Design and Control of the Micromotor Swarm Toward Smart Applications

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Micro- and nanomotors are micro- and nanostructures capable of autonomous movement and collective behavior, mimicking natural counterparts. This review aims to give a recent perspective on micro- and nanomotors driven by intelligent mechanisms in action under the cooperative effect of the swarm of micromotors as their distinctive feature. Different energy sources and the factors that can influence cooperative micromotor motion are comprehensively covered, along with the underlying phenomena and related applications. The motion ability of micro/nanomotors, along with capabilities to reach a targeted destination, holds considerable promise to address remaining challenges in the environmental and biomedical fields.

1. Introduction

Recent progress in nanoscale and nanotechnology provides a convenient solution to many challenges in diverse fields, with new materials such as 2D materials,[1] metal catalysts,[2] organic polymers,[3] etc., offering unique possibilities in such directions.[4] Yet, such materials generally lack self-motion performance for, i.e., targeted drug delivery, which hamper their effectiveness. Indeed, imparting such nanomaterials with the ability of self-targeting to the desired destination in a cooperative manner—mimicking nature—holds considerable promise to develop a myriad of applications with unprecedented capabilities, mostly in the environmental and biomedical fields.[5]

Micro/nanomotors are micro/nanoscale devices that can convert different energies into motion. The self-propulsion of micro/nanomotors, along with the turbulent flows created by their motion, has not only improved the efficient micromixing and enhanced mass transfer but also endows such smart robots with targeted delivery functions.[6] Different energies, such as chemical fuels,[7] magnetic fields,[8] electromagnetic radiation,[9] and ultrasound,[10] have been used for efficient micromotor propulsion in complex biofluids. By integrating some specific recognition elements through surface modification, pathogens,[11] cancer cells[12] or toxic chemicals capture,[13] targets sensing,[14] and cancer cells/pathogens killing[15] can be achieved. Using the controllable motion of micro/nanomotor, single cells can be manipulated to a specific location, which is important for biological research such as cell–cell communication.[16] Combined with bioocompatible energies, such as light or magnetic fields, micro/nanomotors offer considerable potential for disease diagnosis or therapy.[17] Most importantly, micromotors can exhibit an orientation determined by a specified force, that is to say “tactic” behavior by the action of different stimulus, such as chemical, magnetic, or light fields, which also help them to work cooperatively. In other words, micromotors can sense and respond to changes in the surrounding environment and move away or toward specific locations. As all the micromotors present in the solution will experience the same behavior, all the population will move in response to the stimulating, thus working cooperatively. Also, this will increase the density of micromotors in a defined area, creating new phenomena arising from the influence of the motion of one micro-motor toward surrounding ones. Such “tactic”-collective behavior in micromotors can be induced by different stimuli or signal sources. In that way, a vector field is established by the signal source, which is “sensed” by the micromotor and can be exploited to realize a myriad of applications. Yet, it should be mentioned here that asymmetry needs to be introduced in the micromotor structure for successful distribution and interaction with the signal vector. The first and most commonly known signal sources are chemical gradients of fuels—such as hydrogen peroxide—which induce an electrosporethetic aligning torque in the asymmetric micromotor structure, which, in turn, reorient along the direction of the chemical gradient.[18] A second group of stimulus for the creation of the vector field are magnetic and light fields.[7,18b,19,20] Indeed, very recent publications illustrate...
the chemotactic and/or magnetotactic behavior of a light-emitting diode (LED) swimmer integrating Mg and Pt foils as the anode and cathode, respectively. The spontaneous oxidation of a Mg foil and the reduction of $\text{H}_3\text{O}^+$ on the Pt and Mg foils were exploited in the presence of gradients of such fuels to illustrate the targeted movement, with the LED allowing for easily track the swimmer motion in complex trajectories.$^{[18b,18c]}$ In this case, the micromotor asymmetric body experiences a direct torque and aligns with the vector field, exhibiting a straight and directed trajectory.$^{[76]}$ If anisotropy occurs in the micromotors, another tactic phenomenon or rheotaxis can occur due to the interplay between the polarity of the particles and their alignment by the viscous torque.$^{[21]}$ Scheme 1 shows a schematic of the different micromotor behaviors explained here.

In this review, we will focus on recent advances in cooperative micromotors-based strategies to solve complex practical challenges in both biomedical and environmental fields. The review is structured into five main subsections according to different energy sources that cause different swarming and cooperative motions of the micromotors, namely: 1) chemical; 2) living cells-powered micro/nanomotors; 3) magnetic; 4) acoustic, and 5) electromagnetic micro/nanomotors. In each subchapter, the underlying phenomena along with main recent applications will be given. The cooperative action of micromotors can reach targeted areas for localized delivery. Prospects will be given in Section 7, along with a critical overview of the main advantages of each strategy.

2. Cooperative Motion by Chemical Energy-Driven Micromotors

Micromotors driven by chemical energy mainly depend on the catalytic decomposition of a chemical fuel ($\text{H}_2\text{O}_2$, urea, etc.) or the consumption of reactants themselves (Mg, Zn, etc.) to produce bubbles for propulsion. Chemical propulsion can be referred as the production of oxygen or other gas bubbles or electrophoretic motion via the generation of a gradient of “fuel” decomposition products that accumulate in one side of the micromotor. Indeed, micro/nanomotors are designed into asymmetric or tubular structures for spontaneous directional motion by symmetry breaking. Such asymmetry allows them to reorient their direction toward chemical gradients via an indirect electrophoretic aligning torque.$^{[5]}$ Such chemical gradients (pH, peroxide, surfactants, etc.) are produced during cell metabolite in living systems or can be supplied in the environment. For example, metabolite gradients have been found in tissue-engineering constructs mimicking living cells. In addition, hydrogen peroxide is a key redox intermediate generated within cells, and gradients of such chemical can exist in wounded tissues.$^{[22]}$ For instance, Janus micromotors with different hemisphere surfaces are introduced for such aims. By coating only one side of the particles with a catalyst (Pt, MnO$_2$, enzyme, etc.), asymmetric bubbles ($\text{O}_2$, $\text{H}_2$, $\text{NH}_3$, etc.) are generated in inducing a propelling force as well as velocity on the opposite of the catalytic motor surface. Another typical example comes from the tubular micro-motor design, whose catalytic reaction happens in the inner wall of the tube. In this case, catalysts are deposited inside the inner surface of the microtube, and gas molecules then nucleate and further grow into bubbles inside the microtube, and finally eject from one opening of the micromotor. For the synthesis of catalytic Janus micro/nanomotor, physical vapor deposition (PVD),$^{[23]}$ layer-by-layer (LBL) assembly, and shape transformation methods$^{[24]}$ have been introduced, and for tubular micromotor, template-assisted methods$^{[25]}$ and rolled-up technology$^{[26]}$ are used frequently. Many materials have also been studied and used as catalysts, which can be mainly divided into inorganic catalysts/materials and enzyme-based catalysts.

2.1. Chemical Micro/Nanomotors Powered by Inorganic Catalysts/Materials

Chemical-powered micro/nanomotors using inorganic counterparts can be divided into two different types. The first type usually uses some inorganic metals/metal oxides, such as Pt,$^{[27]}$ MnO$_2$,$^{[28]}$ etc. for catalytic decomposition of fuels such as hydrogen peroxide to produce bubbles. In the second type, a chemically powered micro/nanomotors design was realized by consumption of inorganic materials themselves, such as Mg,$^{[29]}$ Zn,$^{[30]}$ CaCO$_3$, etc. In both cases, micromotors were all powered by the as-produced bubbles that come from chemical reactions. The usage of fuel may usually suffer from biotoxicity in some instances, whereas Mg- and Zn-based micro/nanomotors could provide a more biocompatible way for biological applications. Figure 1 shows the representative examples of chemically propelled micromotors with cooperative and chemotactic collective behavior for biomedical and environmental applications.

One important feature of chemical-driven micromotors is the ability to work cooperatively as a swarm of micromotors for improving the detection of important clinical biomarkers or environmental pollutants.$^{[31]}$ For example, Bing et al.$^{[32]}$ fabricated Mn$_3$O$_4$ tubular micromotors for the decomposition of $\text{H}_2\text{O}_2$ in generating oxygen bubbles for their propulsion. By
Figure 1. Chemically propelled micromotors with chemotactic and cooperative motion. A) Tubular micromotors containing a catalytic Mn$_3$O$_4$ layer and a surface coating of MIP for selective recognition and capture of antibiotics. a) Reproduced with permission.\(^{[32]}\) Copyright 2020, Royal Society of Chemistry, and b) glucose biosensing with swarming of Mg/Pt micromotors. Reproduced with permission.\(^{[33]}\) Copyright 2019, American Chemical Society. B) Schematic illustration and mechanism of Mg-based micromotor for decreasing intracellular reactive oxygen species (ROS) by active H$_2$ generation and doxorubicin (DOX) delivery for enhancing chemotherapy. Reproduced with permission.\(^{[34]}\) Copyright 2020, Elsevier. C) Onion-Like Mg micromotors for enhanced Escherichia coli chemotraction and killing: Structure and real-time images of the bacteria trapping by bare micromotors. Reproduced with permission.\(^{[35]}\) Copyright 2020, Wiley. D) Urease-driven micromotors for bladder cancer cell treatment. The bottom part shows fluorescent images of the bladder cancer spheroids before and after incubation of the micromotors, where the red parts indicate the internalization of the micromotors, which are labeled with a fluorescent antibody. Reproduced with permission.\(^{[36]}\) Copyright 2019, American Chemical Society. E) The 2D catalase-modified nanosheet with chemotactic behavior and enhanced drug delivery to cancer cells. The bottom part shows the time-lapse images of the displacement of the micromotors—labeled with a red fluorophore—in a peroxide gradient. Reproduced with permission.\(^{[37]}\) Copyright 2020, Wiley.
introducing the Fe$_3$O$_4$ nanoparticles, such micromotor can also be guided under magnetic field. The surfaces of the tube micromotors were further modified with a molecularly imprinted polymer (MIP) for the selective recognition and capture of antibiotics (Figure 1A-a). The micromotors show higher adsorption ability for doxycycline (DC) compared with the nonmolecularly imprinted polymer micromotors, and no apparent adsorption from two other analogs including minocycline and erythromycin could be observed, indicating the selectivity of the proposed MIP-based method, whereas the cooperative motion of the micromotors allowed the fast detection of such important analyte.

Magnesium-based micromotors are also particularly promising candidates to assist electrochemical detection applications. Figure 1A-b shows the use of a swarm of Mg/Pt micromotors for enhanced glucose biosensing.\[^{[33]}\] We will only give here one representative example, and the reader is referred to a recent review and some articles on the possibilities of cooperative micromotors for sensing.\[^{[34]}\] It should be mentioned here, however, that cooperative motion is extremely relevant for (bio)-sensing in extremely low sample volumes, giving an added value to the overall analytical performance—over existing alternatives—in terms of sensitivity. In other words, the analytical signal can increase greatly by the successful cooperation of the micromotor swarm.\[^{[34b,34c]}\]

Several applications on chemotactic micromotors have been described mainly for drug delivery but also for the treatment of many diseases. Wilson’s group was pioneering on the illustration of such behavior, reporting the use of poly(ethylene glycol)-b-polystyrene nanoparticles (stomatocytes) loaded with platinum nanoparticles as catalysts. The versatility of the strategy allows entrapping doxorubicin (DOX). The micromotors exhibit directional movement or chemotaxis toward hydrogen peroxide gradients.\[^{[35]}\] Pd nanoparticles-coated microspheres powered by peroxide display a chemotactic behavior in response to pH gradients, holding considerable promise in the biomedical and environmental fields.\[^{[36]}\] Yet, toxicity concerns on peroxide usage led to the exploration of alternative materials, such as Mg, CaCO$_3$, etc. For example, CaCO$_3$/Go Janus particles propelled by nontoxic citrate acid move toward HeLa cells by pH gradients for enhanced drug delivery.\[^{[37]}\] Liu et al.\[^{[38]}\] fabricated micromotors using Mg as the chemical catalyst for bubble generation (see Figure 1B). Because of the reaction between Mg and water, the produced active H$_2$ not only acts as a bubble for the micro-motor propulsion but also decreasing intracellular reactive oxygen species (ROS), which is related to some cancer or abnormal cell growth. Such Mg-based micromotor with active motion and swarming-like behavior was further applied for enhanced delivery of DOX for chemotherapy. Indeed, poly(lactic-co-glycolic acid) (Mg-PLGA), Mg, and Mg-motor decreased ROS levels toward HT29 and 4T1 cancer cells. Wang’s group described a Mg-based, onion motile microtrap containing serine as a chemo-attractant and an Ag$^{+}$ layer. The strategy is shown in Figure 1C. As shown, micromotors are propelled to the target site by Mg catalyst, which is dissolved during the process. The remaining core contains serine, which attracts in its interior *Escherichia coli* bacteria, enhancing the contact with the silver layer for enhanced inactivation for future biomedical and environmental (water) treatment applications.\[^{[19]}\] On overall, chemical-driven micromotors—mainly peroxide-driven—exhibit a high towing force for propulsion in complex biomedia without hampered performance or requirements for external sources for propulsion, as the chemical present in the media itself can act as autonomous fuel. Peroxide is a very efficient fuel for the creation of chemical gradients. The versatility in preparation routes—template preparation and LBL assembly—along with the relatively high level of developments and studies in catalytic micromotor results in a myriad of applications and micromotors designs. Indeed, the cooperative swarming results in an enhanced fluid mixing, which can be extremely useful in environmental remediation and drug-delivery schemes or for analytical sensing purposes. Yet, one of the biggest limitations of the catalytic micromotor swarm is the requirement for a high level of toxic fuels, such as peroxide, which hampers further developments regarding in vivo applications or practical applications in diverse field such as the environment. One early convenient solution involves the redesign of the micromotor structure to introduce chemotactic features, as the previously discussed example described by Wilson’s group on stomatocyte micromotors able to move toward the acidic environment of cancer cells for enhanced drug delivery.\[^{[35]}\] Yet, the relatively high levels of peroxide hamper applications in a real setting. As an alternative, reactive micromotors propelled by the media itself were explored, on particular magnesium particles. The high biocompatibility, ability to propel in salt-rich biomedical such as human serum, the nonharmful nature of the propulsion products, and low costs are key features of such designs. Yet, while promising, the limited lifetime of Mg—up to 10 min—and the reactive nature can limit in some cases the overall performance of the intended biomedical—drug delivery—analytical, or environmental purpose, not to mention the nonreusable nature of the micromotors. While useful for some applications (as shown in Figure 1), the inherent limitations demand the exploration of additional designs as will be described in the next section for enzymatic micromotors, without hampering the chemotactic/collective behavior nature.

### 2.2. Chemical Micro/Nanomotors Powered by Enzymes

By integrating enzymes on micro/nanomotors’ structures, such small robots are also able to generate a self-propulsion force due to oxygen bubbles production mainly from the biocatalytic process.\[^{[40]}\] Feringa group was pioneering in the demonstration of self-autonomous propulsion using enzymes as the catalyst. The smart coupling of glucose oxidase and catalase into carbon nanotubes enables an enzymatic cascade that converts glucose into peroxide for autonomous motion. Such first proof-of-concept-application opened the room for further developments with high practical applicability.\[^{[40]}\] Importantly, such design endows the propulsion system with high biocompatibility, which shows great potential for large number of bioapplications, such as biosensing in disease diagnosis\[^{[41]}\] or biosafe drug delivery in disease therapy.\[^{[42]}\] Various types of enzymes, such as urease\[^{[43]}\] catalase,\[^{[44]}\] and glucose oxidase,\[^{[45]}\] have been introduced as biocatalysts for the generation of bubbles in micro/nanomotor propulsion. Urea, H$_2$O$_2$, and glucose were generally used as corresponding catalytic substrates and micro/nanomotor-driven fuel. By taking additional profiles from the microenvironment,
different micro/nanomotor systems based on enzymes with specific intentions have been proposed.

Urease-driven Janus micromotors functionalized with pH-sensitive DNA probes were used for sensing at the cellular level. Urea decomposition during micromotor propulsion results in the release of ammonia that leads to a fast pH increase. Changes in pH in the media are monitored by Förster resonance energy transfer (FRET) sensing, where the cooperative motion of multiple micromotors at targeted sites can increase the overall sensing performance. The same research group used the urease-driven micromotors, working cooperatively, for successful bladder cancer treatment. As shown in Figure 1D, the micromotors are functionalized with an antibody for enhanced penetration in the tumor spheroids, which ultimately induced cell death.

Catalase is another widely used biocatalyst due to peroxide, the specific substrate used for propulsion, is present at relatively high levels in some microenvironments. Zheng et al. fabricated a Janus micromotor by introducing catalase as a bioenzyme for catalytic decomposition of H$_2$O$_2$ into O$_2$ bubbles for propulsion. By further modifying micromotor surfaces with fluorophores and a specific aptamer, the authors also realized the capture and ratiometric fluorescence sensing of cancer cells. HepG2 cells were successfully captured by the micromotor, increasing the fluorescence ratio of I$_{520}$/I$_{450}$. As such, using a bioenzyme as the catalyst for micromotor propulsion and an aptamer as a specific element, such strategy provides a powerful method with dual function for efficient capture and rapid, real-time sensing of cells. A 2D nanosheet decorated with catalase acts as a highly efficient micrometer with chemotactic behavior toward the peroxide-rich tumor microenvironment. The micromotors were loaded with DOX, inhibiting the growth of MCF-7 cancer cells (see Figure 1E). In another smart example, drug-loaded poly(lactic-co-glycolic acid) micromotors encapsulating DOX and half-modified with catalase also exhibit chemotaxis in peroxide gradients. The micromotors were successfully used to treat periodontitis in an in vitro model. The model was tested using macrophage cells of Raw 264.7, which can release peroxide, as to mimic macrophages and other cells present in the body in periodontal infections. The successful micromotor movement and drug release in the targeted site hold considerable promise to treat such infection.

Polymer-brush-grafted Janus gold nanoparticles modified with the enzyme glucose-oxidase display a chemotactic behavior along a concentration gradient of glucose, mimicking the behavior of some bacteria at the macroscale.

Enzyme-driven catalytic micromotors exploit the selectivity of enzymatic reactions in the presence of specific substrates for on-demand swarming and chemotactic motion. From the early works on Feringa’s and Heller’s group, catalase was the first enzyme explored in combination with catalytic micromotors for enzymatic propulsion in peroxide media. Again, the relatively high levels of peroxide hamper practical application but open new avenues for the recent developments. For example, with convenient redesign from tubular to sheet-like micromotors, the chemotactic movement toward the peroxide environment of cancer cells has been achieved with full biocompatibility. Urease is also a very promising enzyme for combination with Janus or tubular designs, with cooperative moving and chemotactic behavior toward urea, a biocompatible substrate present in biological media and, in particular, in the bladder to treat cancer, as already described here. Reusability is another added advantage. Limitations still exist, such as the relatively low level of development as compared with micromotors powered by an inorganic catalyst, not to mention the possibility of denaturation and limited efficiency of enzymes in not ideal media.

3. Cooperative Motion by Biohybrid and Living Cell-Driven Micromotors

Certain natural cells such as bacteria or sperm display excellent motion ability, which can be combined with enzymes or inorganic materials to develop biocompatible and highly efficient micromotors. As such, Escherichia coli, Serratia Marcescens, Alivibrio Fischeri, Vibrio alginolyticus, and sperm cells have been explored for this purpose.

Tang et al. attached urease onto one side of platelet cell surfaces to act as enzyme-driven Janus platelet micromotors. Urease on cell surfaces enables biocatalysis of urea in biological media to produce bubbles (NH$_3$ and CO$_2$), thus driving the motor forward (see Figure 2A). Such biocompatible micromotor showed excellent movement in different concentrations of urea-containing solutions; moreover, the Janus design in enzyme modification process also endows the micromotor with better-driven ability compared with non-Janus (whole) urease-modified micromotor. The urease-modified micromotors were then used to DOX loading and delivery to a breast cancer cell, as well as loading and delivery of an antibiotic drug (ciprofloxacin) for the killing of bacteria. The accumulation and cooperative motion of the micromotors at the target disease site greatly enhance the yield of such processes.

Bacteria hold considerable promise to develop chemotactic micromotors, which have been mainly used for drug delivery. He’s group modified neutrophils loaded with drug-modified mesoporous silica nanoparticles with Escherichia coli as camouflaging strategy. Such modification imparts the micromotors with a chemotactic behavior toward gradients secreted by the Escherichia coli bacteria for enhanced inactivation. Park and coworkers combined Escherichia coli with polyelectrolyte multilayer (PEM) microparticles, as shown in Figure 2B. The PEM microparticles are also loaded with DOX and decorated with magnetic nanoparticles to perform targeted drug delivery with enhanced drug transportation. As such, the micromotors exhibit dual tactic abilities in the presence of chemoattractant gradients and magnetic fields. The efficient inactivation of 4T1 breast cancer cells is successfully illustrated.

Sperm cells have been recently explored in connection with different inorganic strategies. Xu et al. used sperm as propulsion force to drive the movement of micromotor, coupled with a synthetic horn-like microstructure with magnetic guidance and cargo transport abilities. Such design allows the micromotor to move against blood flows assisted by a magnetic field, also called rheotactic behavior (see Figure 2C). Also, the horn-like morphology of the micromotors helps the sperm to reduce the drag forces while going through the blood fluids. In the lateral real application, the authors loaded the sperm-based micromotor with heparin for potential blood clots treatment. As shown in Figure 2C, blood samples treated with bare sperm-based micromotor turn
Figure 2. A) Janus platelet cell micromotor using bioenzyme urease as the catalyst for bubble-production propulsion. Schematic of drug-loaded Janus platelet micromotor for cancer-targeted delivery (top left) and pseudocolored scanning electron microscope (SEM) image showing some platelet micromotors attached to the cancer cell (top right) and schematic illustration of ciprofloxacin-loaded platelet micromotor for bacteria targeting and antibiotic delivery (down left) and pseudocolored SEM showing *Escherichia coli* attached to the platelet micromotor. Reproduced with permission.\[57\] Copyright 2020, American Association for the Advancement of Science. B) Schematic illustration of *Escherichia coli* bacteria-driven micromotor with a chemical and magnetic tactic for drug delivery. Reproduced with permission.\[60\] Copyright 2017, American Chemical Society. C) Hybrid sperm micromotor swimming against flowing blood. The right top part shows an SEM image of the synthetic magnetic scaffold (cap) for combining the sperm. The bottom part shows the treatment of blood cloths treated with bare streamlined-horned cap (SHC) hybrid sperm micromotors (left) and heparin-loaded liposomes immobilized SHC sperm micromotors (right). Reproduced with permission.\[56c\] Copyright 2020, American Chemical Society.
into some fibrin clots, whereas a sperm-based micromotor loaded with heparin keeps well-dispersed single blood cells. Such micromotor design provides controlled movement and excellent drug delivery for the potential treatment of blood clots, or other diseases in the circulatory system. Sperm cells have also been functionalized—by endocytosis—with inorganic payloads, including CdSe/ZnS quantum dots, DOX-coated iron-oxide nanoparticles, and fluorescein isothiocyanate-modified Pt nanoparticles. Sperm from marine animal *Ciona intestinalis* was selected as a model, with chemotactic movement toward gradients of sperm activating and attracting factor. The different payloads allow for magnetic guidance, imaging, and drug delivery for promising future applications.\(^{[63]}\)

Overall, biohybrid micromotors combine the advantages of catalytic and enzymatic micromotors; yet, limitations still exist on the integrity of the living cell in complex media, along with compatibility issues that remain to be explored.

## 4. Cooperative Motion by Magnetic-Driven Micromotors

As noninvasive and biocompatible energy, magnetic fields are used for micro/nanomotors propulsion. Magnetic fields can also go through the barriers such as blood vessels or any other tissues easily. Different materials, such as Ni\(^{[6,62]}\), Fe\(_2\)O\(_4\)\(^{[15b,63]}\), Fe\(_3\)O\(_4\)\(^{[64]}\), Co\(_3\)FePt\(^{[65]}\), CoPt\(^{[66]}\), CoFe\(_2\)O\(_4\)\(^{[68]}\) have been used for the integration of magnetic micromotors. Compared with the extraordinary progress on chemically propelled micromotors, relatively few applications have been described on magnetically propelled micromotors with tactic behavior.

Supramolecular Janus micromotors loaded with magnetic nickel nanoparticles and DOX or double fueled Janus micromotors, prepared by coating silica nanoparticles with platinum nanoparticles, catalase, and magnetic MnFe\(_2\)O\(_4\), exhibited magnetotactic behavior toward a magnetic field induced by a magnet.\(^{[19]}\) A magneto-catalytic Janus micromotor loaded with platinum and ferrite nanoparticles, along with graphene quantum dots, has been used for bacterial endotoxin detection. As shown in Figure 3A, the micromotor displays a magnetotactic behavior and can propel in different reservoirs of a microchip by the action of a magnet, whereas the fluorescence of the quantum dots is quenched in the presence of the target analyte.\(^{[69]}\)

Biocompatible micromotors, also known as “Mushbots,” have been synthesized by coating microcapsules composed by the natural mushroom *Agaricus Bisporus* with magnetic nanoparticles. This is a particular case where the micromotors exhibit a pH tactic behavior that can be controlled by magnetic fields.\(^{[70]}\) Later on, the authors improve the strategy to incorporate antibiotics for highly efficient bacteria biofilm treatment, where a swarm of micromotors works cooperatively upon the action of a magnetic field for highly efficient deactivation.\(^{[71]}\)

Janus droplets/micromotors with inherent magnetic anisotropy can be directed in situ to perform cooperative motions, including alignment, rotation, etc., using an external magnetic field (see Figure 3B). The authors successfully demonstrate the utility of the micromotors for highly efficient pollutant removal.\(^{[72]}\)

## 5. Cooperative Motion by Acoustic-Driven Micromotors

Ultrasound can be defined as a type of mechanical wave with a vibrated frequency greater than 20 000 Hz, opening new avenues for micromotor propulsion and motion control. Indeed, compared with chemically powered micromotors, ultrasound shows biocompatibility with relatively minor harm to the body and long-term motion.\(^{[73]}\) In addition, acoustically powered micromotors can be synthesized in ultrasmall sizes, such as nanowire (NW) or nanorod, which is good enough for them to penetrate cell membrane for intracellular precise therapeutic delivery or...
biomarkers detection. Moreover, the ultrasound could also be used for precise, rapid, and reversible control of the speed of chemically powered micro/nanomotor.

Ultrasound fields can act as a kind of taxis stimulus, able to induce the aggregation of nanorods/wires, which hold considerable promise to increase the signal of, i.e., Raman detection of clinical biomarkers. Li and co-workers illustrate the aggregation of NWs composed of metallic materials and polymers at the pressure node in an acoustic field. Irradiation with light fields induces the separation of the wires as an additional control system. Similarly, Xu et al. took advantage of ultrasim- induced aggregation phenomena of Au nanorods for enhancing the performance of Raman detection. After applying acoustic wave generation, Raman enhancement substrate Au nanorods were aggregated and enriched, thus leading to higher enhancement performance for ultrasensitive target sensing. Figure 4A-a,b shows that Au nanorods are aggregated after exposure to ultrasound, which leads to the enrichment of Raman enhancement substrate for higher detection sensitivity. Such strategy was next used for ultrasensitive sensing of mi-RNA-1246 in serum by modifying Au nanorods surfaces with DNA capture probes to efficient base-pairing the ROX-labeled target DNAs, followed by ultrasound-powered enhanced surface-enhanced Raman scattering (SERS) sensing (Figure 4A-c). Such design combined ultrasound-induced aggregation of Au nanorods for improving Raman enhancement, paving promise way for highly sensitive, efficient, and rapid sensing of biomarkers in clinical disease diagnosis.

Swarms of ultrasound-modified micromotors have been used for intracellular delivery of a myriad of biomarkers and probes for intracellular sensing/treatment. The wires are internalized into the cell by incubation. Once inside, ultrasound energy triggers the cooperative motion of the micromotors for the intended application. In one representative example, Hansen-Bruhn et al. fabricated ultrasound propelled AuNWs nanomotors loaded with caspase 9 (Cas9)/sgRNA complex for direct and rapid intracellular delivery. The AuNWs surfaces were modified with sulphydryl group and further chemically connected with Cas9/sgRNA via a reversible disulfide linkage. Ultrasound was then utilized to drive the movement of the Cas9/sgRNA-modified AuNWs nanomotor for intracellular delivery. Once the NWs are inside the cells, the complex is released for enhanced gene therapy inside the cell. In a similar strategy, biocompatible nano- motors composed of chitosan and the natural plant Camelia sinensis were loaded with ascorbic acid and next used for important biomedical applications. To aid intracellular imaging, the micromotors were modified with a fluorescence tag. As shown in Figure 4B, the micromotors can enter HEK-293 cells and work cooperatively via ultrasound triggering to protect peroxide-induced oxidative damage. In addition, the anionic surface of

Figure 4. A) Ultrasound-induced aggregation of Au nanorods for improving Raman enhancement performance in ultrasensitive and rapid biosensing. a) Schematic illustration of the proposed strategy for ultrasensitive detection. b) Time-lapse optical microscope images of aggregation of Au nanorods after exposure to ultrasound source. c) Ultrasound-induced aggregation of Au nanorods for DNA sensing in serum by SERS. Reproduced with permission.[78] Copyright 2020, American Chemical Society. B) Ascorbic acid-functionalized ultrasound propelled micromotors with collective and cooperative behavior for biomedical applications in inhibiting intracellular oxidative stress by ROS scavenging and for amyloid disruption. The right part shows the different moving patterns and collective motion of the micromotors upon the action of ultrasound fields: a) random collective motion; b) circular motion; c) linear motion; d) circular motion; e) circular-linear motion of a swarm of micromotors; and f) linear collective motion toward oxidatively stressed HEK-293 cell lines. Reproduced with permission.[79] Copyright 2019, American Chemical Society.
the ultrasound-powered micromotors along with enhanced movement and cooperative motion can disintegrate amyloid fibrils for future treatment of neurodegenerative diseases.

6. Cooperative Motion by Light-Driven Micromotors

Light is easy-acquired, renewable, and cheap energy that does not produce any by-products that may be harmful to the environment, as well as showing high biocompatibility to tissue or any cells. Scientists took advantage of such unique characteristics to create micromotors using light as propulsion energy, which shows controllable and long-term motion and has become a hot topic in micro/nanomotors area, especially for biomedical or environmental applications. According to the light-triggered motion mechanism, light-driven micromotors can be classified according to the type of mechanism responsible for propulsion: self-electrophoretic effect, self-diffusiophoretic effect, thermophoretic effect, and bubble-induced propulsion. We will focus here on the first three propulsion mechanisms, due to their higher ability to perform cooperative motion and chemotactic effects.

6.1. Self-Electrophoretic Effect

Semiconductors materials, such as TiO$_2$, ZnO, Cu$_2$O, or Zn$_2$Cd$_1\_2$Se, possess electronic levels and a valence band (VB) and conduction band (CB). Thus, while applying UV, visible, or near infrared (NIR) light to such materials, an electron can be promoted from VB to CB to form electron-hole pairs. The photocatalytic generated holes ($h^+$) can react with water or hydrogen peroxide to produce $H^+$ and $O_2$, as well as generated $e^-$ that move to the metal side to reduce $H^+$ into H$_2$. This causes the asymmetric distribution of ions around the micromotor to create an electric field that propels the micromotor, which is similar to electrophoresis and is named the self-electrophoretic effect. Such asymmetric decomposition creates a gradient across the micromotor, inducing local fluid flows that allow the particle to escape or move toward the light source, exhibiting phototaxis-based collective behavior. For example, isotropic TiO$_2$ phototactic micromotors exhibit negative phototaxis following a similar principle. The phototactic Si micromotors integrating TiO$_2$ branches can generate a gradient of $H^+$ and OH$^-$ on both sides/parts upon irradiation with UV light. This results in a local electric field that allows the nano tree to rotate and along the direction of the UV light, forming as well cooperative patterns. Wang et al. fabricated a photocatalytic TiO$_2$-based micromotor for microplastic removal. Under UV light irradiation, the photocatalytic micromotor can move both in water and peroxide (see Figure 5A-a). Due to the photoexcitation process on the TiO$_2$ side of the micromotor, CB electrons and VB holes were produced at this hemisphere. Authors assumed that such holes oxidize water or peroxide to produce protons, followed by the migration of electrons to the gold cap to reduce protons at this metal side; thus, protons consumption leads to concentration gradient to produce fluid flow across the Janus particle interfacial region, in turn, to cause micromotor movement. It could also be noted that micromotors get higher speeds in H$_2$O$_2$ than in H$_2$O; yet, both cases show steady motion performance. In a further study, polystyrene (PS) passive particles have been used as model systems to study the interaction between cargo and active (metal)-capped micromotor induced by photocatalytic activity. As shown in Figure 5A-b, PS particles were collected under UV irradiation and H$_2$O$_2$ solution due to electrophoretic interaction. Such light-propelled micromotors were used in the microplastics removal, and personal care products were collected rapidly by micromotors and aggregated together under UV light and H$_2$O$_2$ solution.

6.2. Self-Diffusiophoretic Effect

The self-diffusiophoretic effect is caused by producing a gradient of solutes across the particle. For instance, the photosensitive material AgCl can be chemically decomposed after exposure to UV light and produces Cl$^-$, $H^+$, Ag, and O$_2$, thus generating ionic electrolyte concentration gradients around the Janus particles. This further causes an osmotic flow from low-to-high solute concentrations for the self-diffusiophoretic motion. Other materials, such as WO$_3$, Cu$_2$O, Cd$_{1.2}$Se, ZnO, and Ag$_3$PO$_4$ have also been used as photoactive materials for generating chemical gradients for self-diffusiophoretic motion. Different surface modifications or other means can be used to impart the micromotors with a positive or negative phototactic behavior. For example, platinum nanoparticle decorated graphite-like carbon nitride Janus micromotors exhibit both behaviors. Prior to surface modification, the micromotor is negatively charged in solution and exhibits positive chemotactic. Yet, after modification with thiols, the surface is positively charged and experiences negative phototaxis by the action of UV light. The incident light can also be changed to induce different motion patterns on the micromotors. TiO$_2$ micromotors modified with hydroxyl groups can cooperate into flocks in aqueous media. Under light irradiation, the non-electrolyte diffusiophoretic interaction resulting from the overlap of asymmetric non-electrolyte clouds around adjacent micromotors. As such, different collective behaviors have been observed, including negative phototaxis, high collective velocity, and adaptive group reconfiguration (see Figure 5B).

Wang et al. designed a light-propelled nanomotor to serve as SERS substrate for biosensing. First, Ag NW@SiO$_2$ with a core-shell structure was designed into one end retains the SiO$_2$ coating and the other end with the AgNW exposed. Then, the exposed Ag tail was oxidized with FeCl$_3$ into Ag$^+$ to form the AgCl tail on the nanomotors (see Figure 5C). Under UV light irradiation, such AgCl will generate Cl$^-$ and $H^+$. Due to $H^+$ diffuses faster than Cl$^-$, an inward electric field was formed to maintain charge neutrality, creating an ionic diffusion phoretic mechanism. Upon exposure to UV light, nanomotors turn and move toward the light beam center, propelling the SERS probes to the target area and facilitating contact between SERS substrate and targets for higher sensitive detection. Such nanomotor-based SERS substrate was further used in the sensing of MCF-7 cells; compared with the static nanomotor, the moving nanomotor shows much higher SERS signal under UV light irradiation, and no SERS signal could be observed in the absence of nanomotors.
6.3. Thermophoretic Effect

Some materials, such as Au,[99] Ag,[100] TiO$_2$,[101] graphene,[102] MoS$_2$,[103] and Cu$_2$S,[104] can absorb light and convert it into local heat on their surfaces, thus producing a temperature gradient. Based on such photothermal conversion phenomenon, the micromotors can produce a temperature gradient along their surface, causing an osmotic fluid flow from high- (cold side) to low- (hot side) osmotic pressure areas near the interface, allowing them to experience taxis behavior and cooperative motions in a promising application.[105]

On the first set of applications, a swarming of thermophoretic-powered micromotors can work cooperatively to treat many diseases at the intracellular level. For example, Shao et al.[106] synthesized nanoscale polymersomes composed of biodegradable poly(ethylene glycol)-b-poly(ε-lactide) (PLGA-PDLLA) sputtered with gold. Under NIR light irradiation, the half-shell of the gold side undergoes plasmonic absorbance to generate thermal...
gradients around the nanomotor. The polymersomes nanomotors were further used in the intracellular delivery of DOX in HeLa cancer cells. On a similar strategy, Liu et al. [107] prepared Janus Au-silica nanoparticles nanomotors for the modulation of amyloid-β protein (Aβ) aggregation, which is related to Alzheimer’s disease. The nanomotors were modified with Aβ-targeting peptide inhibitor D-RK10-Cys to modulation of Aβ aggregation. Such an experiment proved the apparent detoxification of modified nanomotor along with NIR light and the potential of the as-proposed method for reducing Aβ-mediated cytotoxicity in Alzheimer’s treatment.

Thermophoretic propelled micromotors can also experience a tactic behavior by judicious design of the structure. A liquid-based micromotor prepared by encapsulating spiropyran into oil droplets exhibits both positive and negative phototaxis under white light irradiation based on the interfacial tension changes caused by the photosomerization of the spiropyran. For a detailed mechanism, please see Figure 5D. [108] Microparticles with variable composition have been coated with Fe3O4 nanoparticles as thermoresponsive materials, exhibiting response to light with different wavelengths (320–550 nm). [109] The micromotors exhibit phototactic swarming, with precise manipulation via an “ON/OFF” switch and modulation of light intensity. Upon UV, blue, or green light irradiation, the solution temperature sharply increased within and next gradually leveled off, creating convective flows responsible for the cooperative motion of the micromotors. The bare micromotors or the micromotors modified with lipase were next used for rhodamine and lipase degradation, respectively. A schematic of the propulsion and main related applications is shown in Figure 5E.

7. Conclusion

In this review, we focus on recent advances in micromotors relying on cooperative motions and tactic mechanisms. Different propulsion mechanisms, including chemical, living cells, magnetic, ultrasound, and light energies, have been discussed in detail in the main content, which has shown how researchers are developing more biocompatible, cheap, renewable, controllable, and environmentally friendly energies for highly efficient motors’ motion in specific tasks, ranging from environment cleaning to biomedical treatment.

Most targeted applications are directed to the biomedical field, indicating the relevance of cooperative motions and the introduction of intelligent behaviors in the micromotors for localized action within the human body. Yet, problems remain from those new promising energies, which need to be further improved in the following research works. Enzymes are introduced for biocompatible micromotors by chemical propulsion and show excellent motion performance; however, they may suffer from deactivation or short lifetimes. Hence, promising protein surface modification techniques and enzyme-modified micro/nanomotor storage methods should be developed to keep their high catalytic activity. Light energy shows high promise, flexibility, and biocompatibility in tackling biomedical or environmental tasks, which is an ideal power source in driving such micro/nanomotors. Yet, as a kind of electromagnetic wave with low energies compared to X-ray, light shows low penetrability and may suffer from serious intensity decrease across through the tissues. A similar situation happens to the ultrasound energy, which will also be decreased when penetrating the obstacles. Magnetic fields seems to be the most promising propulsion strategy; yet, few examples have been demonstrated so far, and more research is needed.

Another important point that needs to be considered is the massive production of micro/nanomotors in real applications. [110] As such, new methods to synthesize micro/nanomotors in high yields, cheap, and reusable way are of high importance. The cooperative motion of multiple micromotors can somewhat help to overcome such challenges, yet still need to be proved. Apart from that, biocompatible micro/nanomotors using magnetic, enzyme catalysis, ultrasound, or light as energies are designed for biological or intracellular applications; however, potential immunogenicity needs to be considered. [111] and biodegradability [112] after micromotors achieving their tasks would reduce side effects of such robotic platform. Most importantly, for future on-body diagnosis applications, more strategies to track the micromotors inside the human body should be further developed. Early efforts in this direction demonstrate the potential of photoacoustic computed tomography to track a swarming of micromotors in the intestine of mice or the potential of positron emission tomography to this end. [113] Yet, such studies have been applied in animal models, and more efforts are needed for safe application into the human body, preventing real developments. Controllable motion of the micro/nanomotors makes them excellent candidates for cell manipulation in biological research; however, appropriate motor design should be proposed to reduce their potential mechanical damage to the cells. [114] While applying micro/nanomotors for biomarker sensing, it should also ensure the precision and accuracy of detection results, which may hamper the unevenness of the micro/nanomotors production and is of high importance for potential disease diagnosis.

Overall, the collective behavior and the cooperative motion of a swarm of micromotors are very unique features of such self-propelling particles. A successful micromotor design for the further exploitation of such characteristics can lead to convenient solutions to many environmental, biomedical, and analytical problems. In cancer therapy, we envision that millions of micromotors can act cooperatively in localized areas for on-demand chemotherapy and radiotherapy. In analytical (bio)sensing, the cooperative work can increase the overall analytical signal in extremely low sample volumes, which is very beneficial to reduce patient suffering by the employment of less invasive extraction procedures. In addition, as in the case of cancer treatment, the micromotor swarm can be exploited for in vivo biosensing without loss in the overall analytical performance. In the environmental field, while beneficial, the relatively high volumes demand for a compromise among massive micromotor production in tons of quantities and overall efficiency of the swarm effect.

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