

Chapter 2

Nanorobotic Agents and Their Biomedical Applications

Abstract Application of nanorobotic agents is one of the most-promising perspective for future development and progress in medicine. Molecular machines gain significant attention with an ultimate goal to create a theranostic platform interacting with biological system and being able to perform atomic-level tasks. Such concept requires advanced technological approach i.e. design and assembly techniques, in vivo real-time navigation system, sensing methods as well as data transfer. Currently, both artificial (carbon nanotubes) and biological (DNA, proteins, bacteria) components are investigated as a building blocks of nanobots. This chapter presents advancements in nanorobotic agents biomedical application.

Keywords Nanomedicine • Nanorobot • Molecular machine

2.1 Nanomedicine and Nanorobotics

One of the concept in nanomedicine, described by Freitas [1], describes an idea of introducing nanorobots and related machines into biological systems for cellular and molecular-level tasks. Due to very challenging character of this perspective, multidirectional and interdisciplinary approach is required including selection of nanorobotic agents type, energy source, control and navigation system. Ongoing theoretical and experimental studies in nanomedicine will give a strong support for advancements in nanodevice design and further clinical application.

Nanorobotic agents, structures with overall dimensions in the nanometers size range, are designed to perform predefined tasks including target molecule delivery for therapeutic or/and diagnostic (theranostic) purpose. Particular physical phenomena associated with nanoscale diameter require specific and advanced nano-composites assembly methods as well as control and actuation strategies [2]. Nevertheless a concept of applying nanobots in clinical medicine is relatively new, molecular robotics gains significant attention and recognition reflected by increasing number of demonstrations and publications. Of note, despite significant advancement in the medical strategies prognosis of patients remains unsatisfactory.

Thus, adoption of new technologies is especially of a great interest. The advancement in the field of nanotechnology with improvement in design, sensing, control, as well as better understanding of molecular biology are important steps towards translational medicine.

2.2 Bio-nanorobotics

It is generally said that bio-nanorobotics reflects and incorporates many observations and natural law aspects, what is represented in design, programming, manufacturing and controlling of the nanomachines as shown in Figs. 2.1 and 2.2 [3].

2.3 Nanorobotic Agents in Biomedical Applications

The consolidation of nanotechnology, medicine and surgery provides an exciting evolution in a healthcare sector and medical technology. In 1959 Richard P. Feynman, Nobel Prize laureate in physics, was the first scientist who proposed a vision of nanorobots and atomic level machines application in the treatment of disease in humans i.e. nanorobot-based therapy for heart disorders [4].

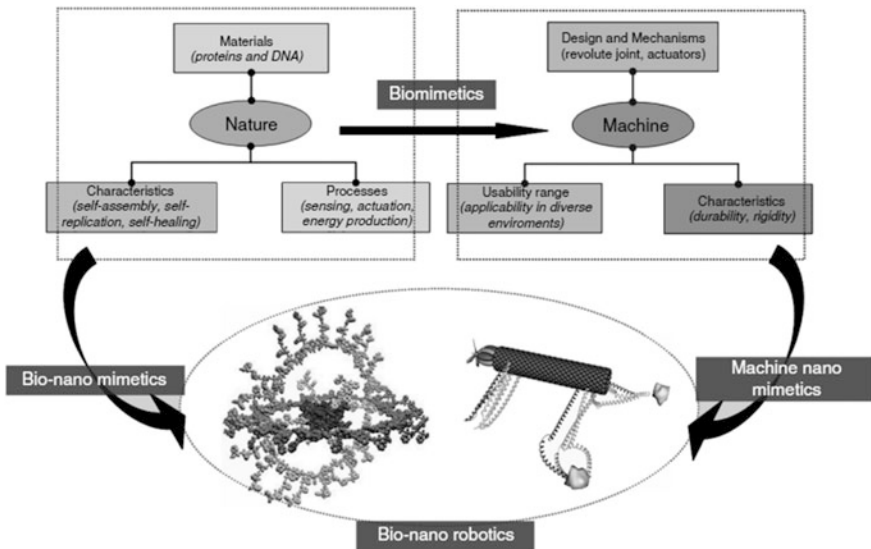


Fig. 2.1 Biomimetics—bio-nano robotics, inspired by nature and machine. Adapted with permission from Ref. [3]

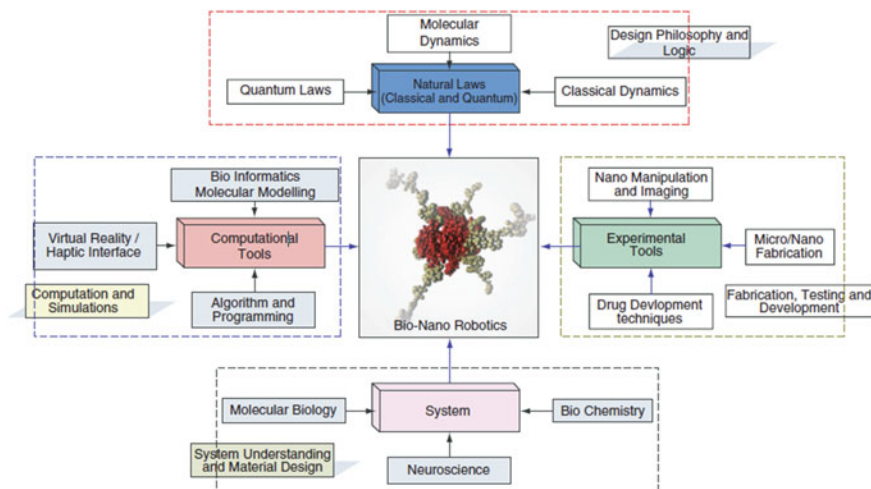


Fig. 2.2 Bio-nano robotics as a multidisciplinary field. Adapted with permission from Ref. [3]

2.4 Biomolecular Machines and Bio-nanorobots

Development in robotic molecular-level complement is a critical step for biomolecular machines evolution, in aim to create a functional motion, force, as well as to sense signal and store information.

Protein and DNA are explored to act as bio-mechanical joints, motors, transmission elements and biochemical sensors. DNA nanotubes can serve as structural elements like links and DNA hinge. Moreover, ATPase protein flagella motors, viral protein motors, DNA-based structures are also being explored as actuators. Interestingly, rhodopsin and Heat Shock Factor proteins are also researched as sensors. These bio-inspired robot components assembled together provide an picture of applicable biomolecular machine.

In aim to functionalize and optimize medical nanorobotic devices, various elemental components like molecular gears, bearings, chemical sensors are required (Fig. 2.3). Thus, complex manufacturing, synthesis techniques and interdisciplinary approaches are incorporated to obtain an operational product. Positional assembly strategy, a concept in molecular manufacturing, relays on combining molecular parts one by one in a controlled fashion. Although the theoretical aspect of atom by atom positional assembly is well established, the nanorobotic experimental researches are still in the early developmental phase [4]. Interestingly, even more futuristic, there are concepts of incorporating biological elements into nanobots (Fig. 2.4).

Cavalcanti et al. worked on application of nanobioelectronics for diabetes mellitus treatment [5]. With computational approach, they proposed a 3D prototype of a device designed to improve glucose management through a external electronic

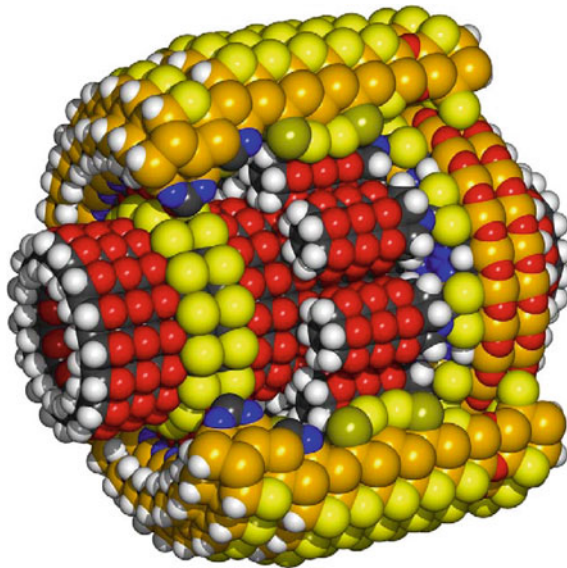


Fig. 2.3 A molecular planetary gear is a mechanical component that might be found inside a medical nanorobot. The gear converts shaft power from one angular frequency to another. The casing is a strained silicon shell with predominantly sulphur termination, with each of the nine planet gears attached to the planet carrier by a carbon-carbon single bond. The planetary gear shown here has not been built experimentally but has been modelled computationally. Adapted with permission from Ref. [4]

device which can communicate with nanorobots. They addressed nanorobotic sensing with chemical signal dispersion using a 3D environment for prototyping and analysis as shown in Fig. 2.5. The model used an embedded chemosensor for glucose monitoring by modulating human SGLT3 protein glucosensor activity and the SG33-P antibody for modelling the integrated circuit. Higher concentrations of proteins can be identified which couples human SGLT3 isoforms to the intracellular bloodstream signalling. Afterwards, the data was transmitted to the external device (i.e. mobile phone).

Martel et al. worked on two complementary systems. The first one is a MRI-based medical nanorobotic platform to access the regions of human body inaccessible to catheterization [6]. The basic principle relies first on exploiting the high homogeneous magnetic field inside the tunnel of the clinical MRI scanner (typically 1.5T or 3T) to bring magnetic entities such as superparamagnetic nanoparticles at saturation magnetization. When at saturation magnetization, such magnetic nanoparticles provide the maximum displacement force for a given magnetic gradient (variation of the magnetic field strength over distance). Indeed, when inside the tunnel of a MRI scanner, no displacement occurs since the magnetic field is uniform. To apply 3D directional magnetic gradients to induce a displacement force along a pre-defined trajectory in the vascular network on magnetic nanoparticles encased in therapeutic

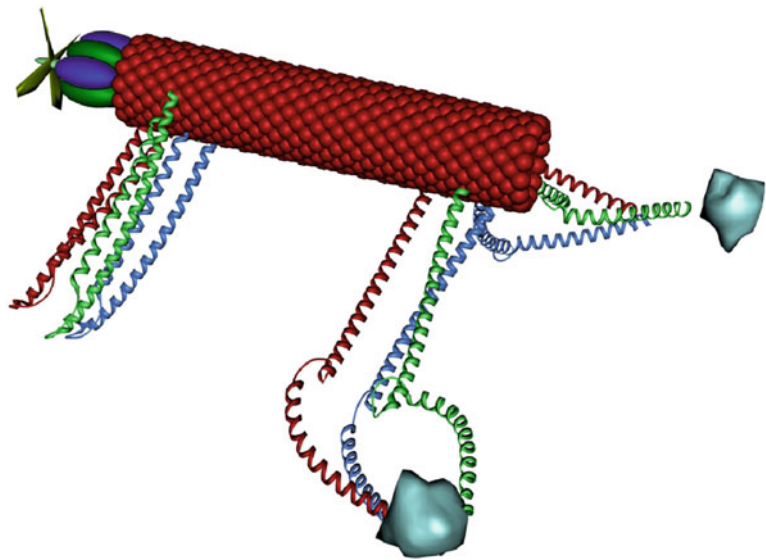


Fig. 2.4 The biological elements will be used to fabricate robotic systems. A vision of a nano-organism: carbon nanotubes (CNT) form the main body; peptide limbs can be used for locomotion and object manipulation, a biomolecular motor located at the head can propel the device in various environments. Adapted with permission from Ref. [3]

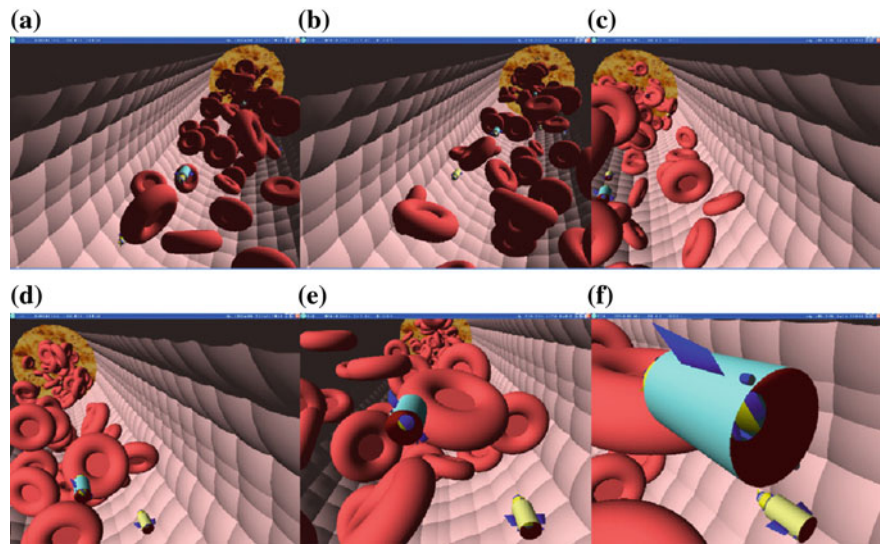


Fig. 2.5 The real-time simulation serves as an advanced tested environment for task-based analysis, providing an extremely useful investigation tool for device prototyping, control, and manufacturing analysis. The nanorobots move through the workspace sensing blood glucose levels. Adapted with permission from Ref. [5]

microcarriers. Such directional gradients can be generated using the gradient imaging coils of the MRI scanner or by distorting the homogenous field of the scanner using ferromagnetic cores introduced at specific locations in the tunnel of the scanner. This is referred to as Magnetic Resonance Navigation (MRN) [7] or Dipole Field Navigation (DFN) [8], respectively. MRN and DFN are more appropriate for navigation in larger blood vessels such as arteries and large arterioles. Technological issues including but not limited to the generation of higher gradients at the human scale and the limit of medical imaging modalities, prevents these technologies to reach the microvascular network.

As such natural nanorobots in the form of flagellated magnetotactic bacteria (Fig. 2.6) have been considered [9]. A special platform dubbed the magnetotaxis platform produces a 3D directional magnetic field that align a chain of intracellular nanoparticles synthesized in the cells during cultivation towards the targeted region to be treated which is typically a solid tumor. This chain acts like a microscopic compass needle that is used to indicate to the bacteria the direction of the tumor. Once inside the tumor, the magnetic field is set to zero to allow the bacteria to seek autonomously regions of low oxygen concentrations which correspond to regions of fast duplicating tumor cells. Each bacterium is previously loaded with the therapeutic agents. These bacteria are very effective in physiological microenvironments such as near and inside the tumoral volume [10]. As such, some types of localized cancers where peritumoral injections are possible such as colorectal and

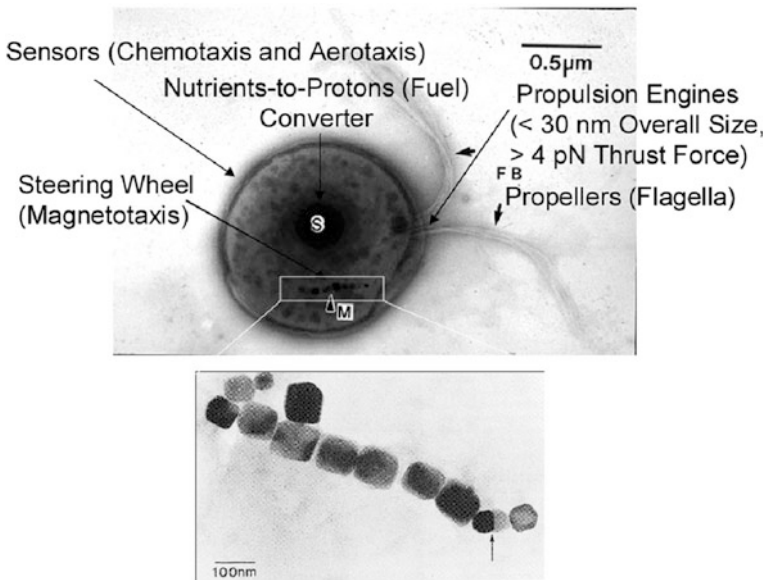


Fig. 2.6 Representation of the MC-1 MTB as a computer controllable bio-actuator with its flagella bundles (FB) for propulsion and its chain of magnetosomes (*bottom*) allowing steering control through magnetotaxis. Adapted with permission from Ref. [9]

prostatic cancers are candidates for this particular approach. But some locations require intraarterial injections. Since the bacteria are ineffective in larger blood vessels due in part to the blood flow and the distance separating the injection site the site of treatment, efforts are also underway to combined MRN and DFN to bring the drug-loaded bacteria encased in special microscopic vesicles closer the tumor where they become more effective.

Mustapha Hamdi proposed an application of DNA for computational designing and multiscale modelling of a encapsulated DNA-multi-walled carbon nanotube actuator, which can be incorporated as a drug delivery carrier and biomolecular transport system [11] as shown in Fig. 2.7. Encapsulated double-stranded DNA was connected to a support electrode and it actuates the sliding inner tube. With variation of temperature in mild acidic medium, the inner nanotube slides due to change in conformation.

Mechanical properties of three nanoactuator structure, A-DNA, Z-DNA and B-DNA were studied through molecular dynamics simulation of DNA denaturation, and Z-DNA showed most powerful and controllable driving performances as described in Fig. 2.8. Encapsulation of DNA inside carbon nanotube was simulated and ionic current feedback sensor was implemented for position determination. In conclusion, the developed system was based on a nanoscale linear servomotor with integrated position sensor.

Hogg and Freitas evaluated numerical models of chemical source power available for nanorobots which oxidize blood glucose [12]. The researchers studied kinetics of oxygen release from red blood cells through haemoglobin saturation as well as the capacity of nanorobots to generate power by processing oxygen. The same authors worked on acoustic-based communication approaches for medical nanorobots [13]. They analysed in vivo acoustic property of body various tissues observing a frequency-dependent changes in attenuation. Based on obtained data, spherical nanorobots designs was proposed. Moreover, the authors showed that a communication rate of 10^4 bits/s is possible with a power supply generated from

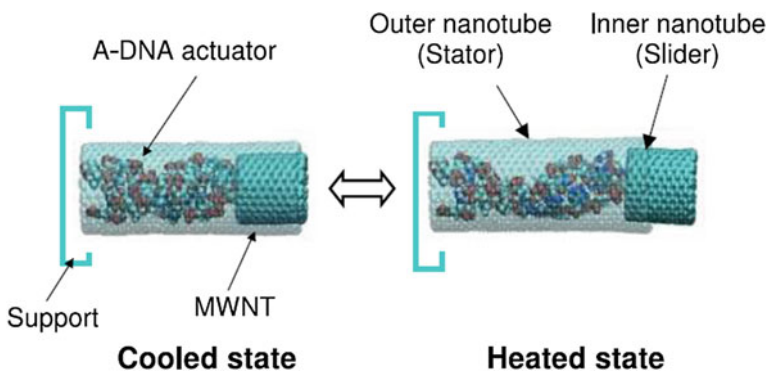


Fig. 2.7 Basic concept of a linear encapsulated DNA-MWNT nanoactuator controlled by the temperature parameter. Adapted with permission from Ref. [11]

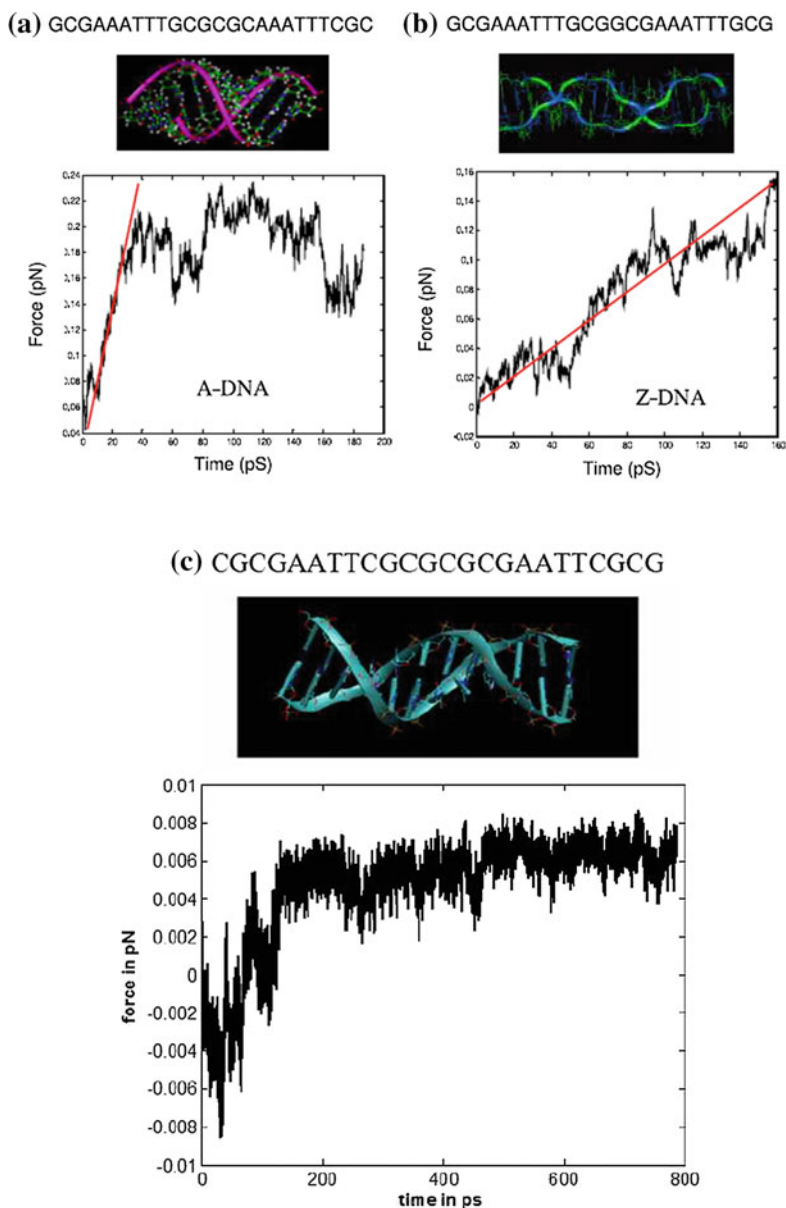


Fig. 2.8 Chemical structure and mechanical force delivered by DNA denaturation for **a** A-DNA, **b** Z-DNA and **c** B-DNA. Adapted with permission from Ref. [11]

oxygen and glucose present in bloodstream. They proposed that the demonstrated system can also be used in a therapy with a short bursts at considerably higher power, without damaging nearby tissues.

Architectures based on self-assembled functional DNA oligonucleotides and interlocked nanomechanical components are also explored [14] (Fig. 2.9). Without any restriction in motion, mechanical interlock allows controlled and specific motion with reduced diffusion. Precise alignment of structural and functional modules of DNA in 2D and 3D is possible through DNA origami technique. This method can be used to synthesise scaffolds for specific integration of multiple functional elements made of DNA. Circular geometrical interlocked DNA nanostructures like dsDNA nanorings (Fig. 2.10) are extensively researched for building artificial nanomachines.

Abi and colleagues worked with 3D DNA nanostructures, self-regulating sensor and other actuator devices [15]. They showed electrochemical switching with these structures self-assembled on gold electrodes. External chemical stimuli-triggered mechanical reconfiguration acts as a nanoswitch, thus, this solution can serve as a functional and operation element in nanorobots and 3D DNA tetrahedral based surface-tethered nanoelectronic devices. Four DNA sequences were annealed followed by immobilization on gold surface through thiol linking at three component strand ends as shown in Fig. 2.11. Chronocoulometric analysis was used for the DNA tetrahedron surface coverage evaluation and nano mechanical switch induced by configuration was electrochemically checked in solutions of high ionic strength. This reconfiguration-based switching induced by molecular stimulus showed high efficiency and for the first time, this research addressed surface immobilization based 3D DNA architecture for electronic nanoswitch.

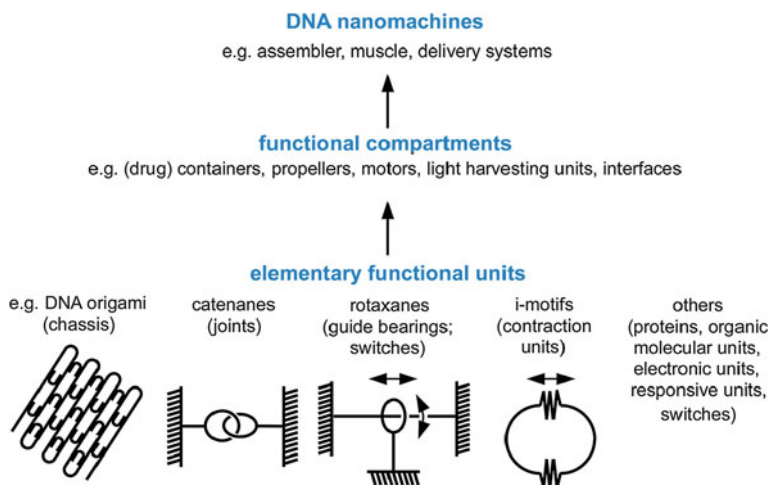


Fig. 2.9 Hierarchical assembly of complex DNA nanomachines from functional compartments. These will consist of elementary units, each featuring a highly specific functionality. Adapted with permission from Ref. [14]

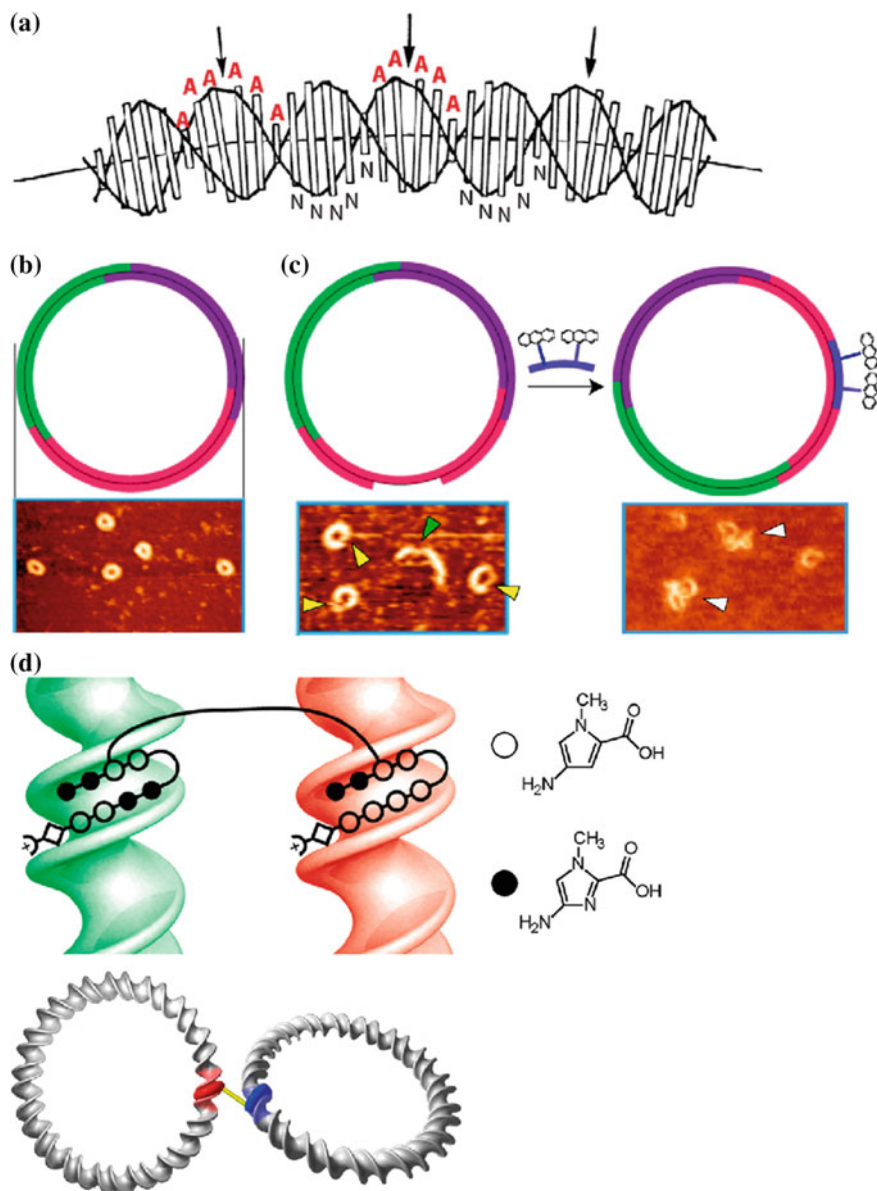


Fig. 2.10 Generation of dsDNA nanorings. **a** Intrinsic dsDNA-bending by repetitive A-tracts. **b** 168-bp dsDNA-nanoring ligated from three 51-mer dsDNAs, flanked by 5-nt ssDNA overhangs (*top*) exhibit a regular, nondistorted shape (*bottom*). **c** Assembly of dsDNA nanocircles into oligomeric aggregates mediated by anthracene intercalation. Adapted with permission from Ref. [14]

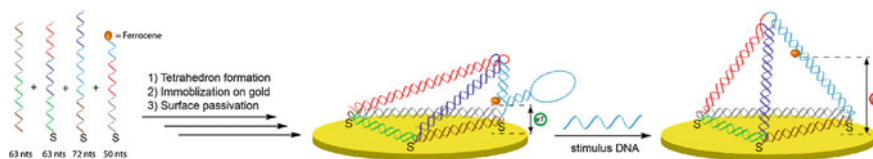


Fig. 2.11 Schematic representation of the gold-tethered DNA tetrahedron containing a reconfigurable edge with a stem-loop (hairpin) structure. Reconfiguration of the tetrahedron takes place after hybridization of complementary DNA (stimulus DNA) to the hairpin region, which results in the change of the distance between the Fc redox probe and the electrode surface and thus in the variation of the ferrocene (Fc) electrochemical signal. Mercapto-1-hexanol (MCH) molecules used to block the gold surface are not shown. Adapted with permission from Ref. [15]

Redox-switchable molecular grippers gain much attention in nanorobotics as they can grab a molecular cargo and translocate it over different location in functionally controlled manner. In this regards, resorcin [4] arene cavitands are known to have two spatial conformations, a contracted vase and an expanded kite, thus, they can act very well as molecular grippers. As an extension, the leg shapes can be used for functionalization and metal surface attachments. Pochorovski and Diederich applied naphthoquinone moiety as a redox-active wall component and cavitands with hydrogen bond acceptor groups as shown in Fig. 2.12 [16]. It was presented that carboxamide moieties can initiate redox-induced conformational switching and alter binding properties. With steric congestion, they found that association constant increased and guest release rates reduced when triptycene-quinone moiety was used instead of naphthoquinone. As the cavitands here were dependent on external proton sources for switching, further research is leading to independent switching.

Zhang et al. demonstrated a contact electrification field-effect transistor (CE-FET) with an external mechanical stimulation-induced charge transfer properties [17]. For this, authors used coupled metal oxide semiconductor field-effect transistor and triboelectric nanogenerator. The CE-FET shown greater sensing range and has a potential application for biomedical nanorobotics (Fig. 2.13).

Hemispherical microstructures of superparamagnetic polymer composite (SPMPCs) with programmed anisotropy was printed by Ergeneman et al. in large array with inkjet printer [18] (Fig. 2.14). With a favourable magnetic properties of embedded nanostructures and added functionality of polymers, SPMPCs can be successfully applied in microsystems construction and nanorobotics. Various operations can be performed using magnetic fields i.e. drug delivery, sensing specific physical and chemical signals. Superparamagnetic magnetite nanoparticles dispersed in SU-8 were used to make magnetic hemispheres. Magnetic field was applied during curing to programme magnetic anisotropy (Fig. 2.15). Authors demonstrated different assembly methods and their independent dynamic control. The fabricated units can be used as microelectromechanical systems and nanorobotic tools for various medical applications, and the magnetic microhemispheres can be easily manipulated at liquid interface.

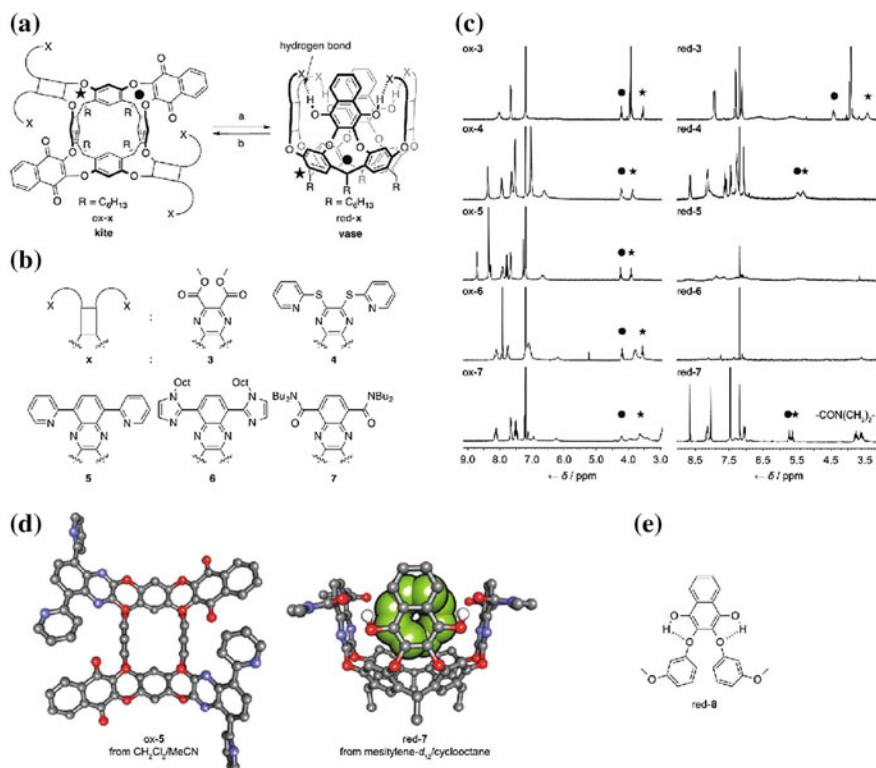


Fig. 2.12 a Parent quinoxaline-based cavitand that is switchable by changing temperature, pH, and Zn²⁺ ion concentration. Cavitands, whose binding properties can be modulated by changes in pH (b), by light (c), and by metal-ion complexation (d). Adapted with permission from Ref. [16]

Kopperger et al. demonstrated the diffusive transport system for molecular cargo, which was tethered to a DNA-based scaffold [19]. With a DNA origami technique, they made a rectangular platform with a molecular tether attached to a flexible hinge preventing diffusive loss of cargo as shown in (Fig. 2.16). AFM images of origami platforms were taken before and after molecule translocation. Authors showed that diffusive motion is much more efficient for easy and quick transfer over long distance.

Vach et al. explored various nanopropellor shapes which can be used in low Reynold number fluid for propulsion in media like biological fluids [20]. Researchers constructed magnetic propellers with a viable optimization strategy, thus getting a higher dimensionless speed than any other previously reported. They studied the correlation between the dimensionless speed and the pseudochirality, and also compared randomly shaped propellers from solution synthesis with previous nanofabricated propellers.

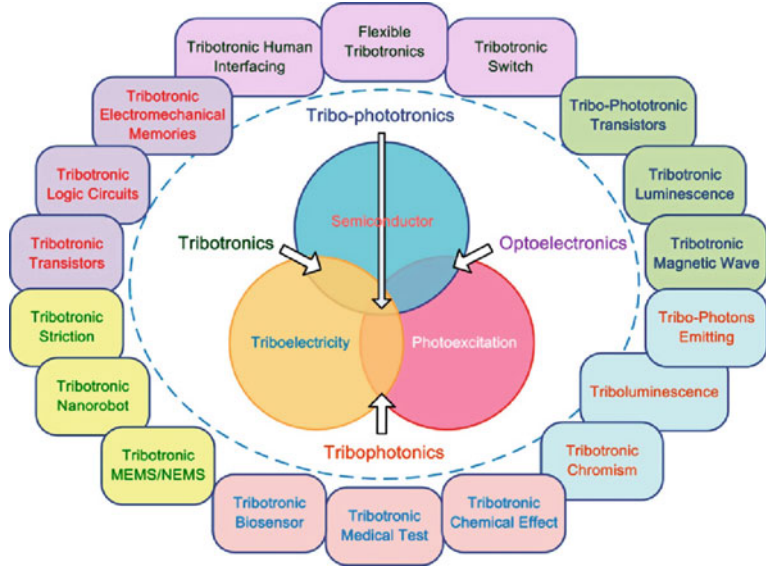


Fig. 2.13 Schematic diagram showing the three-way coupling among triboelectricity, semiconductor, and photoexcitation, which is the basis of tribotronics (triboelectricity semiconductor coupling), tribophotonics (triboelectricity photon excitation coupling), optoelectronics, and tribophotonics (triboelectricity semiconductor photoexcitation). Plenty of potentially important directions and applications are projected and expected to be explored in the near future. Adapted with permission from Ref. [17]

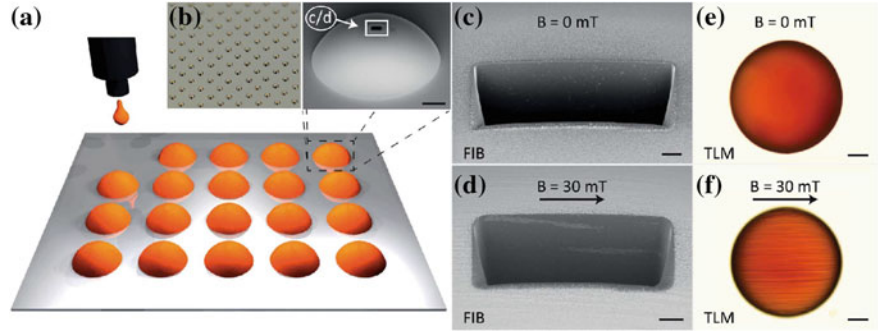


Fig. 2.14 The MPC hemispheres are fabricated by inkjet printing (a) (scale bar of the inlet is 50 mm). The photo of an array of MPC hemispheres is shown (b). The cross-sectional SEM image of the normal MPC (c) and anisotropic MPC (d) obtained by an FIB cut (scale bar is 2 mm). In a normal MPC (c) the nanoparticles are homogeneously distributed in the polymer matrix. In an MA MPC (d) the formed lines are approximately 2 mm apart from each other. The microscope image of the normal hemisphere is shown in (e) and the MA hemisphere in (f) (scale bar is 50 mm). The nanoparticles cannot be seen normally, but the lines of nanoparticles in the MA hemisphere can be seen easily by an optical microscope. Adapted with permission from Ref. [18]

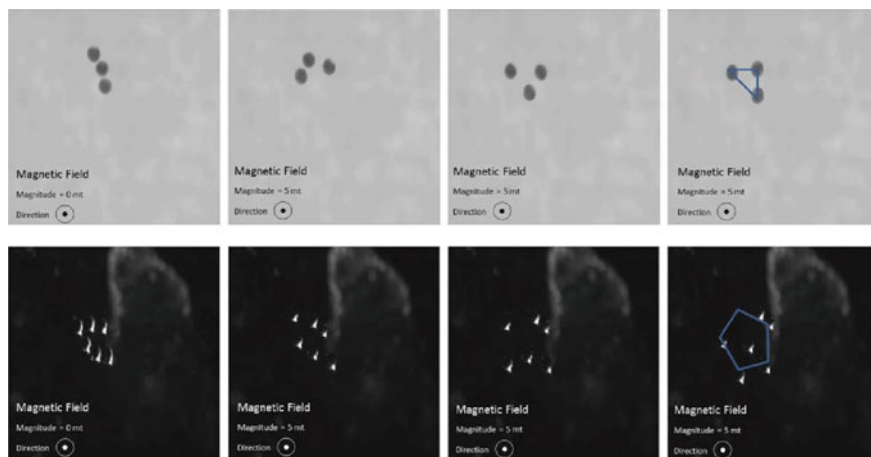


Fig. 2.15 By applying out-of-plane magnetic fields the samples can be magnetized out-of-plane. The dipoles repel each other as they are forced to stay at the interface. A triangle obtained by three samples and a tetragon obtained by five moving parts (4 individual and one couple acting as one). Adapted with permission from Ref. [18]

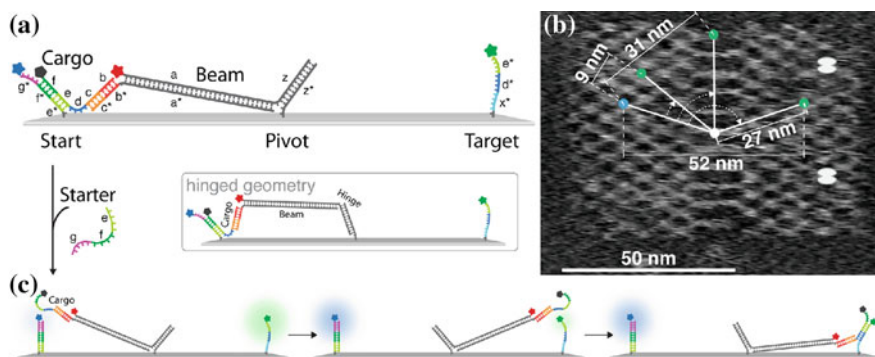


Fig. 2.16 **a** Schematic side view of a DNA origami platform with a rigid tether fixed in the center. The cargo (domains *b, c, d, e, f*) can hybridize to sequence domains at the start (*e*, f**) and a target (*d*, e**) position, as well as to a single stranded extension (*b*, c**) of the rigid tether. The inset shows an alternative binding orientation, which results in a more flexible, "hinged" structure. Complementary sequences are indicated by matching colors as well. All sequence domains have a length of 8 nt except for *ala** (88 nt) and *z/z** (21 nt). **b** Typical AFM image of the DNA origami rectangle, on which the start position (blue) and three different target positions are indicated. The position of two dumbbell hairpin loops (light gray) are also shown, which are placed asymmetrically to create height contrast for AFM imaging. **c** Mechanism of cargo transport and fluorescent labeling. The cargo DNA is functionalized with a Black Hole Quencher I molecule. Duplex formation with start or target strand reduces the fluorescence intensity of the Atto 488 dye (blue) and Atto 532 dye (green), respectively. An additional Atto 655 dye (red) used as a marker for gel electrophoresis experiments is permanently attached to the tether and is not affected by quenching. Upon addition of starter strand (domains *g, f, e*), the beam and cargo are released from the start site, unquenching the blue dye. Upon binding to the target site, the green dye is quenched. Adapted with permission from Ref. [19]

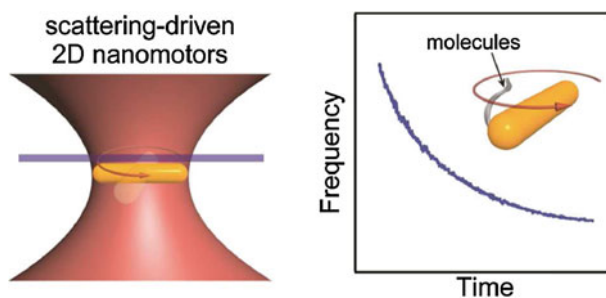


Fig. 2.17 Gold nanorod rotary motors driven by resonant light scattering. Adapted with permission from Ref. [21]

Shao et al. showed that single-crystal gold nanorods can be used as rotary motors in aqueous solutions driven by resonant scattering of polarized laser light [21]. Optical torque is used in this concept (Fig. 2.17). They experimented with rotation of gold nanorods in an optical trap. Against a glass surface, nanorods are trapped in 2D and their surface plasmon resonance property decides the rotational dynamics. CMOS camera was used to monitor rotational dynamics. This motor can be used for viscosity and molecular sensing. The molecular attachment part is highly useful for interaction measurement and conformational change for large bio-macro molecules and polymers.

Xu et al. showed the applications of plasmonically active rotary nanomotors for tunable release of multiplex biochemicals [22]. They showed the active tuning of biochemical releasing rate by rotating nanoparticles. The plasmonic nanomotors were made by assembling nanoparticles. Scanning electron microscopy (SEM) was used to confirm the successful making of the three-layered plasmonic rotors as shown in Fig. 2.18. Raman spectroscopy was used to study the chemistry and releasing rate of each chemicals. Confocal Raman microscope was used at 532 nm excitation with a step size of 250 nm. This confluence of surface enhanced Raman scattering and nanoelectromechanical systems can be easily used for various bio-applications through nanorobotics. They performed both experimentation and analytic modelling and single and demonstrated that multiple analytes can be released at the desirable rates just by controlling the rotation speeds of the nanomotors.

Jabbari et al. reviewed computational approach for complex 3D nanostructures with nucleic acid origami [23]. Through complementary base pairings, these RNA molecules can be designed to form 3D structures. As both, DNA and RNA origami are relatively new research topics in experimental research; there are various challenges and future direction to implement these as biomedical nanorobotic elements.

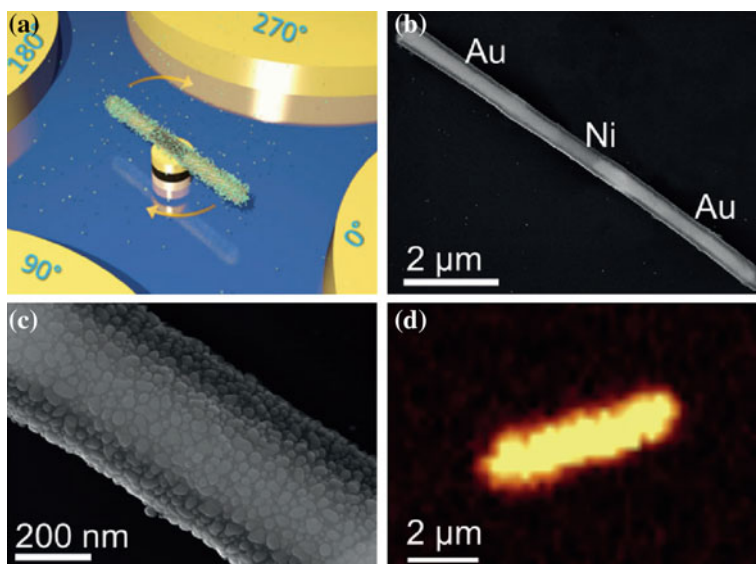


Fig. 2.18 **a** Representation of a rotating nanomotor sensor that releases molecules. **b** Scanning electron microscopy (SEM) images of a plasmonic nanorod for the nanomotor rotor made of a three-layer structure with a Au-Ni-Au nanowire as the core, a silica coating, and a dense layer of Ag nanoparticles on the outer surface of silica. **c** A higher-magnification SEM image shows the dense Ag nanoparticles grown on the silica. **d** Raman mapping of 1 mM R6G dispersed on a plasmonic nanomotor rotor showing essentially uniform SERS intensity on the surface. Adapted with permission from Ref. [22]

Vavassori et al. worked on magnetomechanical nanoactuation which can adopt its shape under remote magnetic external stimulus, and the system works without physical contacts [24]. The 3D magnetic nanostructures were made by focused electron-beam induced deposition (FEED) (Fig. 2.19) with various nanomedical applications.

Chechetka et al. demonstrated supramolecular nanotransporters which were magnetically and near-infrared light-powered and used for remotely controlling enzymatic reaction [25] (Fig. 2.20). It can be incorporated for precise analysis of biomolecular behaviours in cancer cells at the cellular level. The system was made with magnetic iron nanoparticles, liposomes, and carbon nanohorns, and was highly biocompatible with strong magnetic and photothermal properties. They demonstrated the concept by using a magnet and a NIR laser to release substrates in cells and mouse bodies from the structures at the desired location. This nanorobotic concept has a great potential in cancer treatment.

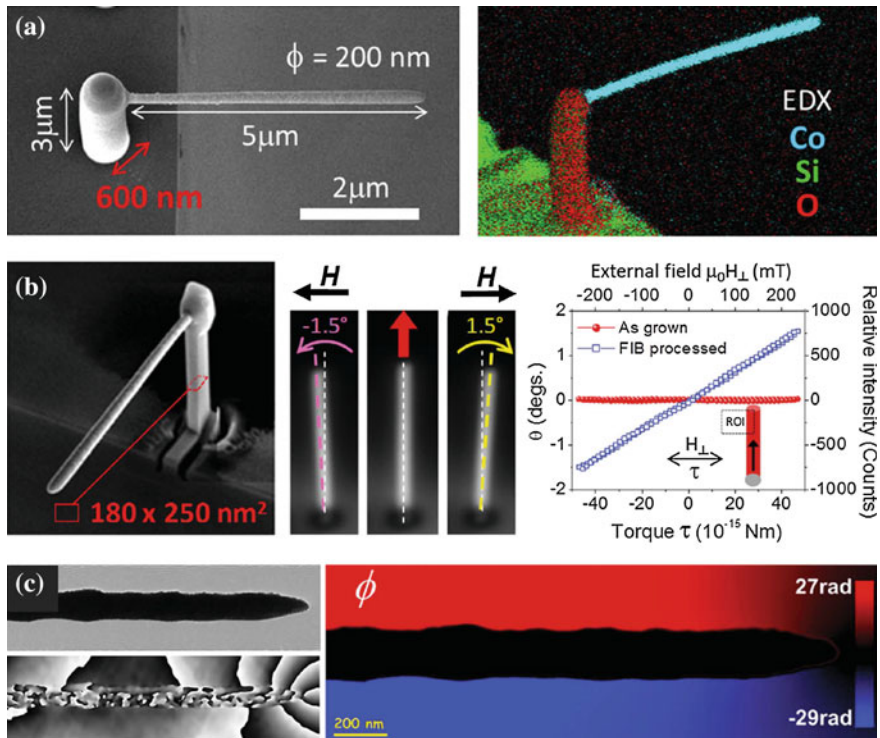
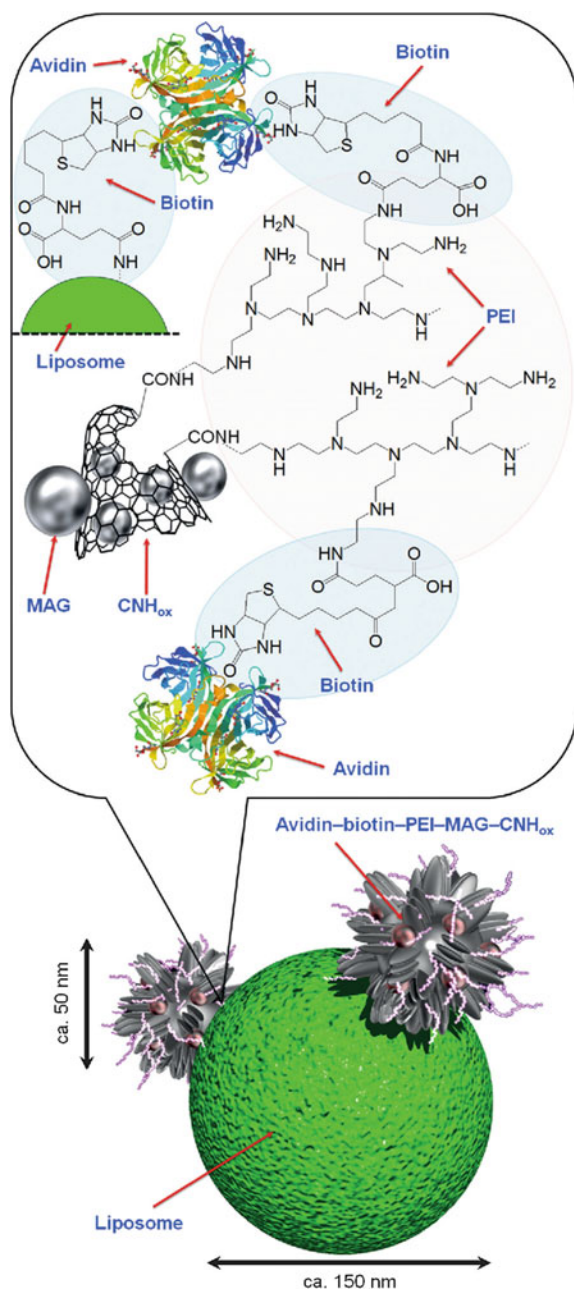


Fig. 2.19 Composite NAMMS cantilever device. **a** SEM image (left) and energy-dispersive X-ray analysis (EDX, right) showing the elemental mapping of the composite Co/SiO x NAMMS. **b** (left) same composite NAMMS device shown in panel (a) after having thinned the SiO x pole using FIB milling; (center) optical images of the field induced angular swing of the suspended Co nanorod in the FIB thinned composite NAMMS device; (right) plots of the field dependence of the angular swing of the original (red dots) and FIB thinned (blue open dots) composite NAMMS device. **c** Raw hologram (top-left panel) and raw phase image reconstructed from the hologram (bottom-left panel) of a magnetically saturated Co cantilever; the right-hand panel (c) displays the unwrapped 2D hologram phase map giving information on the phase difference used for determining the Co saturation magnetization value. Adapted with permission from Ref. [24]

2.5 AFM Based Nanorobotic Systems

Atomic force microscopy has been incorporated as a tool for nanoscale interactions. Li et al. worked with biological samples using a nanorobots system for in situ sensing and manipulations [26] demonstrating that AFM tip, as an end effector, can be used to manipulate objects at nanoscale as shown in Fig. 2.21. In this example, AFM tip was functionalized with specific antibodies, which can identify specific receptors of the cell membrane at high resolution. This method opened the path for studying biological systems at molecular level by conducting in situ imaging, manipulation and sensing at protein and DNA levels.

Fig. 2.20 Schematic illustration of the nanotransporters. Adapted with permission from Ref. [25]



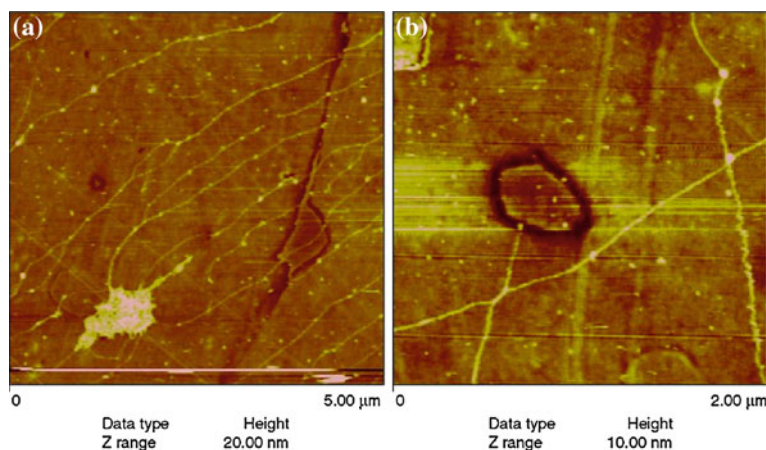


Fig. 2.21 AFM-based nanorobotic system, which includes an AFM system (nanorobot) and the augmented reality environment (visual haptic interface and command generator). Adapted with permission from Ref. [26]

Yang et al. worked with AFM-based nanorobotic manipulator to study biophysical dynamics and ion channel activities in insulinoma β -cells [27]. The nanorobotic platform together with optical observations provided fine dissection of ion channels mechano-property. This provided a novel biomechanical marker with an insight in insulin secretion process for insulin secretion process study.

Similarly, Acosta et al. presented an AFM platform for nanorobotics applications [28]. For manipulation system, protruding tip AFM cantilevers were incorporated in a dual tip system with one as protruding tip and other as quartz oscillator (Fig. 2.22). This settings allows modification of kinematical configurations. The system provided high speed imaging with dynamic force feedback together with efficient nanomanipulation. In comparison to classical AFM, five times faster imaging speed was obtained as the quartz oscillator performs sub-picometer range oscillation.

Chacko et al. developed a biological nanomanipulation system assisted with fast visualization using stimulated emission depletion (STED) superresolution microscope coupled to an AFM [29]. This specific configuration allows single-cell level nanosurgeries and manipulation of cellular structures. Authors carried out a cell manipulation as shown in Fig. 2.23 by testing microtubules labelled with Abberior Star 635P inside the cells of fixed fibroblast. AFM tip was used to probe the cell surface with live monitoring. STED and confocal image were applied for the resolution enhancement.

The summary of main navigation systems and potential nanorobotic agents for medical applications are presented in Tables 2.1 and 2.2, respectively.

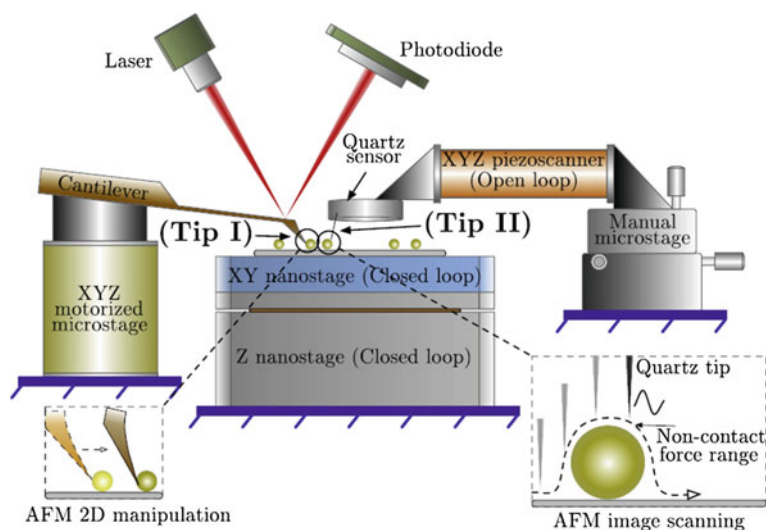


Fig. 2.22 System diagram for the new configuration of the two-tip system. The quartz is integrated into the system for true-non-contact-mode imaging. Adapted with permission from Ref. [28]

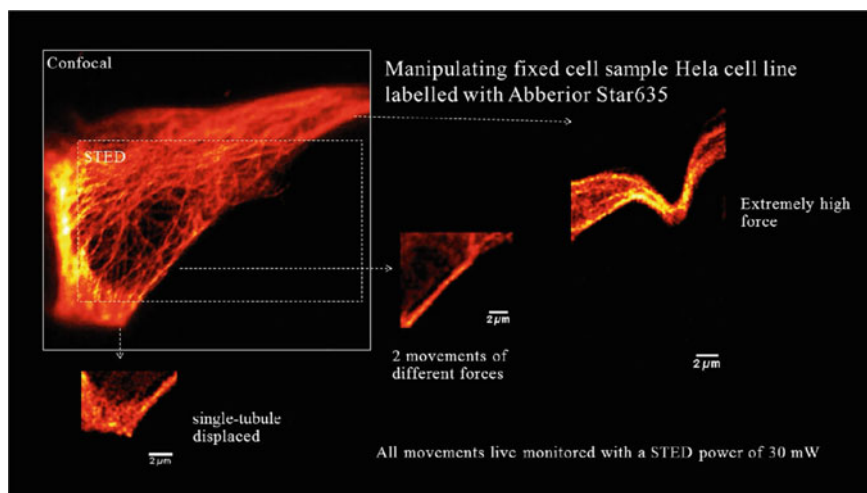


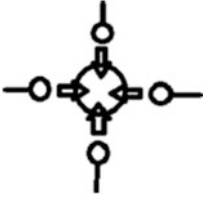
Fig. 2.23 Manipulation performed on a fixed cell: three different movement areas are recorded in this video segment. The confocal and STED images are shown to demonstrate resolution difference. The three different movements shown uses different forces. The still images were done at the lower most part of the cell, and the AFM interaction is recorded at a different height so that movement can be visualized. Adapted with permission from Ref. [29]

Table 2.1 List of main navigation platforms for nanorobotic agents

Technological platforms	Principle	Specifications	Physiological areas
<p>MRN</p> 	Exploits of the magnetic fields inside the tunnel of a clinical MRI scanner to navigate n a no robotic agents, the uniform B_0 field saturates the magnetic agents, while the imaging gradients induce 3D displacement forces on the nanorobotic agents	Highest magnetic field strength (1.5T–3T) to saturate all types of magnetic agents, fast but relatively low directional gradients (0.04T/m), provides real-time tracking of magnetic agents and physiological tissue imaging	Arteries, arterioles
<p>DFN</p> 	Distorts the uniform magnetic field inside the tunnel of a clinical MRI scanner to create high directional gradients	Highest magnetic field strength (1.5T–3T) to saturate all types of magnetic agents, high (0.3T/m) preset directional gradients	Arteries, arterioles
<p>FFN</p> 	Mechanically moves the patient typically in the fringe field surrounding a clinical MRI scanner	High magnetic field strengths possible (0.5T–1.5T) to increase the magnetization level of agents slow directional but very high (above 2T/m possible) gradients	Arteries, arterioles with no directional change preferred
<p>EMA</p> 	Electromagnetic directional fields generated by ratios of electrical currents passing in surrounding coils	Very low magnetic field strengths (approximately 0.1T) requiring larger magnetic volume per agent, fast and high (0.3T/m) directional gradients	Arteries and larger physiological areas
<p>MPI-based actuation</p> 	Displacement of the FFP (region of low field strength) by changing the ratios of electrical currents passing in surrounding coils	Relatively low field strength depending on the distance from the surrounding coils, fast and very high (max. 2T/m) directional gradients, provides realtime tracking of magnetic agents	Arteries, arterioles

(continued)

Table 2.1 (continued)

Technological platforms	Principle	Specifications	Physiological areas
<p>Magnetotaxis</p> 	Generation of a 3D zone (known as the aggregation zone) with directional fields generated by surrounding coils capable of directing and constraining the displacement of self-propelled magnetically guided (torque-based) agents in such a targeted zone	Typically above approximately 15 gauss outside the aggregation zone and towards zero inside the aggregation zone	Microvascular networks, interstitial and tumoral microenvironments, capillary vessels

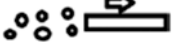
Adapted with permission from Ref. [30]

Table 2.2 Main types of potential medical nanorobotic agents

Medical nanorobotic agents	Description	Compatible platforms and specifications	Physiological areas
<p>TMMCs</p> 	Biodegradable polymeric micro-structures containing magnetic nanoparticles and therapeutic payloads	MRN, DFN, FFN, MPI—can be scaled down to approximately 50 μm in diam. (typ. around 150 μm for human interventions such as liver chemoembolization)	Arteries, arterioles
<p>MTB-based agents</p> 	Magnetotactic bacteria cells transporting payloads and being directed to the target site using magnetotaxis and aerotaxis	Magnetotaxis platform—1 to 2 μm in diameter allowing the cells to target tumoral regions, typ. 100–150 body lengths per second in good environmental conditions, MTB-LP carries approximately 70 drug-loaded 170 nm liposomes, chain of MNPs in each cell allows magnetic directional torque to be used, while an oxygen sensor	Microvascular networks, interstitial and tumoral microenvironments, capillary vessels

(continued)

Table 2.2 (continued)

Medical nanorobotic agents	Description	Compatible platforms and specifications	Physiological areas
		combined with the microaerophilic behavior of the MC-1 MTB allows the delivery of pay loads in hypoxic regions of tumors	
<div>Magnetic microcarriers</div> <div></div>	Special TMMCs capable of transporting typically MTB-based agents towards micro-vascular networks where MTBs are more effective	MRN, DFN, FFN, MPI initially followed by the magnetotaxis platform—Same dimensions as TMMCs with embedded super paramagnetic nanoparticles for the induction of a directional force and MRI-tracking, contains drug-loaded MTB-based agents instead of drug molecules alone to be released at a specific embolization site	All vascular network
<div>Magnetically steerable microorganism-propelled microstructures</div> <div></div>	Magnetic microstructure allowing a directional magnetic torque to be induced and being propelled by one or more microorganisms	Magnetotaxis platform—self propelled agent larger than MTB-based agent (typ. tens of micrometers ill diameter)	Typ. too large for capillary networks, interstitial spaces and tumoral micro-environments, no sufficient force for arteries
<div>Catalytic microjets</div> <div></div>	Chemically propelled agent capable of being directed through the induction of a magnetic torque	Magnetotaxis platform—present overall lengths in tens of micrometers, self-propelled agents that can be directed using a magnetic torque	Smaller arterioles, too large for capillaries, and not adequate for arteries

(continued)

Table 2.2 (continued)

Medical nanorobotic agents	Description	Compatible platforms and specifications	Physiological areas
Magnetic microrobotic agents 	Capable of high degrees of freedom but much larger than nanorobotic agents	EMA—agents rely on a larger magnetic induction volume in the order of a few tens of micrometers	Arteries and physiological areas allowing larger microrobotic agents
Helical micro- and nano-swimmers 	Biomimetic constructs typically in the form of artificial flagella actuated by a rotating magnetic field that induces a torque for directional displacement	Magnetic platforms capable of generating weak rotational magnetic field—a relatively weak rotating magnetic field is needed to achieve displacements of only a few body lengths per second	Smaller arterioles, not adequate for arteries and tumoral environments

Adapted with permission from Ref. [30]

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