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Nanorobotic Platforms for Precision Drug Delivery: Engineering Strategies, Mechanistic Insights, and Pathways Toward Clinical Translation

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ABSTRACT

Nanorobotic systems represent a rapidly evolving frontier in targeted drug delivery, offering unprecedented precision in therapeutic interventions. This review provides a comprehensive examination of nanorobotic design strategies, functional mechanisms, and their potential to revolutionize clinical practice. Pivotal engineering approaches, including biomimetic structures, stimuli-responsive actuation, and surface functionalization, are discussed in relation to enhancing drug targeting efficiency and minimizing systemic toxicity. Functional mechanisms such as autonomous navigation, controlled release, and site-specific accumulation are highlighted to demonstrate their translational relevance. Clinical applications across oncology, infectious diseases, and neurological disorders are critically analyzed, with emphasis on preclinical outcomes and early-stage trials. Finally, the review addresses translational challenges, including biocompatibility, large-scale manufacturing, regulatory hurdles, and ethical considerations. By integrating design principles with clinical perspectives, this work highlights the importance of nanorobotics in advancing precision medicine while identifying the barriers that must be overcome for successful clinical translation.

Keywords Nanorobots, Drug delivery systems, Nanomedicine, Precision medicine

INTRODUCTION

The evolution of drug delivery science has been intrinsically linked to the pursuit of precision in delivering therapeutic agents to the right site, at the right concentration, and at the right time while minimizing systemic exposure and adverse effects (1). Conventional drug delivery approaches, despite significant advancements in formulation science, often remain constrained by non-specific biodistribution, premature drug degradation, suboptimal intracellular uptake, and dose-limiting toxicities (2,3). These limitations are particularly pronounced in the treatment of complex and heterogeneous diseases such as cancer, chronic infections, and neurological disorders, where biological barriers, altered microenvironments, and cellular resistance mechanisms compromise therapeutic efficacy (4-6). In this context, nanotechnology has emerged as a transformative force, reshaping strategies for drug transport, targeting, and controlled release (7,8).

Nanomedicine initially gained momentum through the development of passive and active nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, and inorganic nano-systems designed to improve pharmacokinetic profiles and enhance tissue selectivity (9-11). While these systems marked a significant departure from traditional dosage forms, their performance remains largely dependent on physiological phenomena such as the enhanced permeability and retention effect or ligand-receptor interactions, which can vary considerably among patients and disease states. The inability of most nanocarriers to actively sense, navigate, and respond to dynamic biological environments has prompted the exploration of more intelligent and multifunctional delivery platforms. This need has catalyzed growing interest in nanorobotic systems, which represent an emerging paradigm at the intersection of nanotechnology, robotics, material science, and biomedicine (12-14).

Nanorobotic drug delivery systems are conceptualized as nanoscale or microscale devices capable of autonomous or semi-autonomous operation within biological environments. For scientific precision, however, these systems should be distinguished from conventional nanocarriers as differentiated according to their size, propulsion, degree of autonomy, and biological function, particularly because several reported robotic delivery platforms operate at the microscale rather than at the true nanoscale. Microbots generally operate at the microscale and employ engineered or biological components for active navigation, whereas true nanoscale

nanorobots remain largely conceptual and are envisioned to integrate sensing, processing, actuation, and therapeutic functions at the nanoscale. Bihybrid robotic systems represent another distinct category in which biological entities are incorporated for propulsion, sensing, or targeting. Unlike passive nanoparticles, nanorobots are engineered to integrate sensing, actuation, logic processing, and payload delivery within a single platform (15,16). These attributes confer the potential for real-time decision making, adaptive navigation, and site-specific therapeutic action. By mimicking aspects of biological machinery, such as chemotaxis, molecular recognition, and energy harvesting, nanorobots are envisioned to overcome biological barriers that limit conventional therapies, including vascular heterogeneity, immune clearance, enzymatic degradation, and restricted cellular penetration (17).

Design strategies for nanorobotic systems are central to their functional performance and clinical feasibility. Contemporary research demonstrates that nanorobot architectures increasingly draw inspiration from biomimetic principles, leveraging natural systems such as bacteria, spermatozoa, and cellular organelles to achieve efficient propulsion and navigation in viscous biological fluids (18,19). Helical structures, flagella-like appendages, and soft body configurations have been explored to facilitate controlled movement under external stimuli such as magnetic, acoustic, or optical fields. Complementing these physical design elements, surface functionalization plays a critical role in mediating biocompatibility, immune evasion, and target specificity. The incorporation of polymers, peptides, antibiotics, or cell-derived membranes enables nanorobots to interact selectively with diseased tissues while minimizing non-specific protein adsorption and phagocytic uptake (20).

Equally important are the stimuli-responsive mechanisms that govern nanorobot activation and drug release. Endogenous triggers, including pH gradients, enzymatic activity, redox potential, and hypoxia, are frequently exploited to ensure that therapeutic payloads are liberated only within pathological microenvironments. Exogenous stimuli, such as magnetic fields, ultrasound, near infrared light, or electric fields, provide an added layer of spatiotemporal control, allowing response modes within a single system, thereby highlighting the versatility of nanorobotic platforms and highlighting their potential to deliver combination therapies or sequential treatments tailored to disease progression (21,22).

Functional mechanisms underpinning nanorobotic drug delivery extend beyond passive targeting and controlled release. Autonomous navigation enables nanorobots to traverse complex vascular networks, localize disease-specific biochemical cues, and accumulate at target sites with enhanced precision. Some systems are designed to perform cooperative behaviours, such as swarm-like aggregation or collective cargo release, thereby amplifying therapeutic impact while reducing the required drug dose. Moreover, advances in nanoscale sensors allow nanorobots to monitor local physiological parameters, providing opportunities for theranostic applications that combine therapy with real-time diagnostic feedback. Such capabilities are particularly relevant in precision medicine, where individualized treatment strategies depend on continuous assessment of therapeutic response (23).

The translational relevance of nanorobotic systems is increasingly evident across a range of clinical domains. In oncology, nanorobots have demonstrated promising preclinical performance in achieving deep tumor penetration, improving intratumoral drug retention, and reducing off-target toxicity associated with conventional chemotherapy (24). In infectious diseases, nanorobotic platforms offer strategies to localize antimicrobial agents within biofilms or intracellular reservoirs, addressing important challenges related to drug resistance and recurrent infections (25). Neurological disorders present another compelling application, as nanorobots may be engineered to traverse or bypass the blood-brain barrier, enabling targeted delivery of neurotherapeutics that are otherwise excluded from the central nervous system. Although most clinical efforts remain in early translational stages, these proof-of-concept studies highlight the broad therapeutic potential of nanorobotics (26).

Despite these advances, the path towards clinical implementation of nanorobotic drug delivery systems is accompanied by substantial challenges. Biocompatibility and long-term safety remain paramount concerns, particularly given the complex interactions between nanorobots and biological systems at the molecular and cellular levels. Issues related to biodegradability, controlled clearance, and avoidance of unintended tissue accumulation must be rigorously addressed. From a manufacturing perspective, reproducible large-scale production of structurally complex nanorobots poses significant engineering and economic hurdles. Ensuring

batch-to-batch consistency, functional reliability, and quality control at the nanoscale remains an ongoing challenge for industrial translation.

Regulatory and ethical considerations further shape the trajectory of nanorobotic development. Existing regulatory frameworks for pharmaceuticals and medical devices are not fully equipped to evaluate hybrid systems that combine therapeutic, diagnostic, and robotic functionalities. Clear guidelines regarding safety assessment, clinical trial design, and post-marketing surveillance are essential to facilitate responsible advancement. Ethical discussions surrounding patient consent, long-term monitoring, and the potential misuse of autonomous nanosystems also warrant careful consideration as the field progresses (27).

A clear and balanced understanding of nanorobotic design principles, operational mechanisms, and clinical applicability is essential as this field continues to mature. Progress in nanorobotics depends not only on advances in materials science and engineering but also on meaningful integration with clinical insight and translational research. While current systems demonstrate remarkable promise in targeted drug delivery, their successful transition from laboratory prototypes to clinical tools will require coordinated efforts to address safety, manufacturability, regulatory evaluation, and ethical considerations. This review, therefore, brings together important developments in nanorobotic design and functionality, critically examines emerging therapeutic applications, and highlights the practical barriers that must be resolved to realize their full potential. By bridging engineering innovation with clinical needs, the nanorobotic drug delivery system may play a decisive role in shaping the next generation of precision medicine.

FUNCTIONAL GOALS OF NANOROBOTIC SYSTEMS (28,29)

Nanorobots are designed to achieve a wider range of biomedical tasks through their specialized structural and chemical properties. However, these functional goals encompass both capabilities demonstrated in experimental or preclinical settings and more advanced objectives that remain conceptual or theoretical. Distinguishing between these categories is essential for maintaining scientific precision.

Their intended functions include:

- Tailoring physicochemical features for diverse therapeutic applications.
- Utilizing large surface-to-volume ratios for controlled drug payload distribution.
- Enabling straightforward attachment of ligands or biomolecules for targeted delivery.
- Provide continuous physicochemical monitoring and feedback mechanisms. While basic sensing and stimulus-responsive functions have been investigated experimentally, comprehensive real-time physiological monitoring with adaptive feedback within a single autonomous platform remains a future objective.
- Modifying biological functions, repairing tissues, and clearing vascular or respiratory pathways. Such functions, particularly the autonomous mechanical clearing of biological pathways, remain largely proposed applications rather than established practices.
- Acting as sutonomous microsurgical agents within the human body. Autonomous microsurgery, including complex tissue repair or other highly sophisticated interventions, remains primarily a visionary or therotical goals and has not been established as a clinical capability.
- Maintaining smooth circulations within the biological system while transporting larger therapeutic loads than conventional molecules.
- Incorporating a propulsion system for precise navigation. Contemporary robotic systems have demonstrated active propulsion and externally controlled sttering using stimuli such as magnetic, acoustic, or optical fields; these experimentally demonstrated capabilities should be distinguished from fully autonomous navigation, which remains an emerging objective.
- Leveraging nanoscale dimensions to enhance binding and site specific accumulation.
- Detecting pathological conditions such as cancer at early stages.

From an engineering perspective, the physical and operational characteristics of nanorobotics systems must also be matched to the constraints of biological environments. Reported medical concepts generally consider

dimensions in the mocrometer range for circulation within biological systems, while nanoscale subcomponents may be incorporated for molecular level sensing and actuation. This distinction is important because several robotic drug delivery platforms operate at the microscale rather than at a true nanoscale.

Biocompatible interfaces are commonly designed using polymers, peptides, or cell-derived membranes to reduce immune recognition and nonspecific interactions. Although diamond coated external surfaces have been proposed as a theoretical strategy to reduce protein adsorption and immune detection, this approach remains speculative and requires further experimental validation.

Power and communication also remain important considerations. Theoretical models have proposed very low power requirements for highly advanced robotic concepts, while conceptual communication systems operating through carrier-wave frequencies have been proposed for external monitoring. However, such communication concepts have not been practically established for in-vivo operations.

Similarly, extended functional longevity and self-replication represent advanced theoretical objectives rather than established biomedical capabilities. Long-term stability in complex biological environments remains insufficiently demonstrated, while self-replication presents substantial safety, ethics, and regulatory concerns.

CHARACTERISTICS OF NANOROBOTS (30,31)

For optimal biomedical utility, nanorobots should demonstrate the following characteristics:

- Dimensions between 0.5-3 μm, with subcomponents as small as 10 nm. To facilitate clinical development, robotic platforms are categorized by their scale and functional architecture. It is important to note that while the term “nanorobotics” is often used broadly, many systems operate at the microscale (1-100+ μm) to ensure functional complexity and avoid the risk of obstructing capillary flow.
- Diamond coated exteriors to evade immune detection.
- Communication via carrier wave frequencies (1-100 MHz), converting encoded signals into acoustic outputs for physician monitoring.
- Self-replication remains laegely a theoretical construct, with early-stage explorations highlighting significant safety, ethical and regulatory challenges.

CATEGORIES OF ROBOTIC DELIVERY PLATFORMS

Microrobots and Biohybrids

Microrobots represent the most established category of active delivery agents. These systems can be classified as:

Biological/Biohybrid Robots: These leverage natural motility, such as magnetotactic bacteria guided by external magnetic fields to deliver drugs directly to diseased tissues.

Synthetic Microrobots: These rely on micro-electromechanical systems (MEMS) and include components like microgrippers for delicate cellular manipulation. Their movement is governed by kinematic modeling and external magnetic or chemical propulsion.

Specialized Medical Nanorobot Designs (Theoretical & Experimental)

The following platforms represent specialized designs tailored for specific physiological tasks. While some have demonstrated preclinical potential, others remain advanced conceptual models.

Pharmacytes: These are medical robots with a diameter of 1–2 μm and drug reservoirs of 1–3 μm. They are designed to use chemotactic sensors for precise targeting and derive energy from glucose and oxygen in biological fluids.

Respirocytes: Conceptualized as artificial red blood cells (0.2–2 µm), these devices utilize rotors to control gas exchange. While conceptual models suggest significantly enhanced oxygen-carrying capacity compared to natural red blood cells, these performances await experimental validation.

Microbivores: Spheroidal nanorobots (2 µm x 3.4 µm) designed to digest pathogens with a phagocytic efficiency greater than natural macrophages. They are modeled to operate at a low power level of 200 pW.

Clottocytes: Designed as artificial platelets (~2 µm), these agents adhere to vascular injury sites to accelerate coagulation and initiate rapid haemostasis.

Chromallocytes: A purely visionary category of diamondoid nanorobots intended for genetic repair and cellular rejuvenation.

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POTENTIAL BENEFITS OF NANOROBOTIC APPLICATIONS (32)

Nanorobots offer several advantages in clinical practice:

- High durability and rapid operational efficiency.
- Reduction of off-target drug effects by maintaining therapeutic inactivity outside target zones.
- Minimally invasive intervention requiring limited aftercare.
- An extended functional lifespan has been theoretically proposed, although long-term stability remains to be validated in experimental and clinical settings.
- Effective eradication of pathogens before systemic spread.
-

LIMITATIONS AND RISKS OF NANOBOTS (33)

Despite being promising candidates, nanobots present notable challenges:

- Risk of aggregation when multiple types are introduced simultaneously.
- High production and installation costs.
- Variability in design and function may lead to unpredictable or harmful outcomes.
- Foreign nanorobots may cause damage similar to pathogenic microorganisms.
- Self-replication could generate hazardous variants.
- Restricted ability to communicate directly with biological systems.
-

CATEGORIES OF NANOROBOTIC DEVICES

- **Microbots (34-36)**

  Microbots are emerging as powerful tools in precision medicine, designed to perform tasks that go far beyond conventional drug delivery. Microbots represent the most established category of active delivery agents. These tiny machines can actively transport therapeutic agents, manipulate cells, assemble microstructures, and even act as biosensors within the human body. A notable example is the use of magnetotactic bacteria, which can be guided by magnetic fields to deliver drugs directly to diseased tissue, showcasing how natural motility can be harnessed for medical purposes. These systems can be classified as biological/biohybrid robots, which leverage natural motility, such as magnetotactic bacteria guided by external magnetic fields to deliver drugs directly to diseased tissues. In contrast, synthetic microrobots rely on engineered systems such as micro-electromechanical devices (MEMS), which provide components like microgrippers for delicate operation at microscopic scales. Their movement is governed by kinematic

modelling and external magnetic or chemical propulsion. Their movement is carefully controlled through kinematic modelling and motion planning, ensuring they reach precise targets safely. Microrobots can be biological, exploiting natural sensing and propulsion, or non-biological, using magnetic or chemical mechanisms for navigation. What makes them particularly exciting is their multi-functionality. They can diagnose, treat, and monitor simultaneously, offering a minimally invasive and highly responsive approach to healthcare. **Figure 1** gives an illustration of microbots.

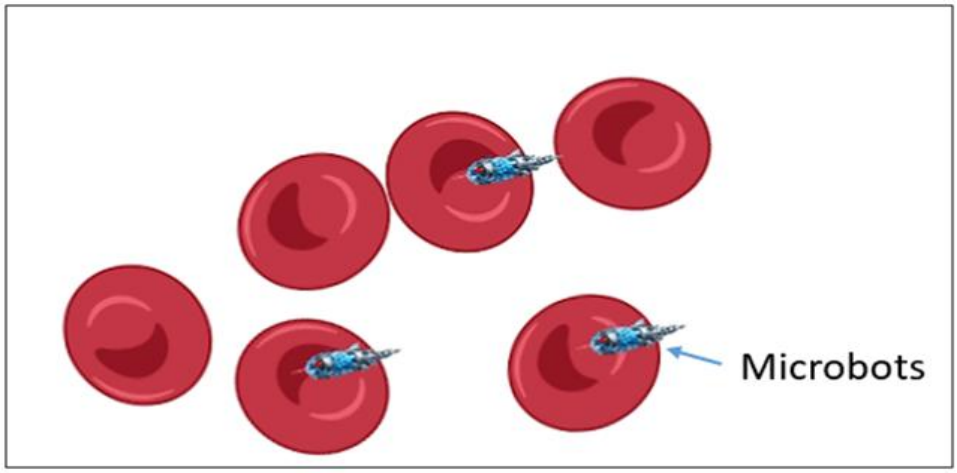

Figure 1 Illustrative image of fictional microbots

- **Pharmacytes (37, 38)**

The following platforms represent specialized designs tailored for specific physiological tasks. While some have demonstrated preclinical potential, others remain advanced conceptual models. Pharmacytes are medical nanorobots with a diameter of 1-2µm and drug reservoirs of 1-3µm. They are designed to use chemotactic sensors for precise targeting and derive energy from glucose and oxygen in biological fluids. They employ mechanical systems to regulate pumps and utilize chemotactic sensors or molecular markers for precise targeting. Energy is derived from glucose and oxygen within biological fluids. Post-treatment, they can be retrieved through centrifuge nanopheresis.

- **Diagnostic microchips (39)**

Nanorobots equipped with microchips interact with biomolecules to detect disease markers. Upon recognition, the chip transmits electrical impulses, enabling diagnostic functions such as blood sugar monitoring. These devices are advantageous due to ease of use and low operational cost, and they are also applied in vascular imaging.

- **Respirocytes (40)**

Respirocytes are artificial red blood cells with diameters ranging from 0.2-2 µm. They contain chambers for oxygen, carbon dioxide, and buoyancy regulation. Rotors control gas exchange and glucose intake, providing energy for function. Compared to natural RBCs, respirocytes have been reported in conceptual models to exhibit significantly enhanced oxygen carrying capacity compared to natural red blood cells; however, such performances remain to be validated experimentally.

- **Microbivores (41,42)**

Microbivores are spheroidal nanorobots (2 µm x 3.4 µm) designed to digest pathogens. They are modelled to operate at lower power levels. Operating at 200 pW, they exhibit phagocytic efficiency significantly greater than macrophages, making them highly effective in microbial clearance.

- **Clottocytes (43,44)**

  Clottocytes function as artificial platelets, approximately 2 µm in size. They adhere to vascular injury sites and initiate rapid haemostasis, mimicking natural platelet activity while accelerating coagulation. These agents adhere to vascular injury site to accelerate coagulation and initiate rapid haemostasis.

- **Chromallocytes (45)**

  Chromallocytes are conceptual nanorobots designed for genetic repair. A purely visionary category of diamondoid nanorobots intended for genetic repair and cellular rejuvenation. They can replace entire chromosomes to correct genetic abnormalities and potentially reverse cellular aging. These diamondoid repair machines assess cellular structure and function at the molecular level, enabling comprehensive cellular rejuvenation.

COMPARISON OF REPRESENTATIVE SYSTEMS

To bridge engineering design with clinical utility the following table provides a detained analysis of representative micro-and nanorobotics systems. It highlights the gap between current preclinical success in animal models and the visionary goals that remain in the conceptual phase.

Table 1: Expanded comparison of nanorobotics and microrobotic delivery platforms.

System	Dimensions	Materials	Propulsion	Targeting strategy	Payload	Disease/ experimental model	Outcome	Translational stage
Magnetotactic bacteria	Microscale	Biohybrids	Magnetic field/ Natural motility	External magnetic guidance to tissue	Therapeutic drugs	Oncology/ animal models	Increased retention	Preclinical
Helical swimmers	Micro/Nano	Synthetic / Helical structure	External Magnetic Fields	Precise 3D steering via magnetic torque	Chemotherapeutics (implied)	Solid tumors / Animal models	Enhanced deep tumor penetration vs. free drug	Preclinical
Pharmacytes	1–2 µm	Mechanical/ Chemotactic sensor	Internal Glucose & Oxygen	Chemotactic sensors / Molecular markers	Targeted drug reservoirs	General targeted therapy	Theoretical high-precision molecular targeting	Conceptual
Respirocytes	0.2–2 µm	Artificial Cell	Glucose-driven rotors	Passive circulation / Gas exchange rotors	Oxygen and Carbon Dioxide	Respiratory/Cardiovascular insufficiency	Conceptually enhanced O_2 capacity vs. natural RBCs	Conceptual
Microbivores	2 x 3.4 µm	Spheroidal / Synthetic	Phagocytic (200 pW power)	Active sequestration/ digestion	Localized antimicrobial release	Infectious diseases / Biofilms	Modeled phagocytic efficiency > natural macrophages	Conceptual
Clottocytes	~2 µm	Artificial Platelet	Adhesion-based	Adhesion to vascular injury sites	Mechanical adhesion molecules	Vascular injury / Haemorrhage	Theoretical acceleration of coagulation/haemostasis	Conceptual
Chromallocytes	Microscale	Diamondoid (Conceptual)	Molecular logic	Molecular level cellular assessment	Replacement chromosomes	Genetic abnormalities / Aging	Visionary correction of genetic defects	Visionary

RECENT ADVANCES IN THE DEVELOPMENT AND CAPABILITIES OF NANOROBOTS

- **System architecture:** modular, responsive, and clinic-aware nanorobots

Contemporary nanorobotic platforms combine sensing, logic/ control, actuation/power, and therapeutic reservoirs beneath a purpose-built surface interface. Sensors detect biochemical/physical cues (e.g., pH, redox, enzymes, hypoxia), logic modules implement simple feedback, actuators enable field or fuel – driven motion, and reservoirs provide stimuli-gated release (46). Surface engineering, polymer brushes, ligand displays, or biomembrane cloaks balance stealth with target recognition, echoing long-standing concepts of ultra-smooth, inert exteriors to reduce protein adsorption and leucocyte activation (47). **Figure 2** gives an illustrative systems view of a nanorobot for drug delivery.

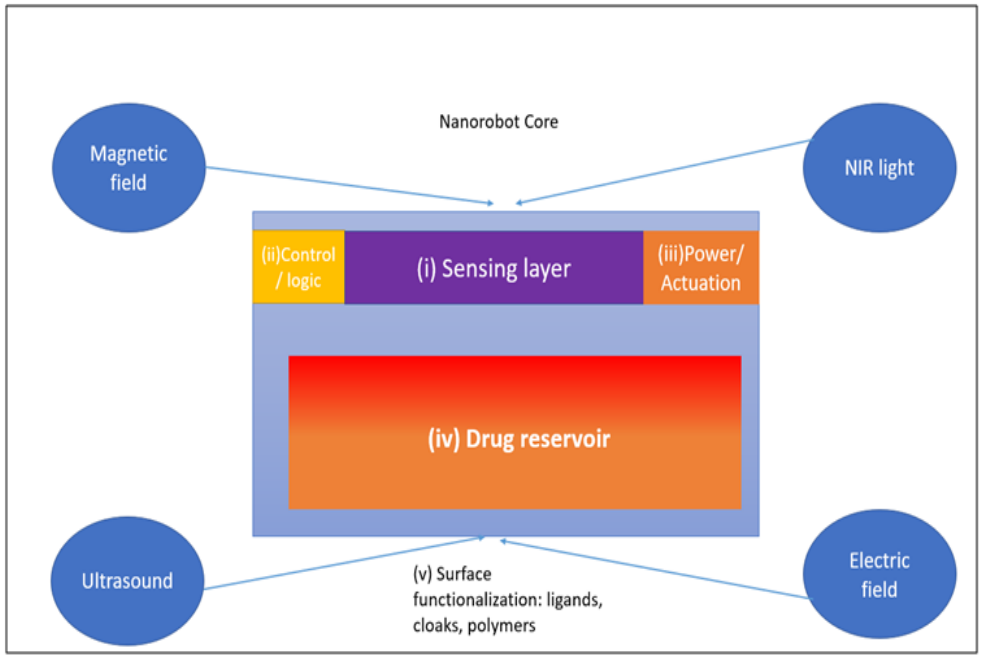

Figure 2. Systems view of a nanorobot for drug delivery The schematic shows (I) sensing layer, (ii) Control/Logic, (iii) Power/Actuation, (iv) Drug Reservoir, (v) Surface functionalization, and typical external control channels (magnetic, ultrasound, NIR, electric)

- **Propulsion and navigation:** exogenous steering v/s endogenous autonomy (48,49)

Magnetic fields provide deep, safe tissue penetration and support precise 3D steering (e.g., rotating helical swimmers), with MRI often leveraged for localization. Ultrasound offers penetration, real-time imaging, and focal energy deposition for both manipulation and release. Optical (NIR) triggers deliver high spatiotemporal precision where optical access exists (direct or fiber-guided), while electric fields drive electrophoretic/ electro-osmotic motion and rapid valve actuation in confined spaces. Endogenous chemical/ enzymatic strategies (pH/redox/enzymes, benign fuels like glucose/urea) enable autonomy or dual-gated release, though many translational designs pair endogenous gating with magnetic positioning for controllability. **Table 2** gives a brief idea about actuation mode versus clinical constraints and practical considerations (50,51).

Table 2. Actuation mode versus clinical constraints and practical considerations

Actuation/ trigger	Tissue penetration and imaging compatibility	Steering and addressability	Typical release pairings	Safety/risk notes	Applications
Magnetic fields	Excellent penetration; compatible with MRI tracking/ localization.	Precise 3D steering of helicals/ rotating swimmers; swarm guidance feasible.	Magnetothermal gating; valve opening; can combine with enzyme/ pH patterns.	Safe within clinical ranges; monitor heating with ferromagnetic loads.	Deep tumor targeting; endovascular navigation.
Ultrasound	Deep penetration; real-time clinical imaging; focal energy deposition.	Directional pushing and manipulation, often combined with magnetic steering.	Cavitation-mediated shell rupture: hyperthermia-assisted depot release.	High intensities can trigger oxidative stress; careful dosimetry is needed.	Solid tumors; thrombotic interfaces; IR suites.
Optical (NIR/visible)	NIR penetrates mm-cm; fibre delivery extends reach; sensitive readouts.	High precision where optical access exists (superficial/endoscopic)	Photothermal melt/ photocleavage; classic gold-nanoshell release.	UV unsafe; NIR safer but requires thermal monitoring.	Dermato-oncology; GI endoscopy, surgical beds
Electric field	Limited deep penetration; useful in confined volumes or combined modes.	Rapid responses; electrophoretic/electro-osmotic motion; nanomotor rotation.	Electro-gated pores/ valves; precise pick-and-release mechanism.	Higher fields may irritate tissue, metallic content needs assessment.	Intraluminal/local chambers; feasibility pilots.
Endogenous chemical/ enzymatic	No external penetration; exploits pH/redox/enzymes; imaging via MRI/US/optical labels.	Autonomy is possible, often paired with magnetic positioning.	pH-labile linkers; protease gates; redox shells; glucose/urea as benign fuels.	Avoid toxic fuels (e.g., H_2O_2); validate off-target activation risk.	Hypoxic tumors, infected/ acidic niches; GI segments with distinct enzymes.

- **Sensing and decision-making in vivo (52)**

Moving beyond classical ligand targeting, functional targeting combines multiple microenvironmental cues: acidity, hypoxia, proteases, and redox to improve specificity in heterogeneous lesions, and to arm/ trigger payloads only when a composite "disease signature" is recognized.

- **Surface-immune interface (53,54)**

A biocompatible surface limits opsonization and leukocyte activation. Strategies range from inert smooth chemistries (Historically discussed for medical nanobots) to polymer brushes and cell-membrane cloaks;

several concepts include “end-of-mission” unmasking to deliberately enable immune clearance once therapy ends.

- **Payload engineering and release logic (55)**

Endogenous triggers(pH, enzymes, redox) and exogenous triggers (magneto-thermal, ultrasound cavitation, NIR photothermal) underpin on-demand pulses. Early nanoshell-hydrogel concepts established remote release via NIR; nanorobots extend this with navigation and multi-pulse/ clinician-timed dosing at the disease site.

EMERGING THERAPEUTIC APPLICATIONS

- **Oncology (56)**

Magnetically or acoustically guided micro/nanorobots have improved intratumoral retention and on-demand release in animal models compared to free drug or passive carriers. The same platform allows sequential regimens, e.g., microenvironment priming (hyperthermia/ enzymes) followed by cytotoxic dosing and can be integrated with MRI/ultrasound guidance.

- **Infectious disease and biofilms (57)**

Robots that combine mechanical penetration with localised antimicrobial release can tackle biofilms and

intracellular reservoirs, potentially shortening therapy and lowering resistance selection pressure; visionary “microbivore” concepts further illustrate active sequestration/digestion as a long-term direction.

- **Neurology (BBB negotiation) (58)**

Strategies include magnetic navigation with transient BBB modulation, enzymatic triggers for selective opening, or fiber-guided delivery for precise micro-dosed therapy, each leveraging navigation and localized release to access otherwise excluded neurotherapeutics.

- **Cardiovascular/renal/dental micro-interventions**

Concept and preclinical reports showcase plaque modulation, micro-thrombus management, renal adjunct micro-filtration, and dental microsurgery, use cases where minimally invasive on-site action, such as controllable pulses, are advantageous.

- **Theranostics and adaptive dosing (59)**

By embedding sensors, nanorobots can measure-then-treat, checking local hypoxia/pH before dosing to personalize release timing and magnitude within a single procedure.

PRACTICAL BARRIERS THAT MUST BE ADDRESSED

- **Safety and biocompatibility**

Major concerns include immunogenicity, protein corona formation, off-target accumulation, and device lifecycle (biodegradation, retrieval, and immune hand-off). Designs proposing stealth layers that can be shed post-therapy must be validated in toxicology and biodistribution studies with clear “off-switches”. The introduction of foreign robotic systems into the human body presents unique toxicological challenges. (60,61).

a. Immunogenicity and Opsonization: Nanorobots are susceptible to protein corona formation, where biological molecules adsorb onto the device surface, potentially triggering leukocyte activation or rapid immune clearance.

b. Pathogenic mimicry: A major concern is that foreign robotic agents may inadvertently cause tissue damage or inflammatory responses similar to pathogenic microorganisms.
c. Device lifecycle: Clear "off-switches" and "end of mission" protocols are required to manage biodegradation, retrival, or immune mediated clearance to prevent unintended long term tissue accumulation.

- **Manufacturing and quality control (62)**

Hybrid constructs (polymers, metals, biosourced elements) require tight metrology for size, morphology, surface chemistry, and field responses. Translation demands repeatable, large-batch fabrication and functional release testing under GMP-like workflows, even for academic prototypes.

- **Navigation, localization, and clinical infrastructure (63)**

Clinical deployment needs reliable in-vivo tracking (MRI, ultrasound, X-ray fluoroscopy, optical) and standardized actuation protocols with dose-of-energy limits, plus workflow-friendly controllers (magnet arrays, US transducers, light fibres)

- **Regulatory and trial design**

As combination products, nanorobots must satisfy both device and drug standards, device reliability, software/controls safety, PK/PD, and human-factors performance. Early trials should include imaging-visible endpoints (targeting accuracy, dwell time, trigger fidelity) alongside safety and pharmacokinetics to build regulatory confidence (64,65).

a. **Regulatory framework:** there is a need for standerdized protocols for safety assessment, pharmacokinetics (PK), and pharmacodynamics (PD) specifically for hybrid autonomous systems.
b. **Clinical infrastructure:** Successful deployment depends on compatibility with existing hospital infrastructure, such as MRI, ultrasound, and X-ray fluoroscopy, for real-time tracking and navigation (63).

- **Ethics and Patient Consent**

Autonomy at the microscale raises questions of traceability, failsafe recovery, and data governance. Clear patient information, real-time actuation logs, and post-deployment registries can support trust and oversight.

BRIDGING ENGINEERING INNOVATION WITH CLINICAL NEEDS

- **Co-design and indication-first development**

Prioritize indications where field access and imaging are already routine (e.g., interventional oncology, MRI-visible tumours). Co-design narrows device geometries, field strengths, and session times to parameters that clinicians can operate reliably.

- **Clinically meaningful endpoints**

Clinically meaningful evaluation requires a direct connection between controllable engineering parameters and observable therapeutic outcomes. For example, the duration and pattern of externally applied guiding fields influence how long the nanorobotic system remain localized at diseased sites, thereby affecting tissue exposure time. Similarly, the intensity of externally applied trigger signals governs the extent of drug release, enabling controlled and adjustable dosing at the target location. Surface chemistry plays an equally critical role by determining device interactions with biological components, which in turn influences unintended accumulation and systemic exposure (66,67). To ensure translation relevance, studies should report drug concentration achieved within target tissues, the duration for which therapeutic levels are maintained, the total procedure time required for device operation, and patient-reported outcomes related to comfort, safety, and recovery. Evaluation should focus on observable outcomes, such as drug concentration achieved within target tissue, the duration for which therapeutic levels are maintained, and total procedure time.

- **Human factors and workflows**

From the translational perspective, the design of nanorobotic control systems must explicitly account for human factors and clinical workflow constraints. External controllers should be intuitive and allow rapid system preparation to avoid disruption of routine clinical procedures. Real- time feedback mechanisms are essential to enable closed-loop operation, ensuring that navigation, actuation, and drug release automatically adapt to changing physiological conditions and halt safely if predefined limits are exceeded (68-70). Seamless integration with established medical imaging modalities is necessary to provide clinicians with continuous visual confirmation of device position and therapeutic action. In addition, clearly defined abort criteria must be incorporated, allowing immediate termination of the procedure in response to safety concerns (71). Collectively, these requirements ensure that the nanorobotic system aligns with established interventional practices and can be adopted within existing clinical infrastructure. Control systems must be intuitive for clinicians to operate without disrupting routine workflows. Safety interlocks and abort criteria require real-time feedback mechanisms and clearly defined abort criteria that allow immediate termination of the procedure if safety limits are exceeded.

FUTURE PERSPECTIVE

In the coming years, the clinical translation of nanorobotic drug delivery systems is expected to progress through increasingly pragmatic and infrastructure – compatible designs, with early adoption driven by hybrid control strategies that combine external magnetic steering with stimuli-responsive release mechanisms. Such micro-and nanoswimmers are likely to deliver short, clinician times therapeutic pulses directly to imaged lesions, including solid tumours, vascular abnormalities, and localized infections, while operating seamlessly within existing hospital environments such as MRI, ultrasound, and fluoroscopy suites. As the field matures, second-generation platforms are anticipated to move beyond single-cue responsiveness toward richer, multi-analyte sensing capabilities, integrating parameters such as pH, enzymatic activity, and hypoxia to enable context-aware decision -making. When coupled with cooperative or swarm-based behaviours, these systems could perform distributed microenvironmental mapping followed by synchronized drug release, allowing combination therapies to be administered within a single interventional session rather than through repeated systemic dosing. Parallel to these advances, increasing regulatory scrutiny will drive the standardization of device lifecycle management, leading to clearer design consensus around biodegradation timelines, magnetic retrieval strategies, and immune-mediated clearance pathways, thereby addressing long-standing concerns regarding long-term in-vivo residency. From a translational standpoint, scalable manufacturing will become the central focus, with the emergence of community-accepted fabrication playbooks and quality assurance metrics, including standardized panels for size, morphology, surface chemistry, field responsiveness, and reproducible release performance, to ensure consistency across laboratories and production sites. Ultimately, these technological and regulatory convergences are expected to support routine theranostic workflows in which nanorobots first interrogate local disease microenvironments and subsequently deliver tailored therapeutic doses in an adaptive, feedback-driven manner. Such measure-then-treat paradigms hold particular promise for oncology and infection management in day-care and interventional settings, making a shift from static dosing regimens toward truly responsive precision-guided therapy.

CONCLUSION

Nanorobotic drug delivery has advanced from largely conceptual constructs to increasingly credible, mechanism-driven systems capable of sensing, navigation, and site-specific therapeutic release. By combining field-based steering with stimuli-responsive activation, these platforms directly address persistent limitations for conventional nanocarriers, including non-specific biodistribution, inadequate tissue penetration, and systemic toxicity. As demonstrated across applications in oncology, infectious diseases, and neurobiological targeting, nanorobotic systems offer a versatile framework for precise and localized intervention. However, their successful clinical translation will depend on addressing important challenges related to biocompatibility, scalable manufacturing, real-time tracking, and regulatory evaluation of drug-device combination products. Importantly, these challenges are increasingly manageable through interdisciplinary do-design approaches that align engineering innovation with established clinical workflows and imaging infrastructure. With appropriate

indication selection, robust safety and lifecycle controls, and clinically meaningful performance metrics, nanorobotic drug delivery systems are well-positioned to transition from experimental platforms to practical clinical tools, supporting the broader goal of adaptive, patient-specific precision medicine.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

AUTHOR CONTRIBUTION

PSP conceptualized the study, performed the literature review, analyzed the data, and drafted the manuscript. PSP also contributed to the design, structure and final editing of the article.

Dr. NGH provided overall supervision, guidance, and critical review of the manuscript. Dr. NGH also contributed to refining the intellectual content and approved the final version for publication.

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