Catalytic Motors - *Quo Vadimus*?

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Abstract:

Self-propelled, active colloidal systems are of great current interest from both fundamental as well as practical standpoints, with potential applications in nanomachinery, nanoscale assembly, robotics, fluidics, and chemical/biochemical sensing. This perspective focuses on chemically-powered catalytic nano and micromotors. We review the major advances to date in motor design, propulsion mechanisms and directional control, and inter-motor communication leading to collective behavior. We conclude by discussing the next steps in going forward: the fundamental questions that remain to be addressed and new design principles required for useful applications.

Keywords: active colloids, catalytic motors, nanomotors, micromotors, nanomachines, micropumps, propulsion

The study of active colloidal systems is currently an active field of research, drawing on the expertise of chemists, physicists, and materials scientists. With the initial aim to understand and mimic motility in living systems, this field has seen considerable development in recent years with the new designs for synthetic motors, better understanding of several propulsion mechanisms, and an appreciation of the challenges behind deterministic particle motion in fluids. Amongst various prototypes developed, objects that are self-propelled by harnessing energy from localized chemical reactions (catalytic motors) have received particular attention.[1-4] These differ from systems where motion arises from the application of external thermal, magnetic, or electric fields and where the particles exhibit lock-step behavior.[5-7] In catalytic motors, the particles harvest chemical energy from the surroundings, are able to move independently, and can react to information in the form of local chemical or light gradients. In this perspective, we shall focus mostly on chemically-powered systems that are driven out of equilibrium by continuously transducing chemical energy into mechanical motion. There has been substantial effort at attaining precise control over their motion and endowing them with specific functionalities. Keeping this in mind, we also briefly discuss propulsion and directional control of small-scale particles using external acoustic and magnetic fields, which holds considerable promise in future biomedical applications.

Although great strides have been made in the design and study of catalytic motors, the vision of the United States National Nanotechnology Initiative of *"a future in which the ability to understand and control matter at the nanoscale leads to a revolution in technology and industry that benefits society"*,[8] remains to be met. Useful applications of catalytic motors have not yet been demonstrated. It has been little over a decade since the first catalytic motors were designed and perhaps it is useful to take stock of the main successes so far: both in terms of important conceptual understandings and novel experimental findings. This will help us to construct a roadmap for future research and also will guide young researchers in identifying specific areas where they can contribute and promote the overall growth of the field.

1. Evolution of Motor Research

1.1 Molecular Engineering – Scientific interest behind creating small-scale machines is often attributed to Feynman's famous 1959 lecture *There's Plenty of Room at the Bottom* or Isaac Asimov's novel *The Fantastic Voyage,* published in 1966. The concept of making artificial small machines was, however, first popularized by Eric Drexler in his famous *Engines of Creation,* published in 1986. The book not only seeded the desire to create functional nano-assemblies, but also listed the possibilities that such machines could offer. By then, protein engineering was a reality, and Drexler masterfully transferred these concepts to provide the recipe for molecular engineering, creating artificial small molecules capable of functioning in specific ways. In the foreword of Drexler's book, the father of artificial intelligence, Marvin Minsky, summarized the myriad of possibilities which such nanomachines promise: "…*we could manufacture assembly machines much smaller even than living cells, and make materials stronger and lighter than any available today. Hence, better spacecraft. Hence, tiny devices that can travel along capillaries to enter and repair living cells. Hence, the ability to heal disease, reverse the ravages of age, or make our bodies speedier or stronger than before*..." Although Drexler's ideas were later challenged on their feasibility and scientific limitations, he was successful in conveying the excitement and promises of molecular machines and the vision of the future shaped by intelligent nano-assemblers.

1.2 Motor Proteins – Naturally occurring biomolecular motors are promising models for creating artificial small machines. Rather than fabricating something from scratch using bottom-up assembly or modifying the functionality of molecules via intricate engineering, motor proteins offered two distinct possibilities. Literature was available on the functions and structural features of these molecules, and they had already been found to be extremely efficient in transducing energy compared to their mesoscopic counterparts. One could, therefore, use these proteins as *molecular shuttles* by appending them to synthetic structures.[9] However, these molecules needed extremely specific environments (often close to physiological conditions) and also micro-tubular tracks for directed motion. The biggest hurdle was interfacing protein-driven hybrid motors with the macro world, which still remains a challenge.[10]

1.3 Catalytic Motors – In 2002, while studying self-assembly of millimeter scale catalytic structures, Whitesides and his co-workers observed their autonomous motion at the H_2O_2-air interface. This was a remarkable discovery showing that chemical reactions may be used to power the motion of large synthetic structures in liquid.[11] Soon after this finding, autonomous motion of nanoscale catalytic bimetallic rods was reported by the group led by Sen and Mallouk,[12] followed closely by Ozin[13] and coworkers. Although both of these systems used the same catalytic reaction to induce motion in objects, Whitesides' motor was found to move due to the recoil of O_2 bubbles generated in the reaction while the nanorods moved due to electrokinetic mechanisms.[14] These discoveries encouraged researchers to fabricate prototypes of small machines containing *simple* components in order to understand the basic principles of self-powered nano and microscale motion. The studies reported by Whitesides, Sen and Mallouk, and Ozin demonstrated catalysis as one of the most convenient means of powering small objects in liquids, analogous to ATP-driven propulsion in natural biomolecular motors.

1.4 Small-scale Mechanics – Physical principles governing the motion of nano and microscale objects are strikingly different than those that apply to the macro world. Controlled propulsion of small objects cannot be achieved with conventional motor designs and propulsion mechanisms. Motion of macroscopic particles occurs in the high Reynolds number regime and is usually dominated by inertial forces, which scale as the cubic function of particle size. As the particles are miniaturized, the inertial forces diminish faster than the surface forces, which scale as the square function of particle size. As a result, at smaller length scales, motion is dominated by surface forces with negligible effects from inertia. In order to achieve sustained motion, the particles require a continuous supply of energy either from external sources or through locally generated asymmetric force fields. Moreover, viscous forces render the particle dynamics purely reversible and, to achieve net displacements, particles must use swimming strategies that break the time-reversal invariance. This is very different from the macroscopic world where reciprocal motion is commonly employed in inducing motion to objects.

2. Major Successes

2.1 Motor Designs and Propulsion Mechanisms – In the eleven years since the discovery of the first catalytic nanomotors, there has been considerable progress made toward developing more complex and functionalized nano and micro-machines, designed to perform specific tasks. Fabrication strategies have become diversified according to the desired applications of the given colloidal device, ranging from the purely synthetic designs to the self-powered enzyme motifs and the bio-synthetic hybrids in between. These active colloids can be classified in several ways: by their shape and composition, mechanisms of motion, or even by their future applications.

2.2 Phoretic Propulsion – Au-Pt bimetallic nanorods were the first investigated motors design powered by reaction-induced electrophoresis, resulting from ion gradients along the motor surface (Fig. 1A).[14] Several other designs have emerged in recent years that harness the power of self-generated electric fields to power motion at a low Reynolds number. These new nano and micro- machines have moved beyond the original bimetallic rod shapes. For example, Lee et al. fabricated spherical particles with overlapping Pt and Au regions by the dynamic shadowing growth technique (Fig. 1B),[15] while Wheat et al. fabricated spherical Janus particles by evaporating Au and Pt on different halves of spherical microparticles.[16] In a separate study, enzyme-functionalized thin carbon fibers were shown to move autonomously at the liquid-air interface following a similar mechanism (Fig. 1C).[17] Fabrication strategies include template-assisted electrodeposition (used to create the classic gold-platinum nanorods), top-down lithographic and etching or evaporation methods (used to selectively coat or etch different sides of Janus particles), and bottom-up nanoparticle syntheses (used to create particles used in collective behavior studies).[18]

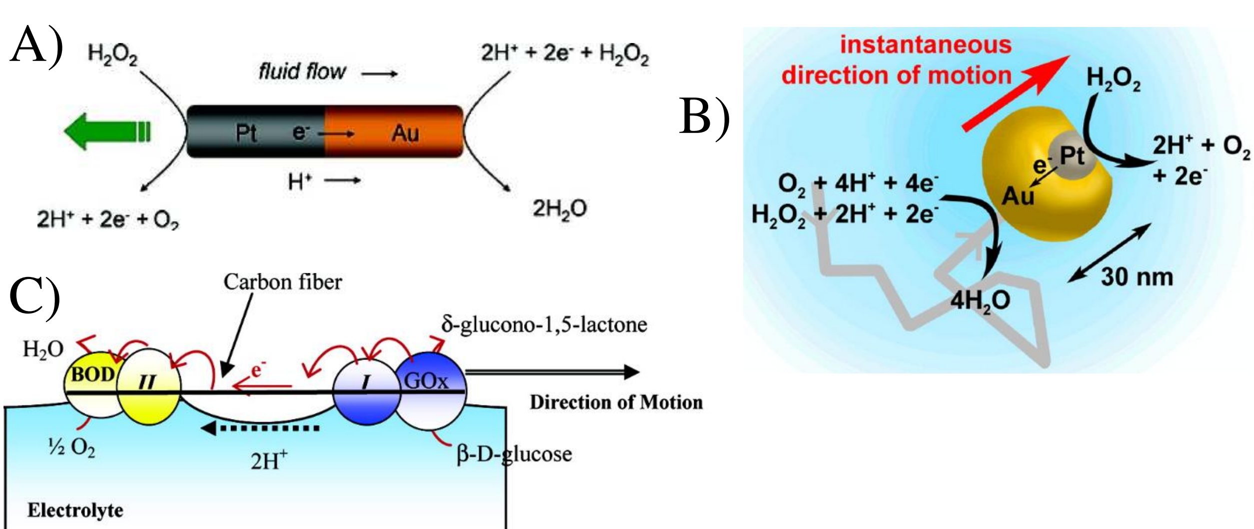

Fig.1. Electrophoretic propulsion of catalytic motors of different geometries undergoing directed motion via asymmetric decomposition of fuel. Shown are the schematic propulsion mechanisms for (A) bimetallic nanorod [Ref. 14], (B) Janus microsphere [Ref. 15] and (c) enzyme-functionalized carbon fiber [Ref. 17]

Alteration of the shape and composition can break the symmetry of the colloidal motors sufficiently to impart reaction-generated torque, leading to autonomous rotation of motors in solution (Fig. 2A).[19] Changing material composition and altering surface profiles can also enhance propulsion speeds of motors in solution (Fig. 2B).[20-23] Several research groups have also developed nano and micromotors that utilize fuels other than the classic hydrogen peroxide. Bimetallic rods have been designed to operate in halogen solutions (Fig. 2C)[24,25] and have been functionalized with segments that can be magnetically[5] and ultrasonically[26] controlled for directed motion. These endeavors demonstrate how particle motion can be controlled for specific applications by manipulating particle shapes, surface features and compositions. Important consequences of the research on self-electrophoretic motors are their proof of principle applications in pumping, sensing, and delivery of payloads.

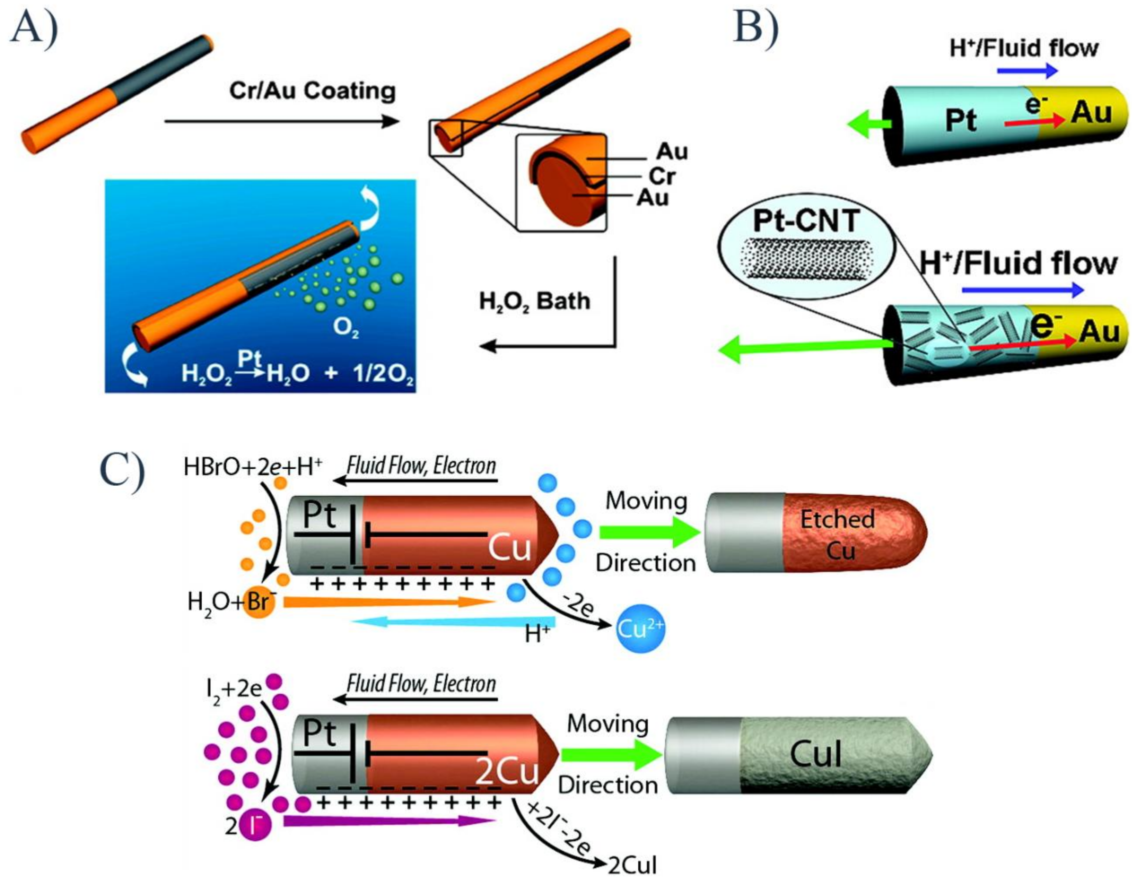

Fig. 2. (A) Chemically-powered autonomous nanorotors with multicomponent rod structures created using on-wire lithography [Ref. 19]. (B) Enhancing propulsion speed of Au-Pt catalytic nanorods by incorporating carbon nanotube into the Pt segments [Ref. 21]. (C) Self-propelled copper-platinum bimetallic nanomotors in dilute bromine and iodine solutions [Ref. 24].

Self-diffusiophoresis has been shown to be another efficient driving force for small-scale colloidal motors. Localized chemical reaction occurring over motor surfaces leads to concentration gradients of reactants and products. Based on the nature of reactants and products, diffusiophoresis can be either ionic or non-ionic in nature. Importantly, the principles of inducing motion in case of ionic and non-ionic diffusiophoresis are similar but not exactly the same. In order to induce diffusiophoretic propulsion of particles, a colloidal system needs to have two characteristics: 1) there should be a non-uniform local gradient of solute and 2) the interaction of the particle with the gradient should be strong enough to generate sufficient hydrodynamic stress within the interfacial layer of the particle.

In case of self-generated ionic diffusiophoresis, motion can be induced in particles via two independent ways. First, a spontaneous electric field generated within the liquid by the diffusing ions can result in electrophoresis of the particles. Second, the thickness of the particle interfacial layer varies inversely with the local ionic strength of the solution, generating a fluid flow within the interfacial layer (chemiphoresis). If the particles are near a wall, the same effect causes electroosmotic flows at the wall surface.

The interplay between these forces was demonstrated in silver chloride, silver phosphate, and titania microparticle systems by Sen and coworkers (Fig. 3A-B).[18,27,28] For example, silver chloride particles in water are reduced to metallic silver, H^+ and Cl^- ions by ultraviolet light ($4\,AgCl + 2H_2O \rightarrow 4Ag + 4H^+ + 4\,Cl^- + O_2$). The diffusivity of protons is significantly higher than that of the chloride ions, inducing an electric field pointing towards the particles. At the same time, electroosmotic flow towards the particles occurs along the wall. When the neighboring particles are close, the diffusiophoretic forces push/pull nearby particles away/towards the active particles, leading to different kinds of emergent collective behavior, such as chemotactic schooling and predator-prey behavior. These particle assemblies are reversible both in time and space, since the chemical reactions that lead to motion are reversed upon the addition of an oxidant, resulting in oscillatory behavior.

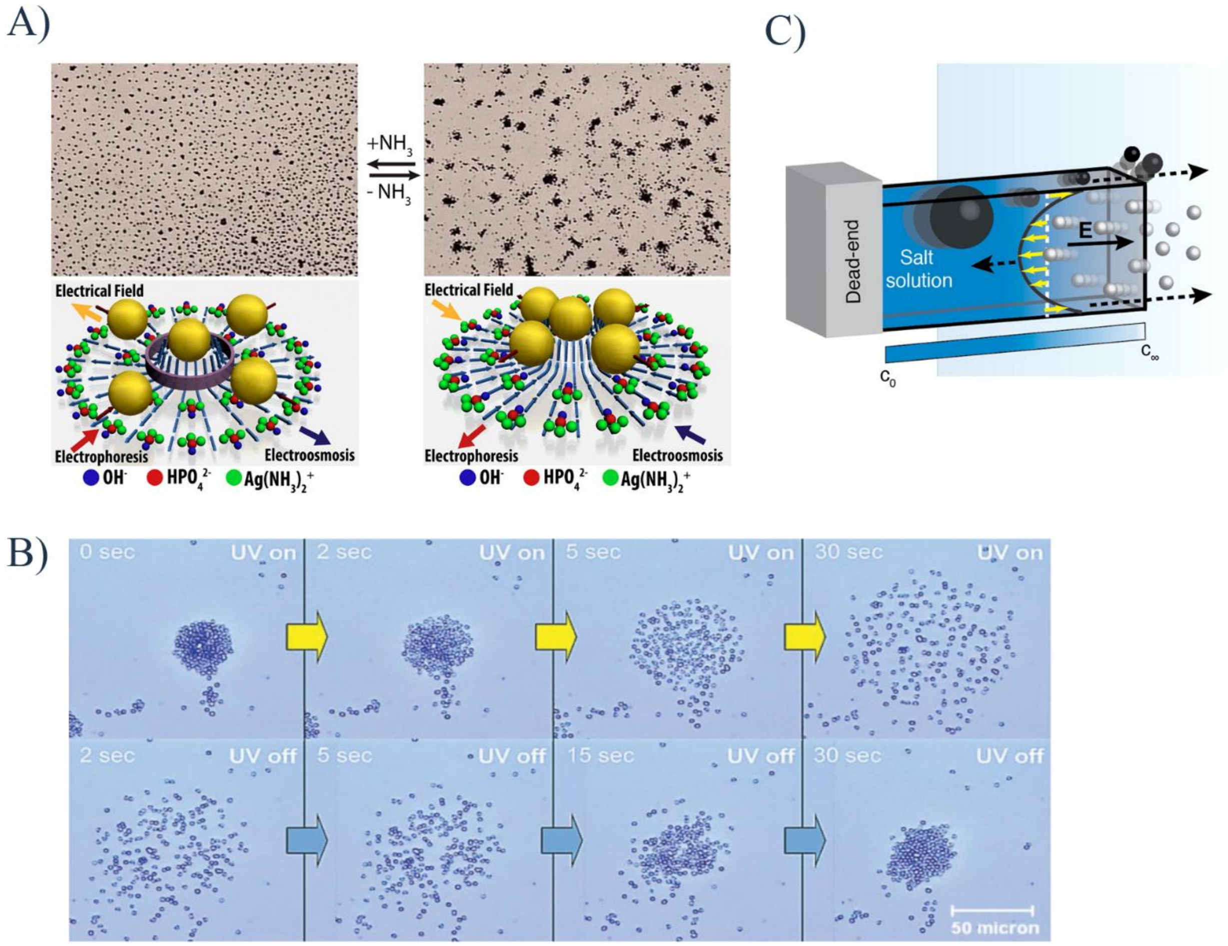

Fig. 3. (A-B) Collective behavior of diffusiophoretic colloids in response to chemical and physical stimuli. [Ref. 27,28] (C) Motion of charged particles in and out of dead-end pores driven by diffusiophoretic/osmotic mechanism. [Ref. 29]

The coordinated movement of dissimilar particles that are not attached to each other makes it easier to transport and deliver cargo at designated areas. In addition, particles with different functions can act collectively, simplifying design of intelligent assemblies

Diffusiophoretic/osmotic mechanism in the presence of an electrolyte concentration gradient has also been shown to drive the motion of charged particles in and out of dead-end pores (Fig.

3C).[29] Since chloride ions diffuse more rapidly than sodium ions in aqueous solution, a concentration gradient of sodium chloride results in an electric field pointing toward the region of low salt concentration. This causes charged particles in solution to be drawn toward or against the electric field, generating fluid flow and particle transport in dead-end pores.

There are fewer examples of motility resulting from self-diffusiophoresis involving neutral solutes. As one example, Sen fabricated a polymerization-powered Janus motor, the first of its kind outside biological systems.[30] These motors utilize Grubbs' catalyst asymmetrically immobilized on silica microspheres. Cone-shaped and spherical motors have also been shown to undergo a variation of self-diffusiophoresis, using a de-polymerization reaction to power their motion. The polymer poly (2-ethyl cyanoacrylate) (PECA) undergoes a de-polymerization reaction in the presence of hydroxide ions that causes propulsion of the motor via reduction of surface tension at one end.[31]

Both self-electrophoretic and diffusiophoretic propulsion mechanisms require low amounts of fuel and can propel nano and micromotors multiple body lengths per second. These are some of the most varied microscale motor systems that have been developed, showing linear motion as well as collective behavior. However, mechanisms based on ion gradients fail in high ionic strength environments because of the collapse of the double layer on the particle surface. Non-electrolyte diffusiophoresis, on the other hand, has no dependence on surface charge and is able to function in high ionic strength media such as those present in biological systems.

2.3 Bubble Propulsion – Bubble-propelled small-scale machines have also evolved greatly since Whitesides' first system.[11] The understanding of bubble-propulsion mechanisms have improved with the use of models that explore the effects of the geometry of the colloidal motors and the bubble generation rate as related to the reaction rate (Fig. 4A).[32] Typically, hydrogen peroxide decomposition resulting in oxygen bubble production has been the propulsion mechanism. Recently, microtubes and spherical Janus particles incorporating active metals (e.g., Mg or Zn) that reduce water to gaseous hydrogen have been reported (Fig. 4B, C).[33-36] These motors have possible biological or environmental applications. Tubular microjets have also been designed to operate by bubble propulsion with tunable speeds based on ultraviolet light irradiation. Tunable speeds are ideal for certain applications where motors must reach a destination quickly but be able to slowly approach a target, or where they encounter opposing fluid flow, e.g. blood, with varying speed and force.

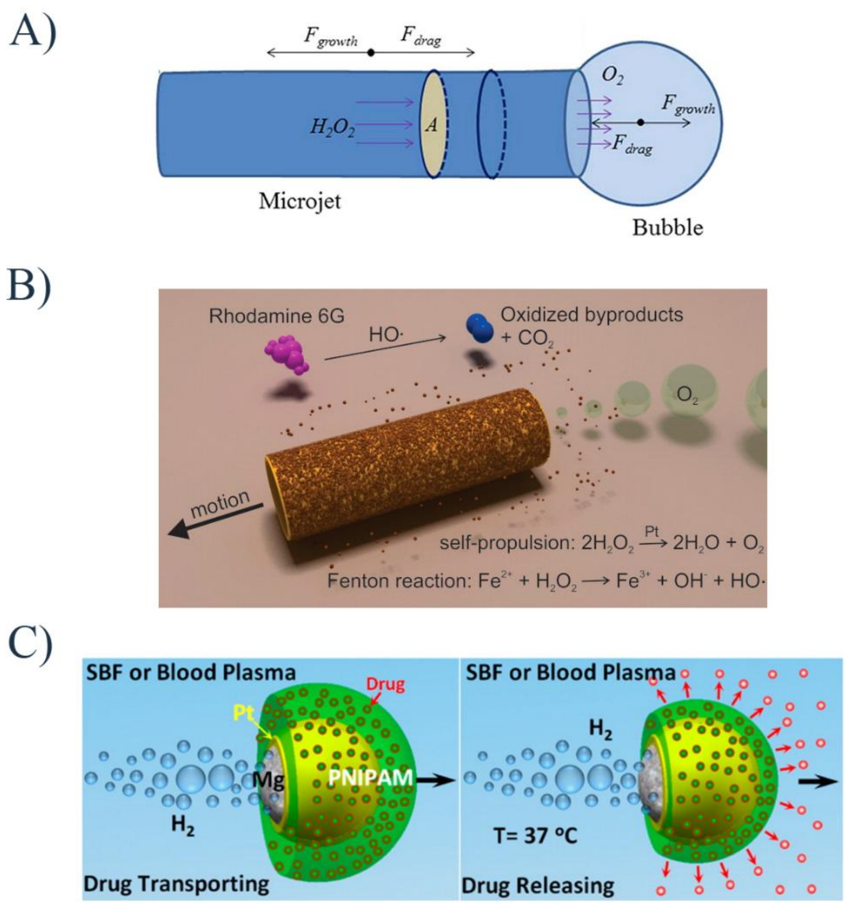

Fig. 4. Catalytic micromotors propelled by asymmetric generation and release of bubbles. (A) A schematic model for bubble propulsion [Ref. 32]. (B-C) Bubble-propulsion motors in water purification and drug delivery applications. [Ref. 36,34]

There are limitations to the use of bubble motors, however. While bubble propelled motors are some of the fastest, bubble formation itself can be an impediment in some real-world uses, such as *in vivo* applications. However, this is not an issue in other applications. For example, motors constructed from iron and platinum can be employed to remove pollutants from water (Fig. 4B).[36] While this is a step in using motors as a motile cleaning agent for water purification, it has yet to reach the efficiency of large-scale water purification systems currently in use or to become comparable in reactivity to nanoparticles that have higher surface area. In order to improve the nanomotors' future prospects in the field of environmental remediation, emphasis needs to be placed on the beneficial role of motor motility.

2.4 Magnetophoresis and Acoustophoresis – In order to make nano and micromotors more controllable and useful for *in vivo* biological tasks, researchers have developed motors that are propelled and/or guided by ultrasound and external magnetic fields (Fig. 5).[5,26,37-39] Acoustophoretic motors are levitated into a nodal plane by acoustic waves and show autonomous motion at high speeds in translational and rotational patterns, forming aggregates or well-assembled chains.[26]

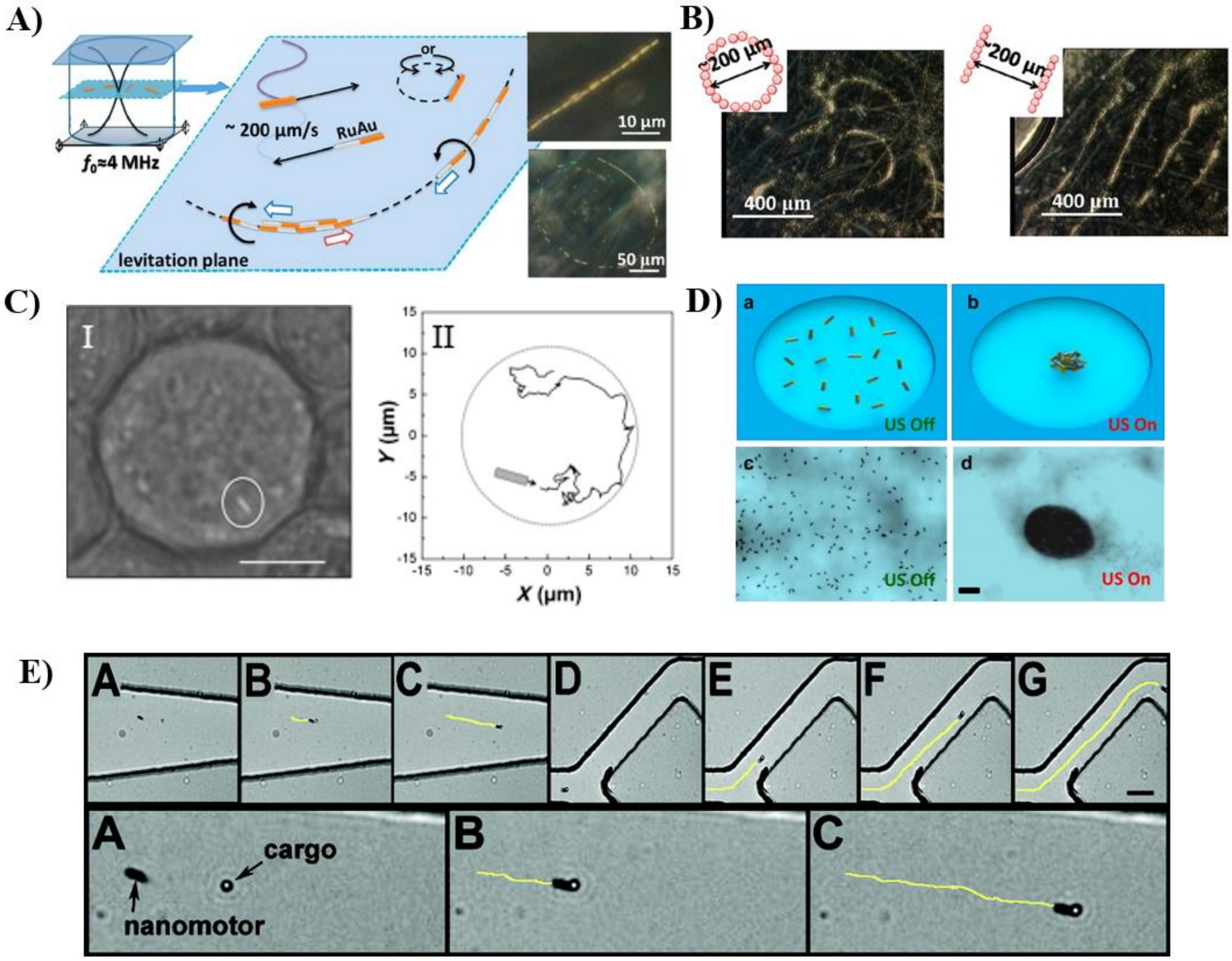

Fig. 5. (A) Translational and rotational motion of acoustophoretic motors and (B) swarming behavior of spherical particles, showing collective patterns forming aggregates and well-assembled chains. [Ref. 26] (C) Acoustically-propelled nanomotors inside live cells, displaying the confined movement of motors. [Ref. 37] (D) Clustering of chemically powered nanorods using ultrasound. [Ref. 39] (E) Directed motion of catalytic motor within a microfluidic channel using external magnetic field [Ref. 38].

Magnetic control has been shown to help nanorods navigate narrow microfluidic channels.[38] Magnetophoretic motors are both propelled and directed by external magnetic fields. Recently fabricated artificial bacterial flagella (ABFs) demonstrate actuation of helical microswimmers by external magnetic fields.[40] Using iron oxide nanoparticles in a magnetic polymer composite (MPC), these synthetic flagellar motors can behave like bacteria, without the lifetime or environmental limitations of bacteria. They are biocompatible and well understood by computational models. Acoustophoretic and magnetophoretic motors are also able to operate in fluids with high ionic strengths, like biological fluids. Acoustophoretic motors have even been used inside living cells and *in vitro* biological fluids, and functionalized for cargo transport (Fig. 5C).[37,41] Preliminary studies showed that the cells were not irreversibly damaged by the movement of the motors inside the cell walls, though long-term cell viability has not yet been tested. This is a significant milestone towards *in vivo* biological applications since it demonstrates the ease of motor endocytosis and that the presence of organelles and the cytoskeleton does not impede its motion.

Magnetophoresis requires an external magnetic field for motor propulsion, and as such, large scale applications become challenging. Over small distances, however, it is a powerful tool that has been shown to move motors in a precise and controlled manner. Researchers have also been able to develop magnetic-triggered target release systems (potential for drug delivery). Unfortunately, deep tissue penetration requires high fields and the magnetic domain of such motors (e.g., nickel) are often cytotoxic at higher concentrations. Also, while it is possible to attract motors to a targeted site via an external magnetic field,[5] the field is not strong enough to guide motors against blood flow. Therefore, magnetophoresis will likely be used more for targeting purposes in a multifunctional motor.

Acoustophoresis, like magnetophoresis, requires an external field and has been demonstrated to be a useful propulsion method for *in vivo* uses due to the low power requirement and negligible cytotoxicity. Unfortunately, the motion of the motors is confined to the nodal planes and does not currently allow for precise manipulation of the motors towards specific targets. An interesting recent development has been the design of motors that are propelled in opposite directions using orthogonal acoustic and chemical fields.[42]

2.5 Enzyme Motors – Recently, it has been found that even free-swimming enzymes exhibit enhanced diffusion while turning over their respective substrates. For example, urease, catalase, and DNA polymerase diffuse more rapidly in the presence of urea, hydrogen peroxide, and nucleotides, respectively.[43,44] This suggests that enzymes can be coupled to synthetic particles to fabricate motors that use biocompatible fuels and can be employed for *in vivo* applications.

One further use for enzymes in nano and microscale devices involves immobilizing enzymes on a surface and employing substrate catalysis to pump surrounding fluid toward or away from the enzyme patch (Fig. 6A).[45] Studies are currently underway to use these enzyme micropumps to detect analytes in the ambient fluid, such as glucose or nerve agents, and concurrently pump out insulin or antidotes. Theoretically, these micropumps can also be used to directionally transport colloidal particles or biological molecules in solution from one place to another, a step towards nano and microscale controlled transport of materials.[45,46]

2.6 Chemotaxis – In order to carry out intricate mechanical tasks, futuristic nano and microscale machines are expected to move towards the source of the signaling molecules or particles (e.g., drugs or antigens). However, Brownian rotation often randomizes the motion of small-scale particles over long time periods. A possible solution involves mimicking the chemotaxis of microorganisms, which move directionally in response to specific chemical stimuli.[47]

Recent studies have demonstrated preferential migration of synthetic motors and even enzymes towards higher concentrations of fuels or substrates.[43,44,48-50] Although the exact mechanism behind artificial chemotaxis remains obscure, a qualitative hypothesis has been provided by Hong et al., based on the enhanced motion of bimetallic nanorods during catalytic turnover.[49] According to their model, substrate concentration-dependent increased diffusivity of catalytic motors leads to their chemotaxis towards areas of higher substrate concentrations. Such directional migration occurs because, with higher diffusivity, the motors experience higher average displacements and continue to move farther as they travel up the gradient. Similar qualitative explanations have also been put forward to explain chemotaxis of polymerization-powered Janus motors,[30] bubble-propelled microengines,[50] and enzyme molecules (Fig. 6B)[43,44,48] in the presence of substrate gradients. This model however, does not shed any light on the reason behind enhanced motion of motors in the presence of higher substrates.

The chemotactic mechanism has been demonstrated to be useful in separation of catalysts with very similar physical and chemical properties (even in separating identical active and inactive enzymes) (Fig. 6C).[48] This is an important advance since separation was accomplished based solely on catalytic activity while most current methodologies depend on differences in structure, size, charge, or particle density.

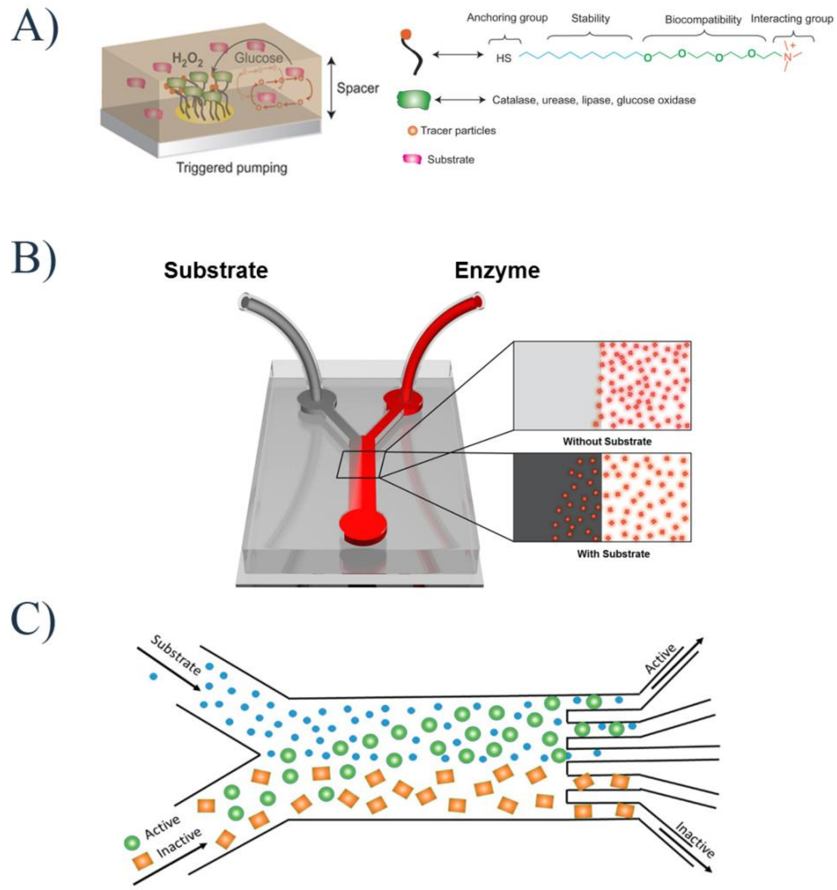

Fig. 6. (A) Enzymes immobilized on a surface behave as self-powered micropumps and cause directional fluid flow. [Ref. 45] (B) Enzyme molecules exhibit enhanced diffusion in the presence of their substrates and show chemotactic migration towards regions of higher substrate concentration. [Ref. 43,44] (C) Chemotactic separation of active catalysts from their inactive counterparts. [Ref. 48]

2.7 Collective Behavior – Self-powered micro and nanoscale swimmers constitute intrinsic out-of-equilibrium systems showing novel emergent phenomena and collective dynamic patterns in response to different chemical and physical triggers. Besides displaying chemotaxis on larger length scales, synthetic motors can also actively seek out chemical signals secreted by nearby active swimmers and display *localized* chemotactic migration. Such interactions usually lead to the formation of interesting dynamic structures and behaviors. A host of different studies have been reported where small-scale active particles displayed predator-prey,[51] schooling,[27,28,51,52] exclusion,[27] and oscillatory motion[18,27,28] in the presence of localized stimuli. The nature of collective oscillation (predator-prey behavior or schooling) depends on system characteristics such as the kinds of particles and their density. By using more than one interaction, transitions between collective behaviors of active microparticles have also been achieved. As an example, silver orthophosphate microparticles (Ag_3PO_4) in aqueous media show transitions between *exclusion* and *schooling*, which are triggered by shifting the chemical equilibrium (by addition or removal of ammonia) or in response to UV light. With two inputs (ammonia and UV) and two outputs (schooling and exclusion), a logic "NOR" gate can be designed, opening up a new avenue for artificial intelligence with synthetic nano and micromachines.[27]

Iron oxide and titanium dioxide microparticles have been shown to act as "living, self-healing clusters".[28,53] Similarly, nanorods and spherical particles exhibit swarming behaviors at the nodal planes in the presence of an acoustic field (Fig. 5B).[26] Finally, acoustically powered multimetallic rods containing magnetic segments display not only autonomous motion, but also come together in distinct "molecular geometries" in the presence of an external magnetic field.[54] The collective behavior of active colloids can serve as models for of chemical communication in nature, such as in bacterial and insect colonies. In addition, systems exhibiting collective behavior can be manipulated to accomplish specific tasks in which there is need for aggregation of particles in desired locations and subsequent dispersal upon completion of the task.

2.8 Theoretical and Computational Successes – Concurrent with the design of synthetic self-powered colloidal motors, several theory groups have developed models to describe the behavior of chemically-powered systems under different experimental conditions. This perspective will highlight a partial list of theoretical contributions while other chapters in this issue discuss modeling of active, self-propelled materials in greater detail. The first model was proposed by Golestanian et al. by considering the case of a spherical colloidal particle, propelled by the asymmetric distribution of reaction-generated products.[55] The study calculated the propulsive velocity of the micromotor in aqueous medium and also the scale of velocity fluctuation. In a separate study, the same group presented recipes for designing active microswimmers powered by self-generated phoretic forces.[56] Explaining the dynamics of active bimetallic nanorods, Kapral et al. proposed a model involving dimer structures comprised of two linked spheres – one of which is capable of catalyzing a reaction in solution, the other being chemically inactive and interacting differently with reactants and products.[57] This study was later extended to predict how, by attaching a reactive colloidal particle or molecular group to the end of a polymer chain, the diffusive motion of the polymer can be converted into directed propulsion.[58] Córdova-Figueroa et al. proposed a different propulsion mechanism for catalytic particles in solution. According to their model, a non-equilibrium concentration of solutes around a colloidal motor, induced by surface chemical reaction, creates an osmotic pressure imbalance on the motor causing it to move through solution.[59] In a very recent study, Colberg et al. modeled self-diffusiophoretic molecular scale motors that are propelled through solutions autonomously.[60] Collective dynamics and emergent behavior of systems involving self-powered motors have also been modeled to predict their temporal and spatial behavior, extracting important information on particle dynamics in response to various stimuli.[28,61-63]

3. *Quo Vadimus*?

From a scientific standpoint, investigating systems involving molecules and small particles is inherently challenging due to the stochastic nature of particle dynamics, the limitations of experimental and modeling techniques in characterizing non-equilibrium systems, and need for multidisciplinary expertise. The interdisciplinary nature of the work also requires that researchers from diverse backgrounds be able to speak the same language.

The ultimate goal of research in this area is to create a new paradigm for the design of active functional materials and systems by leveraging (a) precise chemical control associated with molecular-level manipulation of materials to create functional building blocks, (b) mobility resulting from biomimetic catalytic energy harvesting from the local environment, (c) rapid and reversible assembly capabilities provided by emergent self-assembly, (d) intelligence and communication capabilities that have been demonstrated in groups of interacting microorganisms, and (e) ability to perform specific tasks in response to signals from each other and the environment.

From a fundamental standpoint, the scientific questions that need to be addressed going forward are as follows: (a) What are the possible mechanisms for momentum creation at smaller length scales and how efficient are they in generating useful work in different environments? (b) Are there optimal motor geometries for sustaining directional motion? (c) Mimicking living systems, how well can motion be directed, preferentially by chemical gradients (i.e., chemotaxis)? (d)

What is the nature of inter-particle interactions in active matter? (e) How do the ensemble dynamics of active materials evolve in space-time?

3.1 Innovation for New Systems – The majority of the motors systems to date have not been optimized. There has only been one study so far on efficiency of artificial motor systems by Wang, Mallouk, and collaborators.[64] While the focus of nanomotors has been on the development of new systems and how to make the motors move faster or longer, little has been done on optimization of the fuel or geometries. Such factors will significantly impact motor speed, fluid drag, fuel consumptions and other factors. Many applications have limitations in regard to the amount of fuel that can be used. For example, if a motor system is designed to be used in a lab-on-a-chip setting, increase in fuel concentrations or volume fraction may cause the production of by-products that could interfere with detection or lead to longer analysis times. For example, use of bubble-producing motors in microfluidics requires strict monitoring of fuel concentrations to prevent production and coalescence of bubbles that will interfere with the microfluidic device. Therefore, motor systems need to be examined in greater detail in terms of efficiency and compatibility with respect to intended applications.

The optimization of motor geometries is also critically important. Currently, the majority of motors have cylindrical, spherical or screw-like structures. Such geometries may not be best suited for their future intended applications. Motors for *in vivo* applications have limitations on their shape and size. They must be large enough to propel themselves while being small and flexible enough to squeeze through narrow capillaries. If the interior of living cells is the intended target, the easiest way to enter is through endocytosis which depends on the size and shape of the motor.[65] Wang and collaborators recently demonstrated rod-shaped artificial micromotors that embed themselves into stomach lining and deliver cargo.[66]

Thus far, the focus of motor research has been on the development of motors that move by one dominant propulsion mechanism. However, incorporating orthogonal propulsion mechanisms into a motor offers a greater degree of control. A few publications in 2015 have reported the fabrication and characterization of multicomponent motors. Wang and collaborators published a paper on a magneto-acoustic hybrid nanomotor,[67] while Sen, Mallouk, and collaborators published a study on opposing chemical and acoustic propulsion of bimetallic nanomotors.[42] These are the first steps towards the fabrication of true multifunctional motors by incorporating different components for propulsion (multiple fuels), triggered collective behavior (cargo capture/release, schooling/excluding), and targeting behavior (response to multiple stimuli).

3.2 Driven by Applications – Over the last decade, while the focus has been on motor fabrication and the mechanism of motility, we have yet to approach the important goal of motor systems: To use motors as micro/nano machines to accomplish what our current tools and instruments cannot. While there have been proof-of-concept applications in recent publications,[3,68] we have yet to find a niche where motors are indispensable or the technique of choice for a given application. As such, the field is expected to evolve into one with more emphasis on application-based systems.

There have been several motors created with specific applications in mind. Tubular micromotors have been designed for organic pollution cleanup that use platinum to propel the motors by bubble-generation through reaction with hydrogen peroxide and that use iron to generate a powerful oxidant when combined with hydrogen peroxide, undergoing a Fenton reaction.[36]

Similarly, Janus particles incorporating magnesium that move through hydrogen generation by reaction with water have been designed to purify water and clean the environment (Fig. 7C).[35] Motors have also been fabricated to degrade biological and chemical warfare agents like organophosphate nerve agents (Fig. 7B).[69]

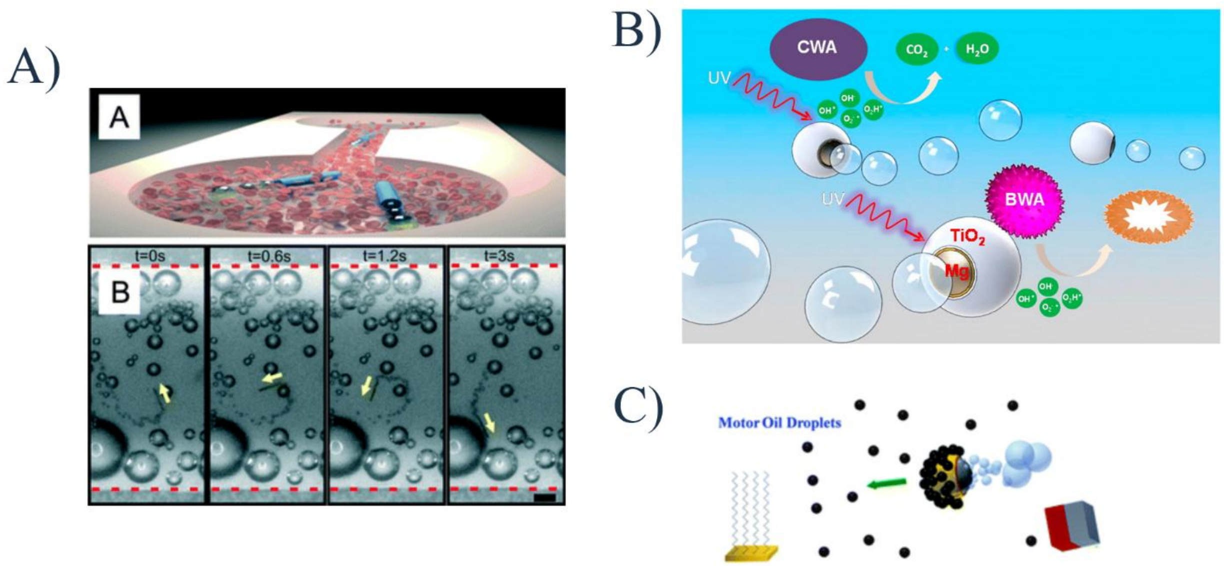

Fig. 7. Applications of nanomotors for (A) applications in blood samples [Ref. 70], (B) the neutralization of biological and chemical warfare agents (BWA and CWA respectively) [Ref. 69], and (C) the removal of oil droplets in water. [Ref. 35]

Perhaps the most attractive application for catalytic motors, given the scenario in Asimov's *Fantastic Voyage,* is medicine. The immense advantage of targeted motion over diffusion, allowing for the use of less material, is a major incentive for the use of autonomous motors for drug or cargo delivery. Biomedical applications of motors, however, remain relatively unexplored, in part due to the difficulty of motor navigation *in vivo*.[70] Very recently, zinc microtubes were used to penetrate the stomach lining of mice and release gold nanoparticles for thermal treatment of disease.[66] There are a few other proof-of-concept studies, such as the use of motors in cellular uptake for structural interference, detection and labeling.[46,71] Most studies on motors are conducted in water with low ion content. This is in contrast to biological fluids, which contain a multitude of ions and other components. Blood, for example, is a non-Newtonian viscous fluid that contains plasma, platelets, red and white blood cells that may affect motors' movement in many different ways. Researchers have only recently attempted to examine catalytic and magnetic motors in diluted blood samples (Fig. 7A).[70,72] In related studies, Mg/Pt-polymer Janus microspheres[34] and silica-Ni magnetic screws or *nanopropellers*[73] display autonomous motion in simulated biological fluids, plasma and other complex viscous media. These motors could be further developed to operate in the bloodstream, allowing the accomplishment of *in vivo* biomedical tasks.

Several additional hurdles remain before practical *in vivo* applications of motors become a reality. First, the nano/microtransporters must be derived from biocompatible materials with surfaces appropriately functionalized to promote cell viability. Second, and equally important, is to design self-powered nano/microbots that can use fuels that are biocompatible, preferably fuels present in the body. Ideally, the nano/microtransporters will employ enzymes as catalysts and fuels (e.g., glucose) present in living systems.[43,44,74] Third, the transporters need to be powerful enough to move against fluid flows,[75] such as blood flow. Furthermore, the energy transduction mechanism should operate in high ionic medium present in biological fluids. Finally, the most "futuristic" scenario involves the design of populations of synthetic nano and micromotors and pumps that have the ability to organize themselves intelligently, based on signals from each other and from their environment, to perform complex tasks. Particularly attractive are designs that allow coordinated movement of particles with different functionalities that are *not* attached to each other, making it easier to transport and deliver cargo at specific areas as per requirements. The discovery of particle assemblies that exhibit chemotaxis and predator-prey behavior is a step in this direction.[18,49-52,76] For many future applications, it will be important to have motors that can independently carry out operations such as sensing and reporting, with different populations of interacting motors performing different tasks. Thus, it is possible to imagine a day when intelligent machines navigate through the body and perform critical tasks, realizing Asimov's *Fantastic Voyage*.[77,78]

4. Concluding remarks

Chemically-powered micro and nanoscale motors offer immense potential towards mimicking natural biomolecular systems – promising a myriad of novel technological innovations. However, the fabrication of tiny, efficient synthetic motors is often associated with scientific and engineering challenges, which need to be tackled with complimentary theoretical and experimental approaches. Since the discovery of the first chemically-powered system, many designs and propulsion mechanisms for autonomous motors have been investigated – demonstrating their applications in transport, assembly, and sensing. Freed of usual biological constraints, we now have the unprecedented opportunity to probe the limits of self-organization in these synthetic systems that operate far from equilibrium.

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Graphical Abstract