

One-dimensional micro/nanomotors for biomedicine: delivery, sensing and surgery

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Key Words:

biomedicine; micromotor; nanomotor; one-dimensional

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ABSTRACT

The rapid development of artificial micro/nanomachines brings promising strategies to overcome challenges in biomedicine, including delivery, sensing and surgery. One-dimensional (1D) micro/nanomotors are one of the most attractive micro/nanomachines due to their high specific surface area, powerful impetus and weak rotation diffusion. In this review, different propulsion mechanisms and motion control strategies of 1D micro/nanomotors are summarized, and recent efforts towards their fabrication methods and biomedical applications are discussed. We envision the multidisciplinary research efforts in the field of 1D micro/nanomotors will pave their way to practical applications in bioimaging and biomedicine.

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<http://doi.org/10.3877/cma.j.issn.2096-112X.2020.01.003>

How to cite this article:

Guo, J.; Lin, Y. One-dimensional micro/nanomotors for biomedicine: delivery, sensing and surgery. *Biomater Transl.* 2020, 1(1), 18-32.

Introduction

Efficient miniaturization of biomedical devices has markedly extended the capacities of medicine in diagnostic, therapeutic and surgical applications. For instance, the da Vinci Surgical System allows surgeons to perform complex surgeries such as radical prostatectomy, pyeloplasty, or cystectomy, using a minimally-invasive approach.¹ However, it remains a great challenge to reach and treat inaccessible parts of the human body like the brain, kidney, or retina.^{2, 3} The advancement of micro/nanodevices can extend our sight and enhance the convenience of surgery. Additionally, it even allows us to diagnose and treat at the cellular or subcellular level.²⁻⁶ In the last decade, various micro/nanomotors have been developed to convert chemical fuels or external energy to mechanical motion.^{7, 8} Tremendous progress has been made in improving independent mobility, remote controllability and multifunctionality of micro/nanomotors, leading to potential applications in drug delivery, disease diagnosis and surgery.⁹⁻¹²

Generally, one-dimensional (1D) micro/nanomaterials are slivers of material constrained in two dimensions

to less than 100 μm or 100 nm, including micro/nano rods, wires, tubes and belts.¹³⁻¹⁵ The anisotropic structure of 1D micro/nanomaterials results in unique physical, chemical and biological properties as well as making 1D micro/nanomaterials one of the most popular materials in bio-sensing, tissue engineering and drug delivery.¹⁶⁻²⁰ In particular, the impetus and controllable motion of the 1D micro/nanomaterials has demonstrated their significance in practical applications *in vivo* and in the fabrication of biomedical devices.^{2, 3, 10, 21} Recently, advances in 1D micro/nanomaterials has brought new opportunities to 1D micro/nanomotors. The 1D micro/nanomotors are usually prepared as a rod-like or tubular shape containing at least one active face that can generate asymmetric force fields surrounding these particles and subsequently propel the motion of 1D motors.^{7, 22} For example, platinum/gold nanorods, as the first 1D nanomotor to be reported, could swim and transport colloidal cargo in H_2O_2 solution via a mechanism of self-electrophoresis.^{23, 24} Meanwhile, tubular micro/nanomotors are usually engineered with an inner catalytic surface normally consisting of platinum or enzyme, and able to move based on a bubble



self-propelled mechanism.^{22, 25} These rod-like or tubular motors possess a large surface area for multi-functionality and a long blood circulation time.^{26, 27} Furthermore, their weak rotational diffusivity avoids the disruption of directional motility due to random Brownian forces.^{28, 29} Particularly, the confined space of the tubular micro/nanomotors generally leads to the high rate of bubble production or diffusion flux, resulting in high speed motion.^{30, 31} The impetus motion, collective behaviour, chemotaxis and remote controllability of the devices have led to greatly promising potential applications in drug delivery, disease diagnosis and surgery.⁶

In this paper, we review the typical propulsion mechanisms, fabrication and emerging applications of 1D micro/nanomotors in biomedical applications. Finally, we provide an outlook of current challenges and future prospects. An electronic search of the Web of Science database from 2000 to 2019 was performed using the following conditions: micromotor or nanomotor or microswimmer or nanoswimmer. Non-Science Citation Index experiments and review articles were also excluded.

Design of One-Dimensional Micro/Nanomotors Propulsion mechanisms

Locomotion of particles in the micro/nano world is dominated by viscous force and Brownian motion.³¹ Traditional power supply is impossible in these tiny devices. The establishment of a locomotion mechanism and disciplines presents the first challenge when minimalizing devices down to the micro/nano scale. Over recent decades, various propulsion mechanisms, driven by chemical energy (e.g., using H_2O_2 , glucose and other highly reactive molecules as “fuels”) and external field force (e.g., light, magnetic and ultrasonic fields) mechanisms, have been proposed for the independent impetus supply of 1D micro/nanomotors.^{8, 32} Although sharing several basic propulsion mechanisms with other types of micro/nanomotors such as bubble self-propulsion,³³ and self-electrophoresis,³⁴ 1D micro/nanomotors could be propelled through unique mechanisms, including jetting effects,³⁵ or flexible flagellae.³⁶

Chemical propulsion mechanisms

Chemically-propelled micro/nanomotors, also termed self-propelled motors, generally contain an asymmetrical distribution of catalyst/active and inert materials within one particle. The catalyst/active part triggers the chemical reaction and produces an asymmetrical force field surrounding the motors. The existence of the corresponding fuel in the microenvironment of micro/nanomotors provides sustainable energy for independent propulsion. It is accepted that chemically-propelled micro/nanomotors possess several advantages, including prolonged navigation, reusability, versatility and chemotaxis.^{7, 37}

As a typical self-electrophoretic mechanism, oxidation and reduction reactions proceed at either end of an asymmetric conductive 1D nanowire, resulting in a flow of protons surrounding the outside of the nanowire, causing the propulsion of the 1D nanomotors (**Figure 1A**).³⁸ For example, H_2O_2 oxidation and reduction at opposite ends of a Pt/Au nanowire, produces an electron flow inside the particle accompanied by directive migration of protons surrounding the particle, leading to the

propulsion of the particle in the opposite direction to the proton flow.^{34, 38} Various metals, including Au, Pt, Ag, Rh, Ni, Ru, and Cu, have been used as the components of self-electrophoretic nanomotors,³⁸⁻⁴⁰ and various different chemicals, such as H_2O_2 , I_2 , and Br_2 have been selected as fuels.^{32, 41} However, because of the existence of the electrical double layer on the exterior surface of motors in real biomedical systems within high-strength ionic solutions, the velocity of self-electrophoretic motors could be greatly reduced, dramatically limiting the application of such self-electrophoretic motors.⁴²

Mei et al.^{43, 44} proposed a bubble self-propulsion mechanism for tubular micromotors which would be less influenced by the ionic environment. In this system, an aqueous fuel such as H_2O_2 is broken down at the surface of a catalyst such as Pt, Ag, or catalase, thus generating O_2 which would form bubbles and result in a propulsion force when they recoil from the inner chambers of tubular motors (**Figure 1B**).⁴⁴⁻⁴⁷ Similarly, Gao et al.³³ utilised recoiling H_2 bubbles generated by the reduction of protons by Zn in acidic solution. This system showed excellent biocompatibility and practical operability in acidic biosystems (for example in the stomach) (**Figure 1C**). However, when the size of the tubular motor decreased to the nanometre scale, bubbles could not be observed at the end of the motors. Ma et al.³⁵ fabricated a SiO_2 nanotube motor (~220 nm diameter) with the inner face of the motor coated with urease. After introducing tracer nanoparticles, a jet of liquid at the end of the motor was observed, which showed that the presence of an internal flux jetting into the external space led to the directional movement of the nanotube (**Figure 1D**).³⁵ Subsequently, Li et al.³⁰ developed a TiO_2/Pt nanotube motor with a hollow chamber of 10–20 nm in diameter and a length of 120–150 nm. Based on the experimental data and the simulation, they proposed that the impetus of nanotubes derived from the diffusion flux and corresponding diffusiophoretic force of the product.

Because the chemical propulsion forces are mainly derived from the molecular flux, the motion behaviours of such 1D motors are very sensitive to their surrounding chemical conditions.^{7, 42} For bubble-propelled micro/nanomotors, the addition of a surface tension-reducing agent such as sodium dodecyl sulphate or Triton X-100 is beneficial to bubble formation and leads to acceleration of velocity.⁴⁸ In other cases, the acceleration of the reaction of fuels can augment the velocity of the micro/nanomotor's movement. For instance, the addition of silver ions results in the deposition of silver onto the Au segment of the Au/Pt nanowire motor, which enhances the speed of the motor due to the increase in the mixed potential difference between anodic and cathodic segments.⁴⁹ Furthermore, the fuel decomposition by metals or enzymes from 1D micro/nanomotors can be regulated owing to the pH- or temperature-dependent catalytic activity of metals or enzymes.^{50, 51}

In many cases, the self-propelled motion of 1D micro/nanomotors possesses a chemotactic nature, i.e. the motors can sense the local chemical gradients and move toward or away from an area with a higher concentration of fuels. For example, Hong and coworkers⁵² observed that Pt/Au 1D nanomotors gradually gathered around the gel generating a H_2O_2 gradient. By comparing the chemotactic

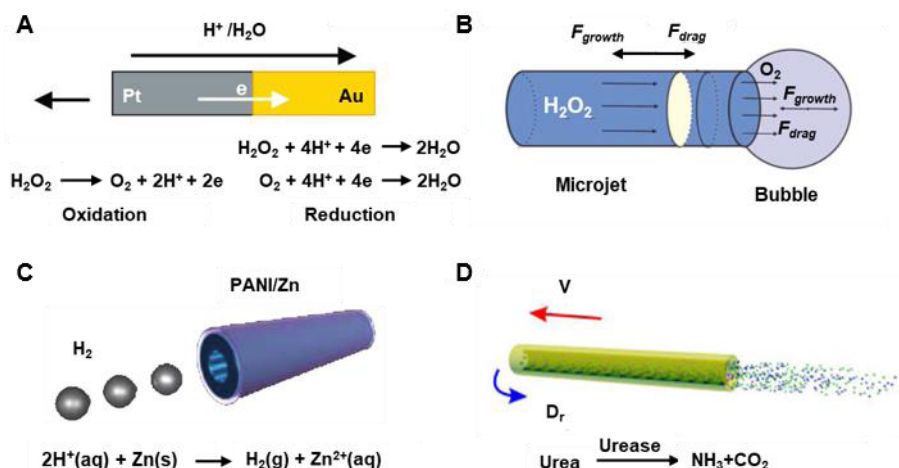


Figure 1. Schematic illustration of chemical propulsion mechanisms used in one-dimensional micro/nanomotors. (A) Scheme of Pt/Au nanowire motors propelled by a self-electrophoretic mechanism in H_2O_2 solution. Reprinted with permission from Wang et al.³⁸ Copyright (2006) American Chemical Society. (B) Scheme of tubular micromotors propelled by ejecting O_2 bubbles in H_2O_2 solution. Reprinted with permission from Manjare et al.⁴⁵ Copyright (2013) American Chemical Society. (C) Scheme of PANI/Zn tubular microtube propelled by recoiling H_2 bubbles in aqueous acid. Reproduced with permission from Gao et al.³³ Copyright (2012) American Chemical Society. (D) SiO_2 /urease tubular nanomotor propelled by the diffusion flux of reaction products. Reprinted with permission from Ma et al.³⁵ Copyright (2016) American Chemical Society. PANI: polyaniline.

behaviour of Janus spherical and tubular micromotors, Baraban et al.²⁸ demonstrated that tubular motors had a lower degree of deviation towards the higher concentrations of H_2O_2 because of the lower rational diffusion coefficient.

External propulsion mechanisms

Although self-propelled 1D micro/nanomotors are very attractive, the general requirement for additional chemical fuels hinders some biomedical applications. Therefore, propulsion driven by an external energy field provides an excellent solution. Externally-propelled 1D micro/nanomotors can efficiently convert exterior field energy (including electric, light, magnetic and ultrasonic fields) to mechanical energy via their corresponding responsive properties.⁸ Besides sustained impetus, these micro/nanomotors generally have strong propulsive power, precise motion controllability and excellent biocompatibility.

Based on the motion of a fluid induced by a low-frequency electric field, 1D micro/nanoparticles could be manipulated by electro-osmotic flux resulting from a direct current or alternating current generated by patterned microelectrodes. Fan and coworkers⁵³ placed charged gold nanowires (AuNWs) in the central region of quadruple electrodes (**Figure 2A**). The nanowires performed longitudinal or transverse motions depending on the electric field direction.⁵³ In addition, the nanowires anchored on the patterned nanomagnets could rotate with precisely controlled angle, speed and chirality within the quadruple electrodes.⁵⁴ Unfortunately, it was very difficult to pattern the electrodes *in vivo* and the charged proteins had an impact on the motor movement.

By contrast, light has been recognised as a practical propellant field due to its advantages of wireless and remote propagation, as well as precise energy input.^{55,56} Generally, light-powered 1D micro/nanomotors could be elaborately incorporated with photoactive materials including photocatalytic and photothermal materials. For instance, Sánchez et al.⁵⁷ fabricated tubular micromotors with

TiO_2 coated on their inner surface. When they were exposed under ultraviolet (UV) light, electron-hole pairs were photogenerated, which reacted with oxygen and water in the medium resulting in highly oxidative species able to decompose acetic acid.⁵⁷ Mou et al.⁵⁸ prepared TiO_2 tubular motors propelled by recoiling O_2 under UV light. The motion state and speed of motors could be wirelessly modulated by UV irradiation. Compared with UV light, near-infrared light has attracted particular interest in biomedical applications on account of its excellent penetrability and near harmlessness for living tissue. He and coworkers demonstrated a tubular micromotor consisting of multilayered alginate/chitosan and gold nanoparticles, which could convert near-infrared light energy into a thermal gradient between the inner chamber and the exterior environment (**Figure 2B**).⁵⁹

Another popular strategy is ultrasonic propulsion which is recognised as a noninvasive approach to manipulate micro/nanomotors *in vitro* and *in vivo* because of its biocompatible nature and excellent penetrability. Wang et al.⁶⁰ pioneered the synthesis of Au/Ru bimetallic nanowires with concave and convex faces, which could be propelled at high speed (200 $\mu\text{m/s}$) by ultrasound treatment (**Figure 2C**). The powerful impetus of the 1D motors relied on an asymmetric distribution of acoustic pressure owing to the energy accumulation near the concave face and energy dissipation near the convex face.

Magnetic fields can also produce strong penetrating and biocompatible energy to propel particles when they are tailored with magnetic materials (e.g. Ni, Fe, Fe_3O_4). For example, inspired by swimming microorganisms, flexible magnetic 1D micro/nanomotors can be propelled via the asymmetric deformation of elastic flexible filaments. Dreyfus and coworkers³⁶ assembled colloidal paramagnetic spheres into a chain structure using DNA as the linker. The chain could be propelled toward the opposite direction of bending-wave propagation in an alternating magnetic field. In another approach, Pak et al.^{61,62} fabricated a Ni/

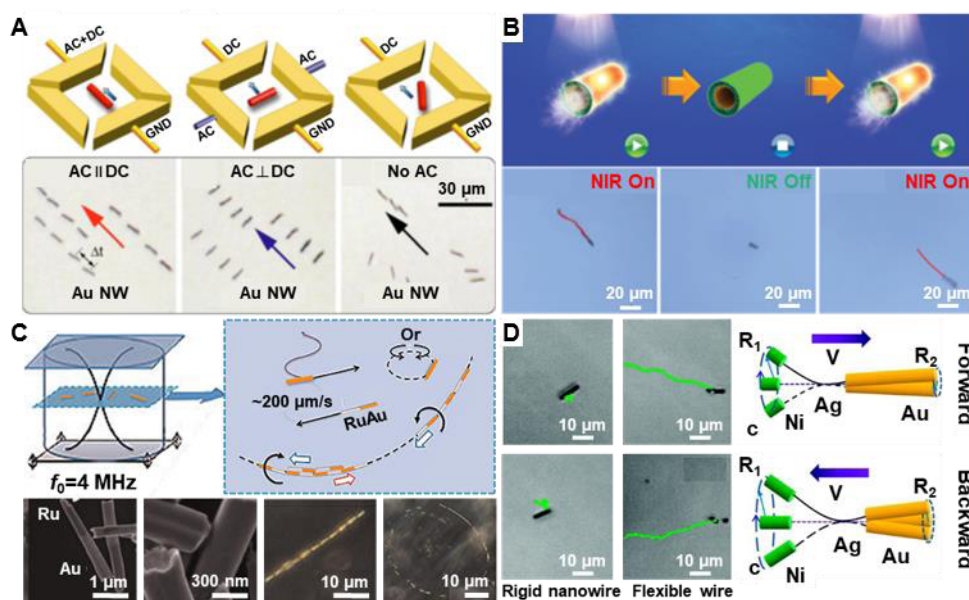


Figure 2. Representative examples of external field propulsion mechanisms of one-dimensional micro/nanomotors. (A) Au nanowire (Au NW) propelled and aligned by AC and DC electric fields in patterned microelectrodes. Reprinted with permission from Fan et al.⁵³ Copyright (2008) American Institute of Physics. (B) Multilayered tubular micromotors decorated with gold nanoparticles propelled by NIR light. Reprinted with permission from Wu et al.⁵⁹ Copyright (2016) John Wiley and Sons. (C) Au/Ru bimetallic nanowire with concave and convex ends propelled by ultrasound as well as its trajectories of axial directional motion and in-plane rotation. Reproduced with permission from Wang et al.⁶⁰ Copyright (2012) American Chemical Society. (D) Ni/Ag/Au flexible nanowire propelled by rotational magnetic field. Reproduced with permission from Gao et al.⁶² Copyright (2010) American Chemical Society. AC: alternating current; DC: direct current; f: frequency; GND: Ground; NIR: near infrared; R1: Ni segment; R2: Au segment; V: magnetic swimming direction.

Ag/Au nanowire, comprising a Ni segment and a Au segment bridged by a flexible silver nanowire (**Figure 2D**). In a rotating magnetic field, the flexible tail made of Ni rotated and propelled the nanowire forward.^{61,62}

Precise navigation of 1D micro/nanomotors is crucial to perform practical tasks in biomedical applications, such as drug delivery, *in vivo* sensing and surgery. However, the precise spatial and temporal control still represents a major challenge in the practical application of 1D micro/nanomotors due to the strong rotation diffusion and complex fluid status *in vivo*.²¹ So far, tuning the external field is still the most effective approach to manipulating the motion behaviour of 1D micro/nanomotors.⁶³

In general, 1D ferromagnetic micro/nanoparticles tend to realign when the particles are magnetised in a strong magnetic field. Accordingly, the motion direction of 1D motors integrated with ferromagnetic materials (e.g. Ni or Fe₃O₄) can be precisely controlled by elaborately tuning a magnetic field. Furthermore, by reversing the magnet, the motion direction of the micromotor can be flipped back by 180° (**Figure 3A**).⁶⁴ In addition, a light source can also be applied to guide 1D micro/nanomotors into the desired directional movement. A Janus silicon (Si) nanowire containing TiO₂ nanotrees fabricated by Tang et al.⁶⁵ exhibited either positive or negative phototaxis. Asymmetric UV illumination on TiO₂ nanotrees led to an unbalanced distribution of photoelectrochemical reaction products (H⁺), which created an electric field parallel to the propagation direction of the light and resulted in an electric force on the TiO₂ head. Furthermore, because of the minority carrier diffusion length in the silicon

nanowire, the rotation of the TiO₂ head could be driven and the angular speed depended on the light intensity. Therefore, the trajectory of a TiO₂/Si microwire could be precisely programmed by adjusting the intensity and propagation direction of the light.

Furthermore, the charged 1D particles can be controlled and manipulated in three dimensions (3D) by an electric field due to their nature of parallel alignment and movement towards the electric field direction. The catalytic nanomotors (Pt/Au nanowire) could be precisely controlled and programmed when the nanowire motors were placed in 3D orthogonal microelectrode sets prepared by Guo and coworkers⁶⁶ (**Figure 3B**). These flexible Pt/Au nanowire motors could capture, transport and deliver cargo to the designated position using this manipulation strategy.⁶⁶

Fabrication of 1D micro/nanomotors

In general, the architecture of 1D micromotors, such as active material distribution, size and shape, significantly influences the formation and distribution of the propelled force, providing an important approach to tune the motion behaviour of the motor. The distribution of active materials is a way to adjust motive behaviour of 1D micro/nanomotors. Compared with Pt/Au two-segment 1D motors, an Au/Pt/Au nanorod coated on one face with a Au/Cr bilayer was able to rotate at a speed of 23.7 r/min in H₂O₂ solution. Additionally, by tuning the longitudinally-distributed ratio of Pt/Au from 1:1 to 4:1, the rotation speed could be adjusted from 9.5 ± 0.7 to 23.7 ± 1.5 r/min because of the shifting of the torque on the nanorods (**Figure 4A**).⁶⁷ Ma et al.³⁵ investigated the effect of the location of active materials on

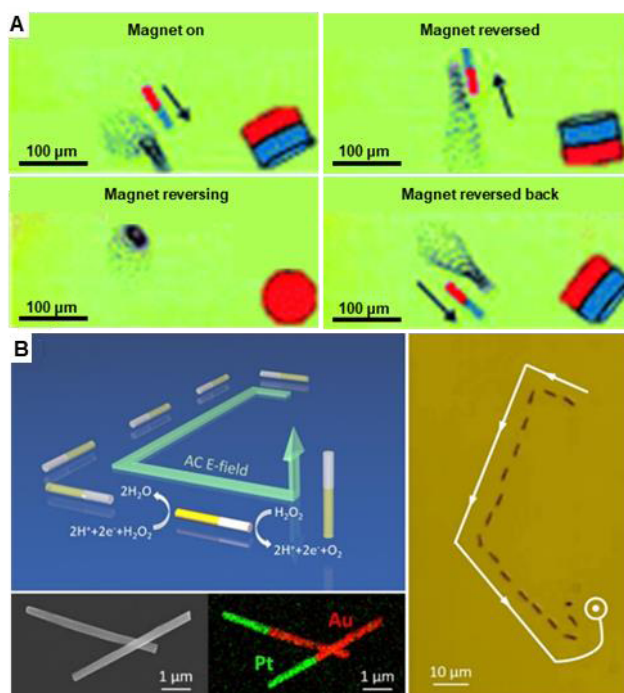


Figure 3. Motion control of one-dimensional micro/nanomotors via external fields. (A) Directional motion and reversing of tubular micromotors remotely guided by a magnetic field. Reproduced with permission from Zhao et al.⁶⁴ Copyright (2012) American Chemical Society. (B) Two dimensions and three dimensions movement of Pt/Au bimetallic nanowire motors manipulated by three-dimensional orthogonal microelectrodes. Reprinted with permission from Guo et al.⁶⁶ Copyright (2018) American Chemical Society. AC: alternating current; hv: light radiation.

the speed of tubular SiO_2 nanomotors (**Figure 4B**). They observed that the tubular motors incorporated with ureases on the inner surface tended to self-propel along the longitudinal direction, whereas the rotation diffusion of the motors was enhanced when the ureases were tailored on the exterior surface. Surprisingly, the longitudinal translational diffusion was greatly increased when the ureases were on both the inner and exterior surfaces owing to the density-driven convective flows created by the decomposition of urea by ureases.³⁵ Meanwhile, the shape of 1D micro/nanomotors also has large effects on the location of active materials and viscous force distribution on the surface of motors. For instance, a copper nanorod with one end in a ratchet shape, fabricated by Liu and Sen,⁴¹ underwent fast rotation (~ 170 r/min) in dilute Br_2 solutions because of the different redox reaction rates along the asymmetric nanorod (**Figure 4C**). In addition, for an ultrasound-propelled 1D gold nanowire motor, the concave or convex shape at one end resulted in an asymmetric distribution of acoustic pressure, subsequently leading to propulsion.⁶⁰ In addition, the length of micro/nanomotors also influenced the velocity of the motor. It was observed that the velocity of nanowire motors (e.g. Pt/Au, Pt/Cu) decreased when their length increased.^{41, 68} In addition, the tuning of the semi-cone angle was able to alter the difference in pressure between the two ends of tubular motors, creating the ability to adjust the velocity of the motors (**Figure 4D**).^{69, 70}

Although several rules concerning the architecture have been established for designing 1D micro/nanomotors, the large scale and repeatable fabrication of arbitrary 1D micro/nanomotors still represents a great challenge. Fortunately, the thriving development of nanotechnology has led to various strategies

and techniques to fabricate 1D micro/nanomotors with diverse architectures and multifunctionality, such as electrochemical deposition, rolled-up, self-assembly, etc.

Electrochemical deposition has been commonly carried out to synthesise well-designed nanowires from different materials varying from several metals to polymers. Generally, as shown in **Figure 5A**, the branched side of commercial track-etched anodic alumina oxide membranes or polycarbonate membranes containing cylindrical or conical pores is used as the working electrode. Subsequently, different metals are deposited to prepare bimetallic or striped micro/nanowire motors, typically composed of Pt/Cu, Au/Pt, Au/Ni/Pt and Au/Ru segments.^{22, 38, 41, 68, 71} Additionally, the segments of these nanowire motors can be conductive polymers, and various ratios of the segments can be adjusted by tuning the charge passed in each step.²⁴ Further, the electrochemical deposition enables fabrication of more complex 1D structures. For instance, Gao and co-workers⁶² reported a Au/Ag/Ni nanowire motor consisting of a flexible thin Ag nanowire bridging the Au and Ni segments. Wang et al.⁶⁰ constructed a 1D ultrasound-propelled nanomotor (Au/Ru) with concave and convex shapes on opposite ends of the nanowire.

Rolled-up technology utilises strain engineering to fabricate micro/nanotubes, pioneered by Mei et al.^{43, 44} Commonly, a pre-stressed inorganic nanomembrane deposited onto a patterned polymer sacrificial layer is released from the substrate surface by selectively removing the sacrificial layer with a solvent, and rolled up into a micro- or nanotube (**Figure 5B**). Due to the complex fabrication procedure and the high cost of the rolled-up technology, considerable efforts have been devoted to simplifying

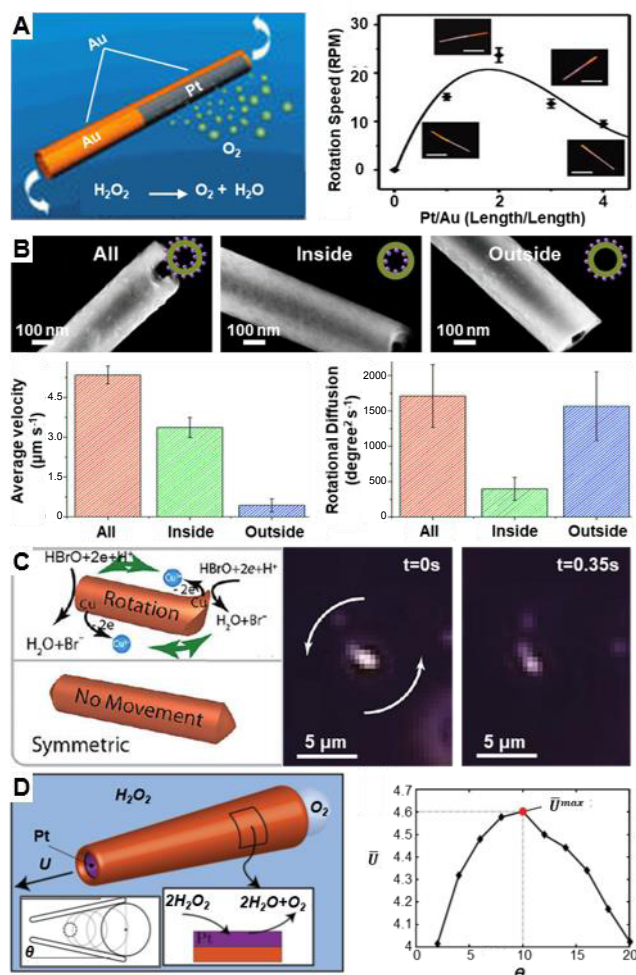


Figure 4. Architectural effects on the motive behaviour of one-dimensional micro/nanomotors. (A) The rotation speed could be adjusted by the distribution ratio of Pt/Au on the Au/Pt/Au nanorods coated with a Au/Cr layer on one face. Reproduced with permission from Qian et al.⁶⁷ Copyright (2007) American Chemical Society. (B) Enzymes on inner or exterior surface of nanotubes enhanced the longitudinal translational and rotational diffusions, respectively. Reproduced with permission from Ma et al.³⁵ Copyright (2016) American Chemical Society. (C) A copper nanowire with a ratchet on one end was able to rotate whereas a symmetric nanowire was not. Reproduced with permission from Liu and Sen.⁴¹ Copyright (2011) American Chemical Society. (D) Tuning the velocity of tubular micromotors by adjusting the semi-cone angle. Reproduced with permission from Gallino et al.⁶⁹ Copyright (2018) John Wiley and Sons.

the rolled-up process and reducing its cost. Graphene oxide (GO) nanosheets coated with Ti and Pt (GO/Ti/Pt) can detach easily from a Si substrate upon sonication and spontaneously roll up into a microtube with GO on the outside.⁷² Additionally, Zhao et al.⁷³ reported two facilitative strategies to produce tubular motors. They selected a transmission electron microscopy grid as a mask and a small magnetron sputtering machine for deposition of thin Pt films on a poly(methyl methacrylate) substrate, subsequently a microtube with the diameter of $\sim 4.1 \mu\text{m}$ and length of 20–60 μm was formed by releasing the Pt film. Recently, the rolled-up technique was applied to fabricate a polyelectrolyte multilayer tubular micromotor. Hu et al.⁷⁴ prepared an alginate/chitosan/Pt nanomembrane on poly(vinyl alcohol), and rolled up the membrane into a tubular micromotor by releasing the stress when the poly(vinyl alcohol) was dissolved (Figure 5C).

Electroplating has been reported to simplify mass preparation of tubular micro/nanomotors. Manesh et al.⁷⁵ raised a template-assisted layering approach, which was carried out by sequentially

depositing platinum and gold on an etched silver template, then dicing and dissolving the template. In order to improve the production and performance of the tubular motors, they established a protocol for the fabrication of a tubular micromotor consisting of Pt and a conductive polymer, including polyaniline, polypyrrole, polythiophene and poly(3,4-ethyl-enedioxythiophene). Initially, the monomers were electropolymerised onto the inner wall of conical polycarbonate membranes, then the metal Pt layer was formed inside the conductive polymer in a metal plating solution.^{76,77} Recently, the conductive polymer has been extended to carbon materials, including C60 fullerene, carbon nanotubes, graphene and carbon black (Figure 5D).⁷⁸

Bottom-up assembly is a greatly attractive strategy for the fabrication of micro/nanomotors. Using this method, various functional building blocks can be precisely assembled into micro/nanomotors, which have multifunctionality, well-defined and tunable architecture and chemical properties, and can form spheres,⁷⁹ plates,⁸⁰ and stomatocyte-like micro/nanomotors.⁸¹

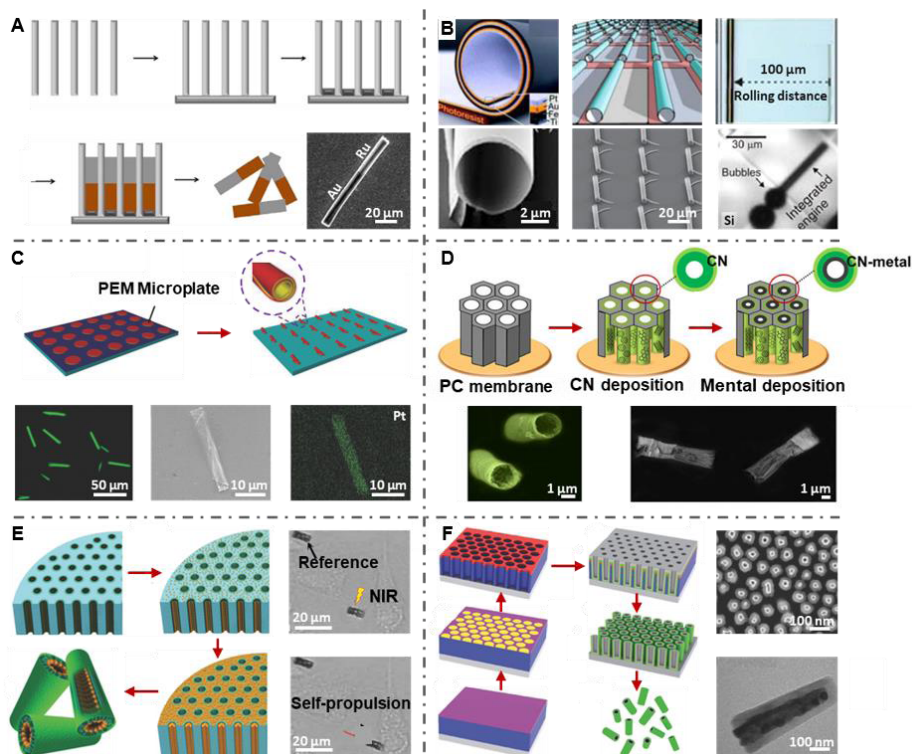


Figure 5. Fabrication of one-dimensional micro/nanomotors. (A) Anodic alumina oxide membrane template-assisted electrochemical deposition for the preparation of metallic nanowires. Reproduced with permission from Wang and Pumera²² and Wang et al.³⁸ Copyright (2015) & (2006) American Chemical Society. (B) Rolled-up technique for the preparation of tubular micromotors. Reproduced with permission from Mei et al.⁴³ and Soloveo et al.⁴⁴ Copyright (2008) & (2009) & (2010) John Wiley and Sons. (C) Combination of layer-by-layer assembly, microcontact printing and rolled-up technique for the fabrication of tubular micromotors. Reproduced with permission from Hu et al.⁷⁴ Copyright (2018) John Wiley and Sons. (D) Electroplating with carbon materials for the preparation of tubular micromotors. Reproduced with permission from Maria-Hormigos et al.⁷⁸ Copyright (2016) American Chemical Society. (E) Bottom-up assembly for tubular nanomotors. Reproduced with permission from Peng et al.⁷⁹ Copyright (2018) Royal Society of Chemistry. (F) Combination of block polymer lithography and atomic layer deposition for the fabrication of tubular nanomotors. Reproduced with permission from Li et al.³⁰ Copyright (2017) John Wiley and Sons. CN: carbon nanotube; NIR: near infrared; PC: polycarbonate; PEM: polyelectrolyte multilayer.

Using a template-assisted layer by layer assembly technique, Wu et al.⁵¹ reported the first multilayer polymer tubular motor assembled with alginate, chitosan and Pt nanoparticles with positive charge by electrostatic interaction. Additionally, various catalytic materials and stimuli-responsive materials could be incorporated into the tubes for the fabrication of various multifunctional tubular micromotors, including enzyme-based, light-propelled and controllably-released motors.^{47, 51, 59, 63} Recently, Toebes et al.⁸² first demonstrated a biodegradable nanomotor created by functionalization of a tubular-shaped self-assembled block copolymer with catalase. The spherical nanopolymersomes self-assembled from poly(ethylene glycol)-*b*-poly(D,L-lactide) and transformed into nanotubes when osmotic pressure was applied. By mixing the azide-terminated polymer (N_3 -poly(ethylene glycol)₆₇-poly(D,L-lactide)₉₀), the propelled units (catalase) and other functional groups, the tubular polymersomes could be easily tailored, which could enable them to be utilised as multifunctional nanomotors (Figure 5E).⁸²

In a real biological system, the shape, structure and function are determined by a highly-ordered self-assembly of molecules. Therefore, the bottom-up assembly strategy has great potential

in the preparation of 1D nanomotors and in regulation of motor motion behaviour at the nanoscale level. In particular, the bottom-up supramolecular approaches have emerged as great candidates for the development of active structures with high control over architecture, which increases the viability for incorporation of multiple reactions or functionalities in the same device and provides a soft interface to improve molecular recognition and cell uptake. However, it is limited to materials that can be used for assembly, the other assembly systems will be developed and combined with other fabrication methods. For example, Wang et al. prepared an ultra-small coaxial TiO₂/Pt tubular nanomotor (length below 150 nm, external diameter under 50 nm and less than 20 nm in inner diameter) combined with block copolymer lithography and atomic layer deposition techniques (Figure 5F).³⁰ The tubular nanomotors could be propelled by the high O₂ diffusion flux from the chamber of the nanotubes at a high speed of 35 μm/s in 15% H₂O₂ solution.

Applications of One-Dimensional Micro/Nanomotors in Biomedicine

The emergence of nanoscale biomedical devices has dramatically

improved diagnostic, treatment and surgical abilities. These tiny motors with independent impetus, precise controllable motion and versatility have the potential to reach and treat all over the human body, including the inaccessible parts such as the brain, kidney, and retina. Furthermore, it even allows us to diagnose and treat at the cellular or subcellular level.⁸³ Diagnosis and operation with these devices are gradually extending our sight and enhancing operation convenience.

Drug delivery

One of the main challenges of nanomedicine is to efficiently deliver therapeutic agents to cells. Because of the highly-specific area, long blood circulation time and outstanding capability to penetrate tissues and biological barriers (such as the brain-blood barrier, cellular barrier), 1D micro/nanomotors are attracting growing attention and have been used to transport organic drug molecules, proteins and RNA.

Firstly, Kagan et al.⁸⁴ fabricated a Ni/(Au₅₀/Ag₅₀ alloy)/Ni/Pt nanowire that could pick up Fe₃O₄/poly(lactic-co-glycolic acid) micro colloids loaded with a common cancer drug, doxorubicin (Dox), via magnetic interaction (**Figure 6A**). In the presence of H₂O₂, the micro colloid caught by the nanowire motor was transported to a predetermined destination under magnetic direction. Subsequently, by applying the reversed magnetic force, the colloid spheres were released in the targeted position due to the drag force overcoming the magnetic attraction.⁸⁴ Later, Wu and coworkers⁵¹ encapsulated Dox in a tubular motor consisting of polyelectrolyte, Pt nanoparticles and Fe₃O₄ nanoparticles. Guided by a magnetic field, the motors moved to the target cells in H₂O₂ solution, where the Dox was released under ultrasonic treatment.⁵¹ In order to further improve the efficiency of drug delivery, the same group added catalase and Au nanoparticles as

well as gelatine to the tubular motor. Guided by a magnetic field, the 1D motors loaded with Dox moved to the targeted cancer cells at a high speed of 68 μm/s. Subsequently, Dox was precisely released in 4 seconds under near-infrared light irradiation because of the photothermal effect of Au nanoparticles and phase transition of the gelatine on the 1D tubular motor (**Figure 6B**).⁴⁷

Protein-based therapy is a promising tool for various biomedical applications, such as dysfunctional or poorly-expressed proteins, antagonizing key intracellular pathways and inducing effects such as apoptosis of cells.^{85, 86} However, intracellular protein delivery involves the challenge of crossing the cell membrane.⁸⁷ Esteban-Fernández de Ávila et al.^{88, 89} reported an approach for intracellular protein delivery with ultrasound-driven AuNW motors. For example, the protein caspase-3 involved in apoptosis was encapsulated on nanomotors with a pH-responsive polymer (**Figure 7A**). It was shown that the active delivery approach resulted in remarkably high apoptosis efficiency within a significantly shorter time and required a lower amount of caspase-3 in comparison to a static nanowire.⁸⁸ Additionally, the AuNW motor could be utilised to accelerate insulin release by tailoring with a mesoporous silica segment, gated with pH-responsive phenylboronic acid-glucose oxidase supramolecular nano-valves. When the motors were exposed to ultrasound, the movement of the motors enhanced fluid mixing, leading to a pH decrease due to the oxidation of glucose. As a result, insulin release was dramatically accelerated because of the acceleration of phenylboronic acid degradation in low pH solution.⁹⁰

Recently, small interfering RNA (siRNA) therapy has emerged as an attractive approach for treating numerous diseases via gene suppression and knockdown. However, the lack of targeting units, relatively low efficiency and internalization barriers greatly

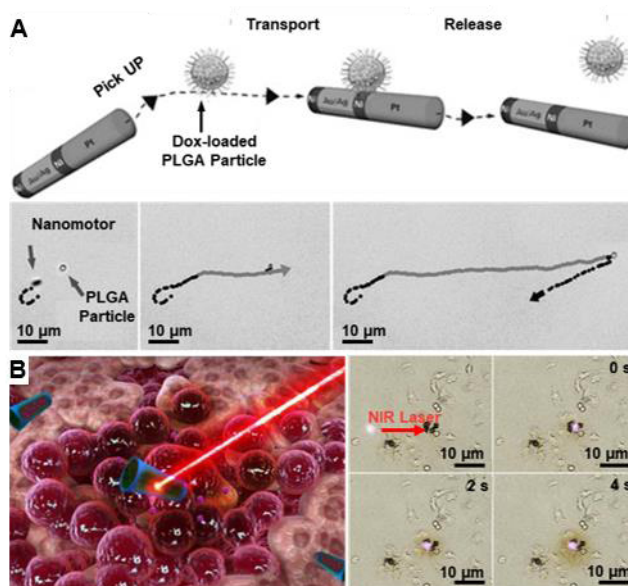


Figure 6. Organic small molecule drug delivery using one-dimensional micro/nanomotors. (A) Ni/(Au₅₀/Ag₅₀ alloy)/Ni/Pt nanowire motors enabled the pick up, transport and release of Dox-loaded PLGA particles at predetermined positions. Reproduced with permission from Kagan et al.⁸⁴ Copyright (2010) John Wiley and Sons. (B) Tubular micromotors encapsulating Dox could move to targeted cancer cells under magnetic guidance and subsequently be triggered to release Dox by a near infrared laser. Reproduced with permission from Wu et al.⁴⁷ Copyright (2015) American Chemical Society. PLGA: poly(lactic-co-glycolic acid).

limits the application of siRNA therapy. Esteban-Fernández de Ávil et al.⁸⁸ reported that a 1D nanomotor could be applied for rapid and efficient intracellular delivery of siRNA (Figure 7B). They immobilised green fluorescence protein-targeted siRNA on ultrasound-driven AuNW motors by rolling circle amplification DNA strand and the silencing efficiency was dramatically improved to 94% under motive conditions.⁹¹

Although the above representative cases indicate that 1D micro/nanomotors can efficiently deliver a drug, they are limited at the cellular level. Recently, Gao et al.⁹² fabricated a tubular micromotor inner-coated with Zn for drug delivery *in vivo*. In this case, retention of the micromotors in the gastric mucous layer was enhanced because of their self-propulsion in the stomach.⁹² Later, the same group replaced Zn with Mg and further coated the outside surface of the motor with a pH-sensitive polymer. As the polymer only

dissolved in intestinal fluid (pH 6–7), by controlling the thickness of the coating polymer, the propelled position of the motors in the gastrointestinal tract could be determined (Figure 8).⁹³

Sensing

Due to their independent impetus and precise controllability, 1D micro/nanomotors have been used to enhance the efficiency of drug delivery. Similarly, 1D micro/nanomotors can transport various types of miniature sensors to the regions of interest, perform local sensing and improve the encountering probability between targeted molecules and sensors.

The sensitivity of locomotion of a 1D motor to its surrounding environment provides an attractive and alternative route for sensing. The chemical detection signal can be inferred from changes in the speed or motion distance of the 1D motor,

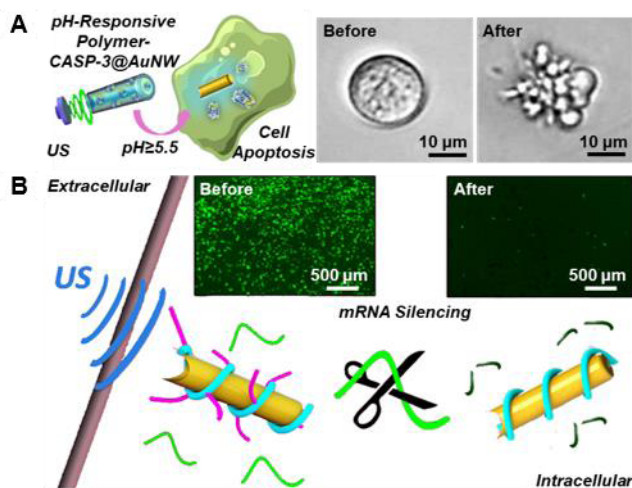


Figure 7. Rapid intracellular delivery of proteins (A) and RNAs (B) with ultrasound-propelled gold nanowire (AuNW) motors. Reproduced with permission from Esteban-Fernández de Ávila et al.⁸⁸ and Díez et al.⁹⁰ Copyright (2017) & (2016) American Chemical Society. CASP-3: caspase-3; US: ultrasound.

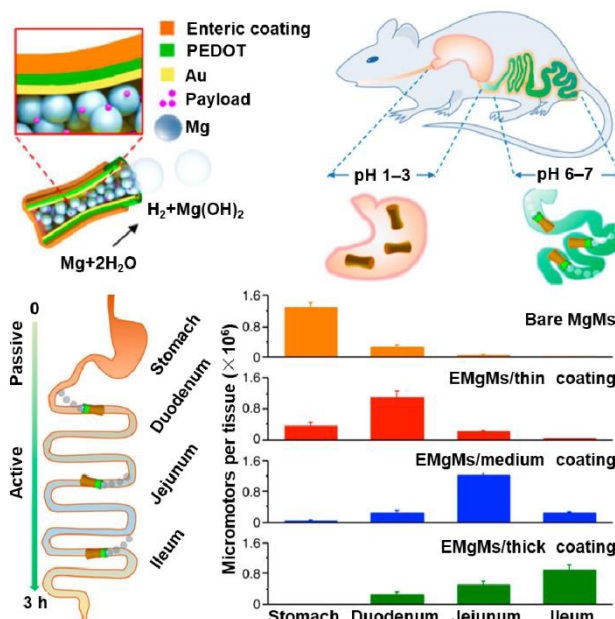


Figure 8. Tuning distribution of drugs in gastrointestinal organs by varying the thickness of a pH-responsive polymer coating on a Mg-based tubular micromotor. Reproduced with permission from Li et al.⁹³ Copyright (2016) American Chemical Society. EMgMs: enteric Mg micromotors; PEDOT: poly(3,4-ethylenedioxythiophene).

One-dimensional micro/nanomotors for biomedicine

which can be monitored by detection methods such as optical microscopy, resonance light scattering correlation spectroscopy or dynamic light scattering.^{30, 94, 95}

Usually, the diffusion of 1D motors is enhanced when the concentration of the corresponding chemical fuels increases. According to this principle, Gaspar and coworkers prepared a nanorod motor consisting of Pt- and polypyrrole-encapsulated enzymes. Several enzyme substrates such as glucose, hypoxanthine and glutamate could be detected by monitoring the diffusion coefficient of the corresponding enzyme loaded in the nanomotors.⁹⁶ Meanwhile, the speed of the 1D micro/nanomotors was sensitive to the additional components. Yu et al.⁹⁴ incorporated a capture antibody into a polyaniline/Pt tubular micromotor. The velocity decreased when incubated with carcinoembryonic antigen, a cancer biomarker and secondary-antibody-modified glycidyl methacrylate microspheres due to the antigen-antibody specific interaction (**Figure 9A**). By monitoring the velocity of the tubular micromotor, the cancer biomarker concentrations can be detected at the levels of 1–500 ng/mL in 5 minutes without the requirement for any washing or separation steps.⁹⁴

Van Nguyen and Minter⁹⁷ used Pt nanoparticles tailored with DNA as catalysts to propel the tubular motors in H_2O_2 solution. The catalyst was only attached to the inner surface of the motor, and motor speed changes could be distinguished even at the concentrations of DNA as low to $0.5 \mu M$.⁹⁷ In order to further improve the sensitivity of this assay, Fu et al.^{98, 99} constructed tubular micromotors by assembling a catalase single layer on the inner surface of the motor. The presence of targeted DNA displaced the double-stranded DNA conjugated with catalase, resulting in deceleration of the motor. Furthermore, they assembled multilayer catalase via the DNA hybridization chain reaction to improve the sensitivity of this assay. By measuring velocity changes, the tubular micromotors could be used to detect the DNA at the concentrations between 10 nM and $1 \mu M$ (**Figure 9B**).^{98, 99}

The guidable motion of 1D micro/nanomotors provides a practical approach for sensing in a predetermined position and even down to the level of single cells. Fan and co-workers fabricated a Ag/Ni/Ag nanorod coated with a silica layer and Ag

nanoparticles as a surface-enhanced Raman scattering unit. Under the guidance of a magnetic field, this nanorod could be accurately moved to the membrane of a single Chinese hamster ovary cell. The nanorod motor was then used to detect the chemicals on the cell membrane by surface-enhanced Raman scattering spectroscopy *in situ* and in real time (**Figure 10A**).⁸³ Additionally, Esteban-Fernández de Ávila et al.⁸⁸ reported that an ultrasound-driven AuNW nanomotor could be utilised for rapid detection of extremely low endogenous microRNA-21 (miRNA-21) at single-cell resolution. The dye-labelled single-stranded DNA/GO coated AuNW nanomotors were able to penetrate quickly into a cancer cell under ultrasound propulsion. Subsequently, the quenched fluorescence, caused by the interaction between GO and dye-labelled single-stranded DNA, was able to recover owing to the substitution of targeted miRNA-21 for the dye-labelled single-stranded DNA. Consequently, the fluorescence signal could be monitored for the detection of miRNA-21 expression levels (**Figure 10B**).¹⁰⁰

Surgery

Minimally-invasive surgery has been widely adopted owing to the reduction of recovery time, medical complications and postoperative pain.³ Compared to macro operating machines, micro/nanomachines have promising abilities to navigate throughout the human body, operate in hard-to-reach positions and even modulate the behaviour of individual cells.

Recent advances in wireless manipulation of 1D micro/nanomotors exhibited their unique capabilities for minimally-invasive surgery. Propelled by various forms of energy, a 1D micro/nanomotor with a nanoscale surgical component can directly penetrate or retrieve cellular tissues for precision surgery. For instance, Kagan and coworkers¹⁰¹ first showed that 1D motors could be utilised to remove targeted cellular tissues (**Figure 11A**). In this system, tubular micromotors based on the fast vaporization of biocompatible fuel (perfluorocarbon), exhibited ultrafast motion at a velocity of 6 m/s under external ultrasound propulsion. The fast speed allowed the 1D motors to penetrate, deform and pierce the kidney tissue by elaborate tuning of ultrasound pulse pressure. Additionally, the micromotor could capture and transport a small piece of tissue after an ultrasound

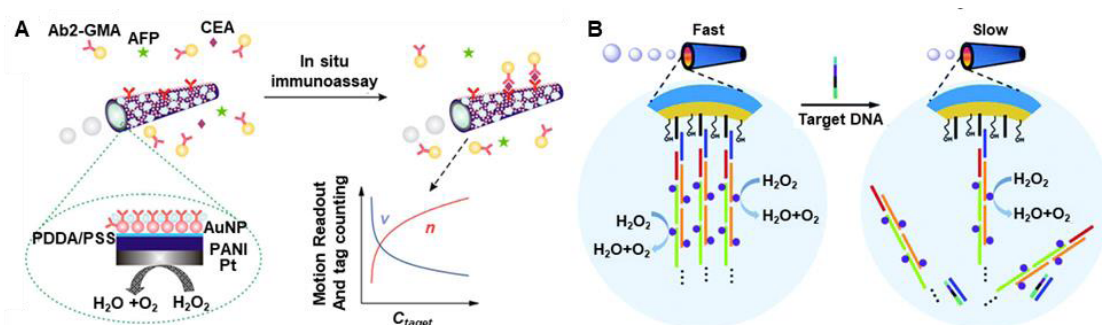


Figure 9. Sensing using one-dimensional micro/nanomotors. (A) Scheme of tubular micromotors tailored with antibody for cancer biomarker detection (e.g. CEA). Reproduced with permission from Yu et al.⁹⁴ Copyright (2014) American Chemical Society. (B) Scheme of tubular micromotors for targeted DNA detection through the detachment of active materials (catalase). Reproduced with permission from Fu et al.⁹⁸ Copyright (2017) Royal Society of Chemistry. Ab2-GMA: secondary-antibody-modified glycidyl methacrylate microspheres; AFP: alpha fetoprotein; CEA: carcinoembryonic antigen.

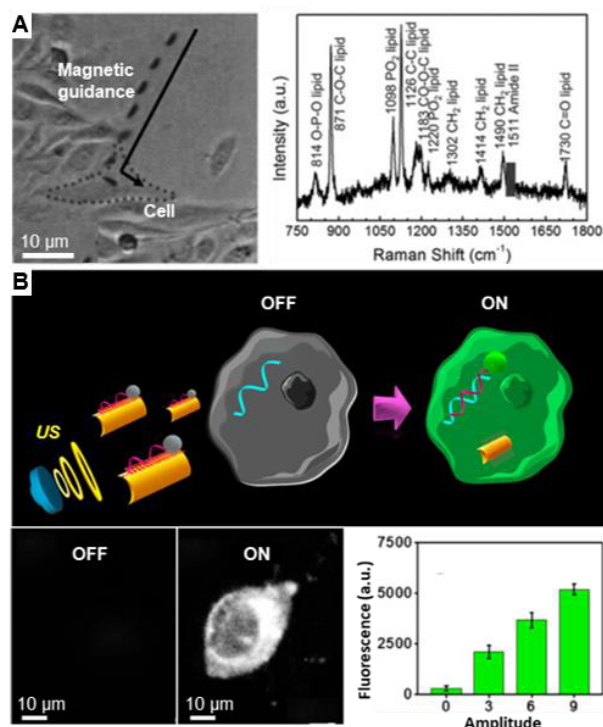


Figure 10. One-dimensional nanomotors for single cell sensing. (A) Ag/Ni/Ag three-segment nanorods coated with Ag nanoparticles used to analyse the chemicals of a single cell. Reproduced with permission from Xu et al.⁸³ Copyright (2013) John Wiley and Sons. (B) Ultrasound-propelled nanorod modified with fluorescent dye-labelled ssDNA for miRNA detection of a single cell. Reproduced with permission from Esteban-Fernández de Ávila et al.¹⁰⁰ Copyright (2015) Royal Society of Chemistry. US: ultrasound.

pulse.¹⁰¹ To further promote the clinical application of 1D micro/nanomotors in surgery, Chatzipirpiridis et al.¹⁰² demonstrated an implantable magnetic tubular micromotor for minimally-invasive ophthalmologic surgery *in vivo* (**Figure 11B**). The motor was injected with a 23-gauge needle into the central vitreous humour of a New Zealand white rabbit, subsequently monitored via ophthalmoscope and precisely manipulated to rotate and translate under the guidance of a magnetic field.¹⁰²

By using 1D micro/nanomotors, the performance of a surgical operation on a single cell has been realised. For example, Cai et al.¹⁰³ presented a plasmid DNA loaded on nanotube-tailored Ni particles at one end for gene transfection. The nanotubes first speared into the cell membrane in a rotating magnetic field and then penetrated the membrane under a gradient magnetic field.¹⁰³ Recently, Hansen-Bruhn et al.¹⁰⁴ incorporated a Cas9/sgRNA complex onto ultrasound-driven AuNW nanomotors by reversible disulphide linkage (**Figure 11C**). The 1D AuNW nanomotor immobilizing the Cas9/sgRNA complex efficiently penetrated into the targeted cells under 5 minutes ultrasound treatment and released the Cas-9/sgRNA complex inside the cells to achieve highly-efficient GFP gene knockout (> 80%) in 2 hours, about 2.5 times the level of static treatment.¹⁰⁴

Summary and Outlook

Over the last decades, a series of propulsion mechanisms and design rules for precise manipulation of 1D micro/nanomotors have been established, resulting in the emergence of numerous 1D micro/nanomotors with excellent functions, e.g. chemotaxis,

targeting navigation, transport and release of cargo.^{6, 21} In this paper, we have highlighted recent works involving 1D micro/nanomotors in cellular and body fluid/biological matrix applications. Although significant progress has been made, the application of 1D micro/nanomotors in biomedicine is still in its infancy.

In vivo, 1D micro/nanomotors will first encounter the blood which has high viscosity and high fluid-flow speed, and subsequently viscous interstitial fluid and dense cellular tissues, which present a great challenge for the self-navigating of the motors. Hence, 1D micro/nanomotors with very powerful impetus and excellent biocompatibility are required for autonomous motion in the strictly physiological environment. In order to precisely manipulate 1D micro/nanomotors *in vivo*, high resolution and real-time imaging motors are greatly desired. Usually, 1D micro/nanomotors are expected to complete multiple tasks in a complex environment, thus it is necessary to develop multifunctional motors with different functional groups and targeting moieties in a single motor. In addition, due to the limitation of the present fabrication strategies, fabrication methods should be developed based on reliable research data and practical application.

Before we move in those directions, the questions that need to be addressed going forward are (a) Are there any new alternative fuels and propulsion mechanisms available for safe and sustainable operation in the human body? (b) How can high resolution and real-time imaging of 1D micro/nanomotors be realised? (c) How can we effectively integrate multidisciplinary expertise to develop

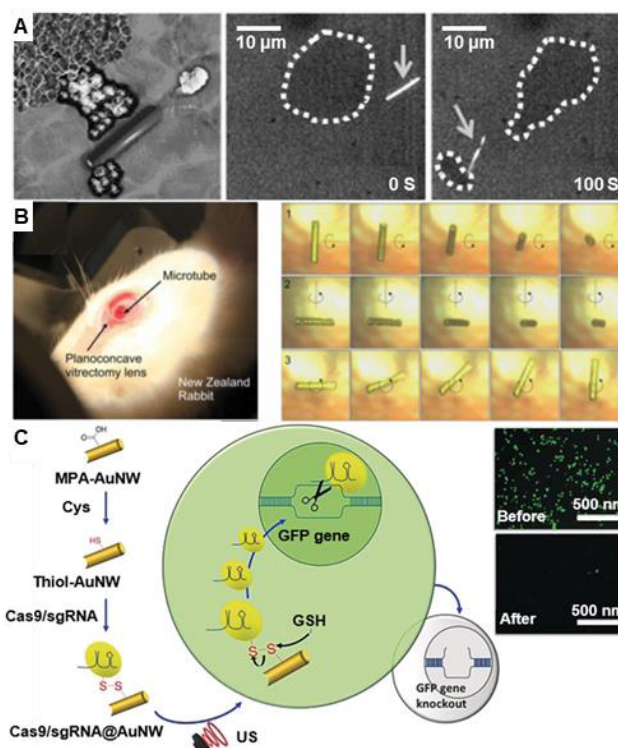


Figure 11. One-dimensional micro/nanomotors for surgery. (A) Tubular micromotors propelled by acoustic droplet vaporization for cellular tissue ablation. Reproduced with permission from Kagan et al.¹⁰¹ Copyright (2012) John Wiley and Sons. (B) Implantable magnetic tubular micromotors for wireless ophthalmologic surgery. Reproduced with permission from Chatzipirpiridis et al.¹⁰² Copyright (2014) John Wiley and Sons. (C) Ultrasound-propelled gold nanowires loaded with a Cas9/sgRNA complex for rapid and efficient gene knockout. Reproduced with permission from Hansen-Bruhn et al.¹⁰⁴ Copyright (2018) John Wiley and Sons. AuNW: gold nanowire; Cys: cysteine; GFP: green fluorescent protein; GSH: glutathione; MPA: 3-mercaptopropionic acid; sgRNA: single guide RNA; US: ultrasound.

multifunctional motors? And (d) what is the next cutting-edge fabrication technique?

Ideally, the 1D micro/nanomotors will employ enzymes as catalysts and use fuel present in living systems. The use of enzymes such as urease, catalase, lipase, and DNA polymerase to power biomotors indicate that single enzyme molecules can generate sufficient mechanical force. Additionally, advancements in artificial enzymes are expected to improve the stability and energy conversion efficiency. If we can make full use of the characteristics of enzymes, it will be possible to achieve motor control in the body.

With the developments in fabrication technology, 1D motors have been gradually realised on the nanometre scale. Especially when 3D printing technology becomes further developed, more elaborate structures of 1D micro/nanomotors can be expected. However, how to accurately track motor motion at the nano scale is a challenging task. Developments in computer simulation and microscopy techniques will help to analyse the motion of 1D motors at the nano scale in future.

Attention should also be given to the versatility and sophistication of the *in vivo* environment. Biomedical 1D nanomotors are designed for environments involving unanticipated biological events, changing physiological conditions, and soft tissues. Therefore, multifunctional 1D nanomotors are highly desired

in complex physiologically-relevant body systems. For future applications, uses of biomedical 1D nanomotors are expected to involve cooperation between thousands of units moving independently but in a coordinated manner to target disease sites. Interaction, communication and cooperation between 1D micro/nanomotors will endow them with the ability to transform into different shapes to perform different tasks.

Natural biological entities have evolved their structures and the way they move in diverse biological settings over a long period of time. Therefore, we believe that an effective strategy is to understand and learn from nature. We believe nature will provide more solutions to address the current issues and with interdisciplinary research efforts, the application of 1D micro/nanomotors in biomedicine can be rapidly promoted and will become a vigorous field. We envision that the clinical transformation of 1D micro/nanomotors will be unimpeded and bring numerous benefits in future clinical practice.

Author contributions

JG contributes to the investigation and writing-original draft; YL contributes to the writing-review & editing, supervision and funding acquisition. All authors approved the final version of this manuscript.

Financial support

This work was partially supported by the National Natural Science Foundation of China (No. 21429401), and the Chinese Scholarship Council (No. 201904910172).

Acknowledgement

None.

Conflicts of interest statement

The authors declare no competing financial interest.

Data sharing statement

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Received: August 11, 2020

Revised: August 21, 2020

Accepted: August 21, 2020

Available online: December 28, 2020