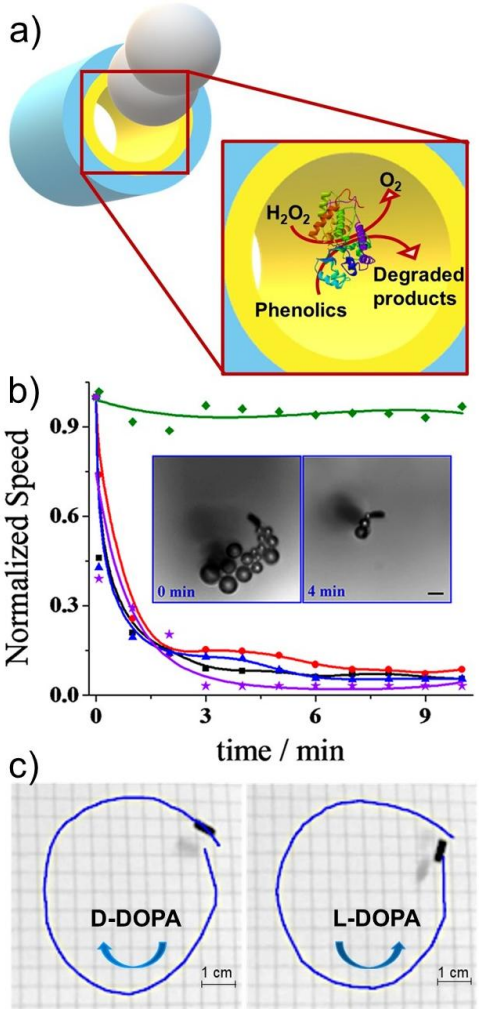
from reference [29••]. b) Biodegradable polymeric nanoswimmer encapsulating GOx and catalase. Adapted from reference [32]. c) Dual-enzyme (GOx-catalase) loaded supramolecular bowl-shaped nanoswimmer. Adapted from reference [31•]. d) Core-shell enzymatic nanoswimmer for synergetic photodynamic (PDT) and starvation therapy (ST). Adapted from reference [33]. e) Janus microswimmer with one hemisphere decorated with GOx and catalase. Adapted from reference [34]. f) Nanoswimmer powered by GOx and catalase trapped in a carbonaceous nanoflask (CNF). Adapted from reference [35]. g) Janus microswimmer decorated with GOx-Pt and trypsin. Adapted from reference [36]. h) Nanoswimmer containing four enzymatic cycles to convert glucose and phosphoenolpyruvate (PEP) into mechanical energy for the propulsion of the nanoparticle. Adapted from reference [37••].

4. Applications

Enzyme-powered micro/nanoswimmers have gained considerable attention in sensing, cargo delivery [38], and bioremediation [39•]. The enzymatic degradation of azo-dye pollutants by using laccase-based poly-(3,4-ethylenedioxythiophene)-polypyrrole/Pt (PEDOT-PPy-COOH/Pt) tubular microswimmers has been reported [40•]. In this case, disproportionation of H_2O_2 on Pt, present in the inner part of the tubes, is used to produce motion, whereas, laccase is immobilized at the outer part of the swimmer in order to catalyze the oxidation of the azo-dye compounds. An interesting alternative is a design of "2 in 1" systems, where the enzymatic reaction enables the propulsion mechanism and catalyzes the decomposition of organic pollutants. For example, lipase-modified mesoporous silica nanoparticles present random-walk in triglyceride/PBS solutions [41]. As motion is triggered by the catalytic decomposition of triglycerides, causing a

concentration gradient, these devices can act as active cleaners of fully and partially soluble oils. In a recent study, PEDOT-Au/peroxidase microswimmers were used as dynamic catalytic systems for the removal of phenolic compounds, such as phenol, bisphenol A, guaiacol, pyrogallol and catechol [39•]. In these devices the immobilized peroxidase not only catalyzes the decomposition of H_2O_2 to form oxygen (bubble propulsion), but also degrades the phenolic compounds (Figure 3a). Different urease-powered pH-responsive swimmers have been designed for the delivery of chemotherapeutic agents and bioimaging probes [3,42,43]. Drug-loaded catalase-powered nanoswimmers have been used for local drug delivery against inflammations [44]. These devices present positive chemotaxis towards H_2O_2 concentration gradients, produced by phorbol ester-stimulated macrophages. Recently, catalase-powered Au-mesoporous silica nanoparticles, functionalized with disulfide-linked oligo-(ethylene glycol) chains, acting as Janus gatekeepers have been reported [45]. These devices exhibit motion via the catalytic decomposition of H_2O_2 and deliver their cargo upon recognition of a reducing agent (glutathione). Finally, enzyme-powered swimmers, equipped with different transducers for pH, DNA, and biomarkers, have been used for sensing [46-48]. An interesting alternative is to take advantage of the *on-off* mode of light emission in the presence of a fluorescent molecule. For example, catalase-powered dissymmetric rods, functionalized with tetraphenylethene (TPE) derivatives and fluorescein isothiocyanate (FITC) as fluorophores, exhibit self-propulsion due to the enzymatic decomposition of H_2O_2, and fluorescence changes from blue to green after the capture of tumor cells [49]. Another approach is the use of the changes in the swimming behavior, *i.e.* trajectory or speed, to detect species of interest. For example, PEDOT/Au-catalase micro-tubes exhibit biocatalytic inhibition of the enzyme in the presence of chemical stress (*e.g.*, heavy metals, pesticides and herbicides), which results in

198 a decrease of bubble production, directly detectable via their swimming behavior (Figure
199 3b) [50•]. Recently, the directional control of self-electrophoretic BOD/Ppy/oligo-BT_2T_4
200 swimmers has been demonstrated [22••]. Enantioselective clockwise or anti-clockwise
201 motion is caused in this case by a site-specific proton flux associated with the oxidation of
202 an enantiomer present in the solution (Figure 3c). In addition, the curvature of the track can
203 be used for the direct visualization of the degree of enantiomeric excess in the solution.



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205 **Figure 3**. a) Scheme of a "2 in 1" peroxide-driven micromotor for bioremediation of
206 phenolic pollutants. The active inner part of the swimmer catalyzes hydrogen peroxide

decomposition (propulsion) and the degradation of phenolic compounds by the immobilized peroxidase Adapted from reference [39•]. b) Normalized speed as a function of time for a PEDOT/Au-catalase micro-tube in the presence of: 100 μM Hg (black square), 0.6 mM Cu (purple stars), 25 μM sodium azide (red circle), 625 mM aminotriazole (blue triangle), and a control experiment without the toxins (green diamond). Inset: time-lapse images of the microswimmer recorded after 0 and 4 min swimming in a 100 μM Hg solution. Scale bar, 6.0 μm. Adapted from reference [50•]. c) Macroscopic enantiospecific motion of hybrid bioelectrochemical swimmers at the air/water interface of a solution containing 5 mM of D-DOPA (left) and 5 mM of L-DOPA (right). Adapted from reference [22••].

5. Conclusions and perspectives

In this review, we have examined recent work in the field of enzyme-driven micro/nanoswimmers based on different propulsion mechanisms. In the case of single-enzyme-powered swimmers, the enzymatic reaction triggers either the asymmetric release of bubbles or the self-generation of chemical or electric gradients, causing the propulsion of the devices. In contrast to this, in multiple-enzyme swimmers, a cascade of enzymatic reactions can generate motion based on bubble propulsion or self-electrophoresis. In addition, different applications of these devices are presented, where the enzymatic reaction is used either for the degradation of organic molecules or as analytical tools. These devices allow biomimetic self-propulsion, associated with improved biocompatibility, and efficient energy conversion. Their size and controlled trajectories might enable their use in different organs and cells. Nevertheless, there are still many issues to address, e.g. the toxicity of some fuels, the easy and direct visualization, the efficient biodegradability and the limited

life-time of the devices (recyclability). However, different approaches have been proposed to solve these problems, like modifying the shape, increasing the catalytic performance of the enzymes or using cascade reactions, and employing materials able to be digested completely by enzymes (e.g., proteases) or in biological media. Finally, the enzyme-based nanoswimmers, in particular those using redox reactions, have shown promises for biomedical applications. However, in order to develop drug delivery systems for "real world" *in vivo* applications, tiny robotic systems inspired by biological reactions in which robots and fuels are entirely biocompatible are mandatory and deserve additional research efforts. Furthermore, many other features of the robots, most importantly stability, biocompatibility, selectivity, directionality and the velocity in different biological environments need to be significantly improved prior to their commercialization.

6. Acknowledgements

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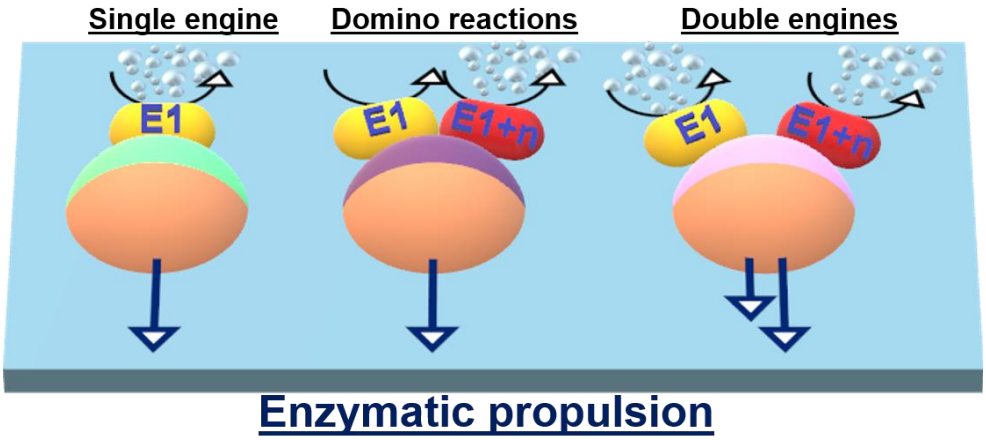
•Inhibition of the enzyme due to chemical stress can be directly correlated with changes in the swimming behavior.

399 Graphical abstract



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