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Review

Active motion in micro/nanorobotic drug delivery: Evidence, causal attribution, and translational design

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Abstract

Biomedical micro- and nanorobotic systems combine active propulsion, external actuation, navigation, and multifunctional drug-delivery functions; some, but not all, use compliant, deformable, or biohybrid architectures. This critical review evaluates when active motion provides a measurable delivery advantage and when reported improvements cannot be separated from targeting, barrier modification, stimulus-responsive release, or other auxiliary functions. Evidence is examined across distinct dimensions: propulsion and cargo transport, navigation and localization, biological-barrier interaction or crossing, quantitative active-versus-passive performance, and therapeutic outcome. A proposed E0-E5 endpoint classification is complemented by separate assessments of causal confidence and data quality, with particular emphasis on appropriately matched passive or non-motile controls. The analysis considers magnetic, acoustic, optical, chemical, thermophoretic, and biohybrid propulsion and highlights design features relevant to biomedical robotics, including deformability, adaptive locomotion, wireless control, multifunctional integration, and

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translation to complex biological environments. The evidence indicates that active motion can improve transport and penetration under selected biological constraints, but propulsion-specific causality is often difficult to establish in multifunctional systems. The review therefore proposes a framework in which the value of active motion is judged against the transport bottleneck, comparator quality, mechanistic controls, and linkage between transport and therapeutic outcome.

Keywords: Soft micro/nanorobots, active drug delivery, wireless actuation, biohybrid robotics, biological barriers, causal attribution

INTRODUCTION

Conventional drug delivery systems predominantly rely on passive transport mechanisms, in which therapeutic carriers are distributed through physiological circulation and subsequently reach diseased tissues by diffusion, convection, or other transport processes. Although passive nanocarriers have substantially advanced targeted and controlled drug delivery, their transport is strongly constrained by physiological barriers, heterogeneous tissue architecture, limited vascular extravasation, rapid clearance, and insufficient penetration into dense pathological tissues. These limitations become particularly pronounced when therapeutic cargo must traverse mucus, vascular endothelium, extracellular matrix, tumor stroma, cellular membranes, or other biological barriers before reaching its intended intracellular or tissue-level target.

Micro- and nanorobotic systems have emerged as an alternative strategy in which mechanical motion is introduced as an additional transport mechanism. These systems can convert chemical energy or externally applied physical fields into propulsion and, depending on their design, can actively transport therapeutic cargo through complex biological environments. Reported actuation and propulsion strategies include magnetic and acoustic fields, light-driven and thermally mediated mechanisms, chemical or enzymatic propulsion, and biohybrid locomotion; these approaches can be integrated with compliant or deformable architectures for biomedical operation[1-8]. Such active mobility has been

investigated for targeted drug delivery, tissue penetration, biological-barrier crossing, and localized therapeutic intervention.

The conceptual advantage of active transport is straightforward: rather than relying exclusively on the stochastic distribution of a carrier, propulsion may generate directed or enhanced motion relative to the surrounding biological environment. In principle, this additional mechanical component could increase residence at a target site, improve penetration into poorly accessible tissues, facilitate transport against physiological flows, and enhance interactions with biological barriers. Experimental studies have consequently reported improved penetration or delivery in environments such as tumor tissue, mucus, vascular interfaces, and other physiologically restrictive compartments.

However, demonstration of active motion does not necessarily demonstrate an active-delivery advantage. This distinction is particularly important because propulsion is frequently integrated with other functional mechanisms within the same platform. Enzymatic nanomotors, for example, may simultaneously generate propulsion and modify the surrounding biological environment; magnetic systems may combine locomotion with deformation, hyperthermia, or externally controlled positioning; and biohybrid systems may exploit the intrinsic biological properties of their cellular components in addition to their motility. Consequently, an observed increase in drug accumulation, tissue penetration, cellular uptake, or therapeutic efficacy cannot automatically be attributed to propulsion itself. The distinction between active motion as a transport mechanism and multifunctional mechanisms operating alongside motion therefore remains essential when interpreting the available evidence.

Several reviews have comprehensively described micro/nanorobot propulsion, targeted transport, navigation, biological-barrier penetration, and biomedical applications. More recent reviews have further emphasized active penetration of physiological barriers and the potential advantages of micro/nanomotors over conventional passive systems. Nevertheless, the central question of how convincingly active motion itself contributes to improved drug delivery remains insufficiently isolated from the broader multifunctionality of these

systems. In particular, studies differ substantially in the quality of passive or non-motile controls, the quantitative metrics used to demonstrate delivery enhancement, the biological barriers investigated, and the extent to which improvements in transport are linked to therapeutic outcomes.

This distinction creates an important evidence gap. A system that demonstrates propulsion and cargo carriage provides evidence of active transport, but not necessarily evidence that active motion improves delivery relative to an otherwise comparable passive system. Stronger causal evidence requires quantitative comparison with an appropriate non-motile or passive control and, ideally, a demonstrated link between improved transport and a biological or therapeutic outcome. The relevant endpoints include locomotion, cargo transport, uptake or penetration, direct barrier crossing, quantitative active-versus-passive performance, and therapeutic outcome; these endpoints are related but do not form one strictly ordinal scale.

Accordingly, this review does not primarily seek to catalogue micro/nanorobotic architectures or propulsion mechanisms. Instead, it critically evaluates the incremental delivery value of active motion across experimental micro- and nanorobotic systems. Studies are examined by propulsion, cargo transport, navigation, target localization, biological-barrier interaction or penetration, passive or non-motile controls, quantitative delivery outcomes, and therapeutic efficacy. Particular attention is given to whether reported improvements can reasonably be attributed to active motion itself or whether they may arise from coupled mechanisms such as enzymatic barrier degradation, targeting interactions, magnetic deformation, chemical activity, or stimulus-responsive release.

On this basis, the review proposes an endpoint-based framework for distinguishing motion demonstrated from delivery advantage demonstrated and, separately, from therapeutic benefit demonstrated. By separating these evidence dimensions and assessing causal confidence, the review aims to determine when micro/nanorobotic propulsion provides evidence of improvement over passive drug transport and when the reported outcome is attributable only to the multifunctional platform as a whole.

METHODOLOGY AND EVIDENCE FRAMEWORK

Review objective and conceptual framework

The primary objective of this review was to critically evaluate whether active motion provides a measurable and causally meaningful advantage for drug delivery compared with passive or non-motile transport. The analysis distinguishes motion, cargo transport, biological uptake or penetration, crossing of a predefined barrier, quantitative comparison with a passive or non-motile comparator, and therapeutic outcome. These are related but not interchangeable endpoints; in particular, barrier crossing does not itself establish superiority over passive transport, and a therapeutic benefit does not by itself identify propulsion as its cause.

The conceptual model below summarizes possible functions in a delivery process. It is a navigation aid for the review, not a claim that every platform follows this exact sequence or that each stage is a higher ordinal evidence level:
Propulsion and cargo transport | navigation and localization | barrier interaction/crossing | active-versus-passive comparison | therapeutic outcome

These dimensions are not strictly sequential or mutually substitutable. A nanomotor may demonstrate rapid propulsion without improved drug delivery; a study may directly measure barrier crossing without a matched passive comparator; and a study may report a therapeutic benefit without isolating propulsion from targeting, barrier modification, or triggered release. Accordingly, E3 and E4 below represent different evidence types rather than consecutive rungs in a single scale.

The analysis therefore focuses on two complementary questions. First, does the active or multifunctional platform produce a measurable improvement in a drug-delivery-related endpoint? Second, can that improvement reasonably be attributed to active motion rather than to other functionalities incorporated into the delivery system?

This distinction is particularly important for multifunctional micro/nanorobotic platforms, in which propulsion may be coupled with enzymatic reactions, chemical barrier degradation, targeting ligands, photothermal effects, reactive oxygen species generation, magnetic deformation, stimulus-responsive release, or biohybrid mechanisms. Such mechanisms were therefore considered potential confounding factors when assessing the causal contribution of active motion.

Literature search strategy

This review is presented as a structured critical evidence synthesis rather than a formal systematic review or meta-analysis. The synthesis gives particular attention to soft, deformable, biohybrid, and stimuli-responsive micro-/meso-/nanorobotic systems used for biomedical transport. The study selection sought original experimental reports that address active transport, targeting, biological-barrier interaction or crossing, or therapeutic delivery. The emphasis on soft systems is thematic rather than an exclusive architecture filter: rigid or non-deformable active nanomotor studies were retained only when they directly informed the active-versus-passive drug-delivery question; they are not classified as soft-robotic architectures. The manuscript does not report a registered protocol, database-specific record counts, duplicate-removal procedure, or independent dual screening; it should therefore not be interpreted as a PRISMA-style systematic review or quantitative meta-analysis.

Targeted searches used combinations of terms related to micro/nanorobots, nanomotors, micromotors, active propulsion, drug delivery, cargo transport, targeting, biological barriers, tumor penetration, and therapeutic efficacy. Search terminology was adapted to the nomenclature used in the literature, and reference lists of relevant primary studies and reviews were screened to identify additional experimental reports. The manuscript does not provide a database-by-database search log or final search date; this limits exact reproducibility and means the search should be understood as targeted rather than demonstrably exhaustive. The resulting study set was screened using the eligibility criteria below.

Representative Boolean search concepts included:

("micro/nanorobot" OR "microrobot" OR "nanorobot" OR "micromotor" OR "nanomotor" OR "nanobot")

AND

("drug delivery" OR "drug transport" OR "cargo delivery" OR "therapeutic delivery" OR "targeted delivery")

AND

("active propulsion" OR "self-propulsion" OR "active motion" OR "magnetic propulsion" OR "acoustic propulsion" OR "light-driven propulsion" OR "enzyme-powered" OR "biohybrid")

Additional searches focused specifically on biological barriers, tumor penetration, mucus penetration, vascular transport, cellular uptake, and *in vivo* therapeutic delivery.

Reference lists of relevant primary studies and recent reviews were also screened to identify experimental reports not retrieved by the initial keyword combinations. No claim of exhaustive citation chasing is made.

Eligibility criteria

Core inclusion criteria were as follows. Priority was given to biomedical micro-/meso-/nanorobotic systems and to soft, deformable, biohybrid, or stimuli-responsive platforms. Other active platforms were retained only when they directly informed the review's active-versus-passive drug-delivery question.

1. The report presented original experimental research on a biomedical micro-/meso-/nanorobot or nanomotor.
2. The platform used active self-propulsion, externally actuated motion, or externally guided locomotion rather than relying solely on passive transport.
3. The system was investigated in a biomedical or biologically relevant transport context and included a therapeutic/model cargo or another explicit drug-delivery-related function.

4. The study reported at least one experimental delivery-related endpoint, such as cargo transport or release, navigation/target localization, cellular uptake, tissue or barrier penetration, drug accumulation, or a biological/therapeutic outcome.
5. The published report provided enough methodological and outcome information to identify the actuation/propulsion strategy, experimental model, and delivery-related endpoint. Passive or non-motile controls were recorded when available, but were not a universal inclusion requirement.

Original research articles were prioritized because the principal objective of the review was to evaluate experimental evidence rather than summarize previously published interpretations.

Studies were excluded when they were exclusively theoretical or computational without experimental validation, focused solely on propulsion engineering without a relevant drug-delivery endpoint, or discussed micro/nanorobots only from a general biomedical perspective without providing experimental evidence relevant to active transport.

Review articles, perspectives, editorials, commentaries, and conference abstracts were not included in the primary evidence matrix, although relevant reviews were used to establish background, identify major research themes, and facilitate reference-chain searching.

Evidence extraction

For each eligible study, information was extracted into a predefined evidence matrix. Variables included study identification, propulsion mechanism, robotic architecture, therapeutic or model cargo, experimental model, motion characteristics, cargo transport, targeting/navigation, biological-barrier interaction, passive or non-motile controls, quantitative delivery outcomes, and therapeutic effects. The primary evidence matrix contains original experimental studies[9-39]; references[1-8] provide review-level background and context.

The presence and quality of passive or non-motile comparator groups were recorded explicitly. Comparisons between an active system and an otherwise closely matched passive system were treated as more informative for causal attribution than comparisons with an unrelated carrier, free drug alone, or a control that also differed in targeting chemistry, architecture, or release behavior.

Endpoint-based evidence categories

The endpoint categories used in the evidence matrix are defined below. They are an author-proposed organizing scheme, not a validated grading scale:

E0 — Motion only

The study demonstrates active propulsion or locomotion but does not provide sufficient evidence that motion contributes to cargo transport or drug delivery.

E1 — Cargo transport

Active motion is demonstrated together with transport of a therapeutic or model cargo, but no clear evidence is provided that active motion improves delivery relative to passive transport.

E2 — Enhanced uptake or penetration

The actively propelled system demonstrates enhanced cellular uptake or tissue penetration, but the experiment does not directly demonstrate crossing of a predefined biological barrier.

E3 — Biological-barrier crossing

The study directly demonstrates transport across a predefined biological barrier, such as mucus, vascular endothelium, epithelium, extracellular matrix, or tumor stroma. This category does not, by itself, require a quantitative advantage over a passive comparator.

E4 — Quantitative active-versus-passive advantage

The study quantifies a delivery-, penetration-, accumulation-, or transport-related advantage of the active system over a passive or non-motile comparator. Crossing a predefined

biological barrier is not a prerequisite for this category, but the comparator and measured endpoint must be specified.

E5 — Quantitative delivery advantage with therapeutic benefit
The study demonstrates a quantitative advantage over a passive or non-motile comparator together with a measurable biological or therapeutic outcome, preferably in an appropriate in vivo model. The classification refers to the study's overall platform unless the experimental design isolates propulsion specifically.

The E0-E5 categories are a proposed, study-specific analytical framework developed for this review; they are not a validated clinical, regulatory, or externally established evidence-grading system. E0-E2 describe observations of motion, cargo transport, and uptake or penetration. E3 denotes direct barrier-crossing evidence, whereas E4 denotes a quantified active-versus-passive advantage; E3 and E4 are different evidence types and should not be ranked as if one necessarily supersedes the other. E5 requires a quantified comparator advantage together with a biological or therapeutic outcome. None of these categories, including E5, automatically implies high causal confidence or high data quality.

Assessment of causal confidence
Causal confidence was assessed qualitatively and separately from endpoint category and data quality. The assessment considered six domains: (i) presence and matching of a passive/non-motile control; (ii) quantitative active-versus-passive comparison; (iii) independent characterization of motion; (iv) control of major mechanistic confounders; (v) linkage of delivery to a downstream biological or therapeutic endpoint; and (vi) relevance of in vivo validation where applicable. These domains guide the review author's overall judgment; they are not converted into a numerical composite score.

The labels Low, Moderate, Moderate-High, and High are qualitative author judgments rather than numerical scores. Because domain-by-domain judgments for every study are not provided, an independent reader cannot reproduce each assigned label from the manuscript

tables alone. These labels should be interpreted cautiously, particularly when motion co-occurs with targeting, catalytic chemistry, barrier modification, heat, or triggered release.

A High qualitative causal-confidence label does not prove that propulsion alone caused the observed effect when active motion remains physically or biologically inseparable from another mechanism. In such cases, the appropriate interpretation is system-level active-transport efficacy with limited propulsion-specific attribution.

Assessment of data quality

Data quality was evaluated independently from causal confidence. The assessment considered clarity of experimental design, appropriateness and matching of controls, quantitative reporting, reproducibility of measurements, characterization of propulsion, suitability of the biological model, and, where applicable, validation in three-dimensional or in vivo systems. These ratings are qualitative judgments, not a validated risk-of-bias instrument.

Studies were categorized as follows:

High data quality: Clear experimental design, appropriate controls, quantitative endpoints, detailed characterization, and strong biological validation.

Moderate-High data quality: Strong quantitative evidence with one important methodological limitation.

Moderate data quality: Valid proof-of-concept evidence but limited controls, restricted biological models, or incomplete quantitative characterization.

Low data quality: Predominantly qualitative evidence, insufficient methodological information, or inadequate experimental controls.

Data quality was not used to determine whether a study was positive or negative. It was used as a qualitative indication of the reported experimental design and evidentiary detail; it

should not be interpreted as a formal risk-of-bias score or independent replication assessment.

Importance of passive and non-motile controls

A central criterion of this review was the presence of an appropriate passive or non-motile comparator. Such controls are essential because an actively propelled system may differ from its passive counterpart in several properties other than motion, including surface chemistry, enzyme activity, targeting ligands, particle size, shape, drug-loading capacity, membrane composition, or stimulus responsiveness.

The strongest experimental design is therefore one in which the actively moving and passive systems are otherwise closely matched, allowing active motion to represent the principal experimental variable.

Where such a comparator was unavailable, the reported enhancement was interpreted cautiously. In these cases, improved delivery could be associated with the overall multifunctional design rather than being directly attributable to propulsion.

Mechanistic confounding

Potential mechanistic confounding was explicitly considered during evidence assessment. Propulsion mechanisms may themselves modify the biological environment. For example, urease-powered systems can alter local pH and generate ammonia, enzyme-functionalized nanomotors can degrade extracellular matrix components, catalytic systems can generate reactive oxygen species, and magnetic or optical actuation can produce thermal or mechanical effects.

Accordingly, an observed increase in tissue penetration, cellular uptake, or therapeutic efficacy was not automatically interpreted as evidence of a propulsion-specific effect when another mechanism could independently account for the outcome.

Studies were therefore interpreted according to the following principle:

Observed therapeutic improvement ≠ propulsion-specific therapeutic improvement.

The distinction between these two concepts represents a central analytical principle of the present review.

The collected studies were organized according to the functional stage at which active motion was proposed to improve drug delivery. These stages included cargo transport, navigation and targeting, biological-barrier penetration, deep tumor penetration, and *in vivo* therapeutic delivery.

For each study, the level of evidence, data quality, and causal confidence were assessed independently. Particular emphasis was placed on quantitative active-versus-passive comparisons and on whether enhanced transport was subsequently associated with improved biological or therapeutic outcomes.

The resulting evidence matrix was then used to identify patterns across different propulsion mechanisms and biological environments. Rather than assuming that all active systems provide equivalent benefits, the analysis examined whether the contribution of active motion depended on the specific transport barrier, propulsion mechanism, cargo, biological model, and additional functionalities incorporated into the platform.

This approach evaluates not simply whether a micro/nanorobot can move, but whether the study documents a delivery-related effect, quantifies any advantage over a relevant comparator, and links transport to a biological or therapeutic outcome with a defensible causal interpretation.

RESULTS AND CRITICAL EVIDENCE ANALYSIS

Overview of the evidence base

The identified experimental studies demonstrate a broad range of micro- and nanorobotic platforms capable of actively transporting therapeutic cargo through biological environments. These systems employ diverse propulsion mechanisms, including enzymatic and catalytic reactions, magnetic actuation, acoustic and optical stimulation, thermophoretic

propulsion, and biohybrid locomotion. Therapeutic cargos have included small-molecule chemotherapeutics, drug-loaded nanoparticles, and other biologically active agents.

Despite the diversity of robotic architectures and propulsion mechanisms, the experimental evidence is not uniform in demonstrating that active motion itself improves drug delivery. The available studies can be positioned along a spectrum ranging from simple demonstrations of locomotion and cargo transport to quantitative comparisons with passive systems and, in a smaller subset of studies, measurable therapeutic benefits *in vivo*.

A recurring observation across the literature is that the strongest claims of improved delivery are generally associated with multifunctional systems. In many cases, propulsion is combined with targeting ligands, enzymatic degradation of biological barriers, stimulus-responsive drug release, photothermal activity, reactive oxygen species generation, or other therapeutic mechanisms. Consequently, the presence of an active-motion component does not by itself establish that propulsion is responsible for the observed delivery advantage.

The evidence was therefore examined across distinct, related dimensions: active propulsion and cargo transport, enhanced penetration, biological-barrier crossing, quantitative active-versus-passive comparison, and therapeutic benefit. This organization is not a single ordinal progression because barrier crossing and comparative advantage are different evidence types.

Representative original experimental studies included in the evidence matrix are summarized in Table 1[9-39]. The endpoint-based evidence categories are summarized in Table 2.

Table 1. Master evidence matrix. *The asterisk marks the 2026 study. E5 and High are review-author classifications based on the published reports and do not imply independent replication. The title and inclusion criteria encompass biomedical micro-/meso-/nanorobotic platforms; rigid/non-deformable systems are included only when directly relevant to active-versus-passive delivery and are not labelled soft robots. E3 (barrier crossing) and E4 (quantified active-versus-passive advantage) are distinct evidence types, not consecutive ranks. DOX, doxorubicin; 5-FU, 5-fluorouracil; CPT, camptothecin; NP, nanoparticle; GOx, glucose oxidase; GSH, glutathione; HFLA, heparin/folic acid/L-arginine carrier; NIR, near-infrared; ROS, reactive oxygen species. Numeric outcomes are reported from individual studies and are not directly comparable across different endpoints or models. Exact fold values for bladder-spheroid internalization are not reported where they cannot be reliably verified from the primary figure or supporting information. For[26], the cargo description refers to the multi-agent chemo/photothermal platform, not the HFLA-DOX carrier discussed for[21].

Study	Propulsion	Cargo	Key delivery outcome	Passive/non-motile control	Evidence	Data quality
Hortelão et al. (2018) [9]	Urease-powered	DOX	~4 × higher release; increased intracellular DOX	Yes / passive counterpart	E4	Moderate-High
Magnetic degradable microrobot (2019) [10]	Magnetic	5-FU	Controlled release + hyperthermia	Limited	E1	Moderate
Gated MS nanomotor (2019) [11]	Urease	$Ru(bpy)_3Cl_2$ / DOX	Urea-enhanced motion; acidic-pH-triggered intracellular payload release and uptake	Comparator reported	E1	Moderate-High
Self-folded microrobot (2020) [12]	Magnetic	DOX	Active delivery + > 90% ultrasound release in 1 min	Limited	E1	Moderate
Porous magnetic microrobot (2021) [13]	Magnetic/acoustic	5-FU	Controlled targeted release	Limited	E1	Moderate
Magnetically guided self-rolled microrobot (2021) [14]	Magnetic	DOX	Targeted transport/navigation	Comparator limited	E1	Moderate-High
Surface microrollers (2020) [15]	Magnetic	Cargo	Targeted delivery under physiological flow	Yes/functional comparison	E1	High

Study	Propulsion	Cargo	Key delivery outcome	Passive/non-motile control	Evidence	Data quality
pH-taxis nanomotors (2020) [16]	Chemically driven	DOX	pH-directed tumor localization	Comparator reported	E1	Moderate-High
Urease nanomotors in bladder spheroids (2019) [17]	Urease	DOX	Higher internalization with urea than antibody-modified passive particles; bare-particle comparison also changes targeting functionality	Matched antibody-modified particles without urea; bare passive particles lack antibody targeting	E4	High
Plasmon-enhanced nanomotors (2022) [18]	NIR/catalytic	Imaging/therapy cargo	≈1.5 mm distance toward deeper tumor sites after five rounds of NIR irradiation, inferred from PAI signals; enhanced accumulation/penetration	Passive diffusion comparison	E4	High
Vasculature penetration nanomotors (2018) [19]	Catalytic	Cargo	Enhanced trans-endothelial penetration	Passive comparison	E3	Moderate-High
Icebreaker Janus nanomotors (2021) [20]	Urease + hyaluronidase	DOX	~2 × tumor drug; >3 × uptake	Comparator reported; urease propulsion and hyaluronidase-mediated barrier modification are coupled	E5	High
NO-driven nanomotor (2021) [21]	NO-driven	HFLA-DOX	Deep penetration + MDR reversal	Comparison included	E4	High
Nanomotor swarm barrier disruption (2023) [22]	Enzyme + light	Cargo	~10-fold overall delivery efficiency in the full light-triggered, sequential-swarm treatment versus nonirradiated samples	Barrier disruption and propulsion are coupled; light-triggered mechanical disruption is itself an active intervention	E4	High
Catalase nanobots (2024) [23]	Catalase	Protein/cargo	28% crossed the mucus barrier; ~60× higher crossing than passive nanoparticles in the reported in vitro model	BSA nanoparticle controls; propulsion and mucus disruption both contribute	E4	High
Bioactive intestinal nanomotor (2025) [24]	Thermophoretic + gas	Cisplatin	~3.5 × cisplatin delivery; 98.6% therapeutic efficiency in vivo, as reported by the original study	Yes	E5	High
Intratumoral Janus nanomotors (2019) [25]	Urease	CPT	Deep penetration + efficacy	Comparator reported	E4	Moderate-High

Study	Propulsion	Cargo	Key delivery outcome	Passive/non-motile control	Evidence	Data quality
MMS/Pt nanomotors (2020) [26]	NIR/catalytic	Multiple therapeutic agents for chemo/photothermal therapy	≈110 vs. 60 µm penetration in 3D tumor spheroids; increased tumor-interior fluorescence/distribution reported in vivo under NIR irradiation	NIR-off/passive comparison; irradiation also activates photothermal and release-related functions, so it is not a propulsion-only control	E4	High
Magneto-nanobots (2020) [27]	Magnetic/self-propelling	Drug	Deep 3D tumor penetration	Non-motile CNT-DOX-Fe_3O_4 and free-DOX controls; targeted nanobots also differ in targeting ligands	E3	Moderate-High
Pt-silica nanomotors (2021) [28]	Catalytic	$Ru(bpy)_3Cl_2$ (model cargo)	Directional transport toward THP-1 cancer cells in a microchip model; model-cargo release is redox-gated	Fuel-off comparison	E1	High
Biomimetic nanorobots (2023) [29]	Active assembly	Drug	Enhanced uptake, transvascular extravasation, and deep penetration; separate in vivo tumor reduction reported with the NIR-responsive multifunctional platform	Passive comparison reported; superassembly, targeting, and NIR-responsive functions may contribute independently	E5	High
Puffball microrobot (2022) [30]	Magnetic	Drug	Targeted locomotion + payload protection	Comparator limited	E1	Moderate-High
Organic nanorockets (2023) [31]	Light-driven	Drug	~300 µm/s; deep tumor transport	Comparison reported	E4	High
Amoeba-like nanorobot (2023) [32]	Magnetic deformation	DOX	~2.1× tumor accumulation; 92.3% delivery; 96.1% inhibition	Controls reported; magnetic deformation, targeting-ligand exposure and triggered release are coupled	E5	High
Liver cancer microrobot (2022) [33]	Magnetic	DOX	Magnetically guided delivery to tumor-feeding vessels; in vivo MRI targeting efficiency 81.6% (left lobe) and 67.3% (right lobe) vs 43% without magnetic guidance; chemoembolization/drug delivery	No-guidance comparator; magnetic localization, embolization, imaging, and drug release are coupled	E5	High

Study	Propulsion	Cargo	Key delivery outcome	Passive/non-motile control	Evidence	Data quality
Algae biohybrid microrobot (2024) [34]	Biohybrid	DOX-NP	Improved distribution/retention; reduced metastasis	Free-DOX and passive-NP controls; algal propulsion is not isolated from other biohybrid functions	E5	High
Sperm-hybrid micromotor (2018) [35]	Biohybrid + magnetic	DOX	Targeted spheroid delivery	Comparator included	E3	Moderate-High
Macrophage magnetic microrobot (2022) [36]	Magnetic + biohybrid	DOX	3D tumor targeting	Comparator reported	E4	High
Glucose-fueled gated nanomotors (2025) [37]	GOx/Pt	DOX	Deep penetration + *in vivo* efficacy	Comparator reported; propulsion, glucose depletion, ROS chemistry and oxygen generation are coupled	E5	High
GSH-responsive Pt nanomotor (2025) [38]	NIR-driven/GSH-responsive Pt	DOX	≈2.1× speed under NIR; ≈5.53× in vitro osteosarcoma-cell growth inhibition for the combined DOX/Pt/ROS/photothermal platform; in vivo tumor inhibition also reported	NIR and component controls; propulsion is coupled to photothermal effects, GSH-responsive release, and Pt-derived ROS	E1	High
Engineered probiotic microrobot (2026) [39]	Biohybrid	DOX	Deep tumor penetration in organoids/in vivo; combined chemotherapy and immune activation reported	Controls reported; bacterial motility, hypoxia chemotaxis, macrophage-membrane targeting, immune activation, and pH-triggered release are integrated	E5*	High*

Table 2. Endpoint-based evidence categories used in the review.

Category	Definition	Interpretation
E0	Motion demonstrated	Shows locomotion only; no delivery advantage established.
E1	Cargo transport	Shows active carriage/transport of cargo.

Category	Definition	Interpretation
E2	Enhanced uptake/penetration	Shows improved uptake or tissue penetration, without direct demonstration of crossing a predefined barrier.
E3	Direct biological-barrier crossing	Directly demonstrates transport across a predefined biological barrier; a matched comparator is not required by this category.
E4	Quantified active-versus-passive advantage	Quantifies superior delivery/penetration/accumulation versus a passive or non-motile comparator; direct barrier crossing is not required.
E5	Quantified comparator advantage + therapeutic outcome	Combines a quantified active-versus-passive advantage with a measurable biological/therapeutic outcome; benefit is system-level unless propulsion is isolated.

Active propulsion and cargo transport

The first level of functional evidence concerns whether active motion can facilitate the transport of therapeutic cargo. Several studies have demonstrated that propulsion can increase the movement of drug-loaded particles or nanostructures relative to passive diffusion.

Enzyme-powered nanomotors provide an early example of this principle[9,11]. Urease-powered mesoporous silica nanomotors loaded with doxorubicin demonstrated enhanced drug release and increased intracellular delivery compared with passive counterparts[9]. These findings support the feasibility of using chemically generated propulsion to increase interactions between drug carriers and target cells. However, interpretation of the propulsion-specific contribution remains complicated because the urease reaction simultaneously alters the local chemical environment. Thus, increased intracellular delivery cannot be attributed exclusively to mechanical motion.

Similarly, magnetically actuated microrobotic systems have demonstrated controlled transport and release of chemotherapeutic agents[10,13]. Magnetic actuation provides an important advantage because propulsion can be externally controlled without requiring chemical fuel. However, many magnetic systems simultaneously exploit additional effects such as hyperthermia or remotely triggered drug release. In such cases, improved therapeutic performance reflects the combined action of active transport and the secondary treatment modality rather than propulsion alone.

These studies establish that active motion can contribute to cargo transport, but they also illustrate an important limitation in the evidence base: demonstration of active cargo movement is considerably easier than demonstrating a propulsion-specific improvement in drug delivery.

Active navigation and target localization

A major proposed advantage of micro/nanorobotic systems is the ability to actively navigate toward a predefined biological target. Magnetic microrobots, for example, can be

guided through external magnetic fields, allowing their trajectories to be manipulated in real time. Studies using self-rolled magnetic microrobots and magnetic microrollers have demonstrated targeted cargo delivery under physiologically relevant flow conditions[14,15].

The ability to navigate against or across physiological flow represents a meaningful distinction from conventional passive transport. In particular, magnetic microrollers have demonstrated upstream locomotion and targeted cargo delivery under blood-flow-like conditions, suggesting that active propulsion may compensate for limitations imposed by physiological convection.

However, navigation should not be equated with improved drug delivery. Successful localization of a carrier at a target site establishes control over transport but does not necessarily establish superior drug accumulation, cellular uptake, or therapeutic efficacy. The magnitude of the delivery advantage must therefore be quantified independently.

pH-responsive taxis represents another strategy in which active motion is coupled to environmental sensing. Nanomotors capable of responding to pH gradients have been investigated for preferential movement toward tumor-associated microenvironments[16]. Although such systems provide an attractive combination of sensing and propulsion, the contribution of motion remains difficult to isolate when chemical responsiveness and cargo release are simultaneously altered by the same environmental stimulus.

Therefore, active navigation provides a mechanistic advantage primarily when the biological environment imposes a transport limitation that passive diffusion cannot adequately overcome. Representative studies of active navigation and target localization are summarized in Table 3.

Table 3. Active Navigation and Target Localization.

Representative system	Navigation mechanism	Target context	Quantitative/functional endpoint	Causal limitation
Magnetically guided self-rolled microrobot [14]	External magnetic field	Tumor targeting	Automated navigation + DOX delivery	Navigation coupled to magnetic actuation

Representative system	Navigation mechanism	Target context	Quantitative/functional endpoint	Causal limitation
Surface microrollers [15]	Magnetic rolling	Physiological blood flow	Upstream/targeted cargo delivery	Surface interactions also contribute
pH-taxis nanomotors [16]	Chemical taxis	Tumor microenvironment	Directed localization + DOX delivery	pH response and propulsion are coupled
Bladder-cancer urease nanomotors [17]	Urease propulsion + targeting ligand	3D cancer spheroids	Higher spheroid internalization with urea than antibody-modified passive particles; bare-particle comparisons also differ in targeting ligand	Targeting ligand and urease chemistry contribute independently; exact fold values not repeated without figure-level confirmation
Amoeba-like nanorobot [32]	Magnetic deformation	Systemic tumor model	~2.1× tumor accumulation	Deformation and motion are inseparable

Active motion across biological barriers

Biological barriers represent one of the most compelling contexts in which active motion could provide a genuine delivery advantage. Mucus, vascular endothelium, extracellular matrix, tumor stroma, and epithelial layers can substantially restrict the movement of conventional drug carriers.

Nanomotor-based systems have demonstrated enhanced penetration across endothelial models, suggesting that active propulsion can facilitate transport through cellular barriers. Similarly, enzyme-powered systems have been developed to overcome extracellular matrix and mucus barriers that normally limit nanoparticle diffusion.

An important example is provided by nanomotor systems designed to overcome the mucus barrier. Catalase-powered nanobots demonstrated substantially greater mucus penetration than passive nanoparticle controls, with reported transport levels approximately 60-fold higher than those of the passive reference system[23]. Such quantitative comparisons provide considerably stronger evidence than demonstrations of locomotion alone because they directly evaluate the performance of active transport against a non-motile system.

Nevertheless, the interpretation of barrier-crossing studies depends strongly on the mechanism by which the barrier is modified. Enzyme-powered nanomotors may simultaneously degrade or alter the barrier while generating propulsion. If the enzyme itself

increases permeability, the resulting transport enhancement cannot be attributed exclusively to mechanical motion.

This issue is particularly evident in systems incorporating hyaluronidase or other matrix-degrading enzymes. In such platforms, propulsion and barrier modification may operate synergistically. The resulting increase in tumor penetration can therefore represent a genuine advantage of the overall active system without necessarily demonstrating that mechanical motion alone is responsible. Studies addressing biological-barrier penetration are summarized in Table 4.

Table 4. Biological-Barrier Penetration.

Barrier	Representative study	Mechanism	Reported advantage	Main confounder
Vascular endothelium	Vasculature penetration nanomotors [19]	Active nanomotor transport	Enhanced trans-endothelial penetration	Nanomotor surface/size effects
Tumor ECM	NO-driven nanomotor [21]	NO propulsion + ECM effects	Deep penetration + MDR reversal	NO biological activity
Collagen barrier	Light-triggered nanomotor swarm [22]	Mechanical disruption + propulsion	~10-fold overall delivery efficiency in the full light-triggered, sequential-swarm treatment versus nonirradiated samples	Light-triggered mechanical disruption is itself active and cannot be separated from the complete treatment by this comparison
Mucus	Catalase nanobots [23]	Catalytic propulsion	28% crossed the mucus barrier; ~60× increase versus passive nanoparticles in the reported in vitro model	Catalase-mediated mucus modification
Intestinal mucus/epithelium	Bioactive intestinal nanomotor [24]	Thermophoretic + gas propulsion	~3.5× cisplatin delivery	Multiple propulsion mechanisms
Stiff tumor stroma	Biomimetic nanorobots [29]	Active assembly/penetration	Deep tumor penetration	Assembly, targeting and NIR functions

Deep tumor penetration

Dense tumor architecture represents a particularly stringent test of active drug delivery. High interstitial pressure, abnormal vasculature, dense extracellular matrix, heterogeneous perfusion, and elevated stromal density can collectively limit the penetration of conventional nanoparticles.

Several studies report improved transport, penetration, or cellular uptake in biologically restrictive models, but the measured endpoints and comparators differ substantially[17,19,22-30,38]. For example, urease-powered particles have been assessed for internalization into bladder-cancer spheroids, Janus nanomotors have been evaluated for trans-endothelial transport, enzyme-powered swarms have been used to disrupt extracellular barriers, and NIR-responsive systems have been assessed for tumor penetration. These findings should not be treated as a single comparable effect-size series: some measure barrier crossing or penetration depth, whereas others measure uptake, distribution, accumulation, or therapeutic response.

The magnitude of the reported improvements varies substantially between studies. Some experiments demonstrate increased penetration distance, whereas others report higher tumor accumulation, greater cellular uptake, or improved therapeutic efficacy. These endpoints should not be treated as equivalent. Penetration depth provides evidence of spatial transport, whereas therapeutic efficacy additionally depends on drug release, cellular internalization, intracellular activity, and tissue-level pharmacodynamics.

An important example is the use of biomimetic nanorobotic assemblies designed to penetrate tumors with stiff stroma[29]. Such systems have demonstrated improved transvascular transport, extravasation, deep tumor penetration, and cellular internalization. These findings support the hypothesis that active transport can address multiple sequential transport barriers. However, the system also incorporates other functional features that contribute to tissue interaction and triggered drug release, making it difficult to isolate propulsion as the sole cause of the observed therapeutic benefit.

Therefore, the strongest conclusion supported by these studies is that active multifunctional transport systems can improve penetration into otherwise restrictive tumor environments. The more specific claim that propulsion alone is responsible for this improvement remains less consistently established. Representative evidence for deep tumor penetration is summarized in Table 5.

Table 5. Deep Tumor Penetration.

Study/system	Model	Propulsion	Penetration evidence	Therapeutic relevance
Intratumoral Janus nanomotors [25]	Tumor tissue	Urease	Deep penetration from intratumoral depot	Antitumor efficacy
MMS/Pt nanomotors [26]	3D spheroids/*in vivo*	NIR catalytic	≈110 vs. 60 μm penetration in 3D spheroids; increased tumor-interior fluorescence/distribution under NIR reported in vivo (exact fold not stated here)	Combined chemo/photothermal therapy; NIR-related effects are not propulsion-specific
Magneto-nanobots [27]	3D tumor model	Self-propelling magnetic	Deep 3D penetration	pH-responsive intracellular delivery
Organic nanorockets [31]	Tumor model	Light-driven	~300 μm/s; enhanced transport/penetration	Antitumor therapy
Biomimetic nanorobots [29]	Stiff-stroma tumors	Active superassembly	Extravasation + deep penetration	NIR-triggered therapeutic release
Glucose-fueled gated nanomotors [37]	Cells/spheroids/*in vivo*/organoids	GOx/Pt	Deep tumor penetration	Anticancer efficacy

Quantitative evidence for active-versus-passive advantage

Quantitative comparison with an appropriate passive or non-motile control represents a major transition in evidence strength. Without such a comparison, the absolute performance of an active system cannot readily be interpreted as an improvement attributable to propulsion.

Several studies provide quantitative evidence supporting an active-delivery advantage[9,17,23-26,38]. However, each effect must be interpreted against its comparator. In the bladder-spheroid study[17], the primary report describes higher internalization for antibody-modified nanomotors in the presence of urea than for antibody-modified passive particles. Comparisons against bare particles additionally change the targeting functionality and therefore cannot isolate propulsion. Because the exact fold differences could not be re-confirmed against the relevant primary figure and supporting-information data in this final pass, no specific fold value is repeated here. Other systems report changes in release, tumor accumulation, penetration distance, or barrier crossing, but these endpoints are not interchangeable and may also be affected by coupled mechanisms.

Reported improvements varied substantially across experimental endpoints and models, including tumor accumulation, penetration depth, cellular uptake, barrier crossing, and

therapeutic response. Because these endpoints represent different biological quantities, their fold changes were not pooled and should not be interpreted as directly comparable effect sizes. Particularly large effects were often reported in environments where passive transport was strongly constrained, such as mucus, dense extracellular matrix, and three-dimensional tumor models.

The numerical magnitude of an observed enhancement should not be interpreted independently of experimental design. A large increase obtained against a poorly matched control may provide weaker causal evidence than a smaller increase obtained using a rigorously matched passive comparator. Quantitative effect size and causal confidence must therefore be considered as separate analytical dimensions.

From enhanced delivery to therapeutic benefit

The highest level of evidence is achieved when enhanced active transport is accompanied by improved therapeutic efficacy. Several recent studies have progressed beyond *in vitro* transport measurements to demonstrate increased tumor accumulation, enhanced drug delivery, reduced tumor burden, or improved survival *in vivo*.

A magnetically driven amoeba-like nanorobot provides a representative example of whole-process active drug transport[32]. The platform was designed to transport doxorubicin through multiple stages and the study reported increased tumor accumulation, tumor-cell delivery, and tumor-growth inhibition. These are important system-level results, but they cannot be attributed to locomotion alone: magnetic deformation, tumor-environment-dependent exposure of a targeting ligand, and alternating-magnetic-field-triggered drug release are integral to the platform. The study therefore supports the efficacy of the combined system more directly than it isolates the independent causal contribution of propulsion.

Algae-based biohybrid microrobots loaded with drug-containing nanoparticles have been investigated for delivery in lung metastasis models[34]. The reported system improved cargo distribution, accumulation, and retention and was associated with reduced metastatic

burden and improved survival relative to the study's controls. These findings support a system-level biohybrid delivery advantage. However, the passive nanoparticle and free-drug controls do not by themselves isolate motility from the algae's other biological properties; propulsion-specific attribution should therefore remain qualified.

Nevertheless, biohybrid systems also illustrate the importance of causal attribution. Cellular motility, surface interactions, biological recognition, and other intrinsic properties of the living carrier may contribute to delivery in addition to locomotion. Thus, the evidence supports the therapeutic value of active biohybrid transport but does not necessarily establish that mechanical propulsion alone accounts for the improvement. In vivo delivery and therapeutic evidence across representative systems are summarized in Table 6.

Table 6. *In vivo* delivery and therapeutic evidence. Causal-confidence labels are qualitative review-author judgments based on comparator matching, motion characterization, mechanistic controls, outcome linkage, and model relevance; they are not validated scores, independent replication assessments, or proof that propulsion alone caused the therapeutic outcome.

System	Cargo	*In vivo* setting	Delivery outcome	Therapeutic outcome	Causal confidence (qualitative)
Amoeba-like nanorobot [32]	DOX	Systemic tumor model	~2.1× accumulation; 92.3% tumor-cell delivery	96.1% tumor inhibition	Moderate-High
Liver-cancer microrobot [33]	DOX	Orthotopic liver tumor	Magnetic targeting of tumor-feeding vessels; MRI targeting efficiency 81.6% (left lobe) and 67.3% (right lobe) vs 43% without guidance	Therapeutic benefit	Moderate-High
Algae biohybrid microrobot [34]	DOX-NP	Lung metastasis	Improved distribution, accumulation and retention	Reduced metastatic burden; improved survival	Moderate-High
Icebreaker Janus nanomotor [20]	DOX	Tumor model	~2 × tumor drug; >3 × uptake	Improved therapy	Moderate-High
Bioactive intestinal nanomotor [24]	Cisplatin	Colorectal cancer model	~3.5 × cisplatin delivery	98.6% therapeutic efficiency in vivo, as reported by the original study	Moderate-High
Glucose-fueled gated nanomotor [37]	DOX	Tumor + organoid models	Deep penetration	Enhanced anticancer efficacy	Moderate

Multifunctionality and biohybrid systems: Limits of propulsion-specific attribution

A major pattern emerging from the evidence matrix is that the most therapeutically successful micro/nanorobotic systems are often multifunctional. They may combine active propulsion with targeting, barrier degradation, controlled release, imaging, photothermal therapy, hyperthermia, catalytic activity, or biological-cell-mediated transport.

Biohybrid platforms require particular caution because motility is inseparable from biological identity, adhesion, receptor interactions, metabolism, and cell-mediated transport. These systems can provide strong evidence that active biological transport is therapeutically useful, while providing weaker evidence that locomotion itself—independent of the living carrier—is the causal determinant of improved delivery.

This multifunctionality is advantageous from a therapeutic engineering perspective but creates a fundamental challenge for causal interpretation. When several mechanisms are activated simultaneously, an improvement in therapeutic efficacy represents the outcome of the complete system rather than necessarily the effect of propulsion.

For example, an enzyme-powered nanomotor may simultaneously increase convective transport, modify extracellular matrix composition, change local chemical conditions, and enhance cellular interactions. Likewise, an optically activated nanomotor may produce both mechanical propulsion and photothermal effects. In such cases, attributing the entire treatment benefit to active motion would overstate the available evidence.

The appropriate interpretation is therefore to distinguish between system-level efficacy and propulsion-specific efficacy. A multifunctional active system may be highly effective even when the independent contribution of motion remains uncertain.

Study distribution across evidence dimensions

Across the 31 studies in Table 1, the assigned categories were E1 (n = 10), E3 (n = 3), E4 (n = 10), E5 (n = 7), and E5* (n = 1; the 2026 study); no study was assigned E0 or E2 as its primary category. These frequencies describe the review's assignments rather than a strict

hierarchy: E3 and E4 capture distinct evidence types, and the studies differ in models, endpoints, and comparator quality.

This pattern is important because it indicates that the field has largely established the technical feasibility of active propulsion but has comparatively less consistently established the incremental clinical value of propulsion.

The evidence is strongest when three conditions are simultaneously satisfied: first, the active and passive systems are appropriately matched; second, the delivery advantage is quantitatively measured; and third, the advantage is linked to a meaningful biological or therapeutic endpoint.

Conversely, studies that demonstrate only propulsion or cargo movement provide important proof-of-concept evidence but should not be interpreted as definitive evidence that active motion improves drug delivery.

Overall critical interpretation

The available evidence supports the conclusion that active motion can improve drug transport under selected biological conditions, particularly when passive diffusion is strongly constrained by physiological barriers, tissue architecture, or fluid flow. The advantage appears most plausible when propulsion directly addresses a transport limitation that cannot be efficiently overcome by passive carriers.

However, the evidence does not support a universal conclusion that active motion intrinsically improves drug delivery in all micro/nanorobotic systems. The magnitude and causal interpretation of the benefit depend on the biological environment, propulsion mechanism, cargo, experimental design, and additional functionalities incorporated into the robotic platform.

The most convincing evidence therefore comes not from the demonstration that a robot can move, but from experiments showing that a closely matched non-motile system performs

worse under the same conditions and that the difference is quantitatively associated with active transport.

Accordingly, the central finding of this review is that active motion should be regarded as a potential enabling mechanism rather than an inherently therapeutic mechanism. Its value is greatest when it overcomes a specific transport bottleneck and when that contribution can be experimentally separated from the effects of targeting, barrier modification, stimulus-responsive release, or other auxiliary functions.

Causal-attribution and experimental-design evidence is summarized in Table 7; propulsion-specific confounders and recommended controls are summarized in Table 8.

Table 7. Causal attribution and experimental design.

Design feature	Strong evidence	Weak evidence	Why it matters
Matched passive/non-motile control	Active and passive systems closely matched except propulsion	No passive comparator	Separates motion from particle chemistry/structure
Quantitative delivery endpoint	Drug concentration, penetration depth, uptake, accumulation, retention	Qualitative 'enhanced' images only	Allows effect-size assessment
Motion characterized independently	Speed/directionality measured separately	Motion inferred from outcome	Confirms that propulsion is actually present
Mechanistic control	Fuel-off, enzyme-inactive, ligand-free, NIR-off, *etc.*	Multiple mechanisms changed simultaneously	Tests whether motion itself is causal
Therapeutic linkage	Delivery → pharmacodynamics → efficacy	Only endpoint is tumor shrinkage	Connects transport to clinical relevance
System *vs.* propulsion efficacy	Explicitly distinguishes platform effect from motion-specific effect	Attributes all benefit to propulsion	Prevents causal overinterpretation

Table 8. Propulsion-Specific Confounders and Recommended Controls.

Propulsion mechanism	Major non-motion confounder	Recommended control
Biohybrid	Cell recognition, adhesion, metabolism, and intrinsic motility	Appropriate non-motile or biological-property-matched control
Magnetic	Deformation, aggregation, hyperthermia, and field-induced localization	Field-exposed non-motile/structural control
Ultrasound/acoustic	Cavitation, mechanical effects, and triggered release	Ultrasound-treated non-motile control
NIR/light	Photothermal and photochemical effects	NIR/light-treated non-motile control
Pt/catalytic	ROS generation and catalytic chemistry	Catalyst-containing non-motile control
GOx/Pt	Glucose depletion, acidification, H_2O_2/ROS chemistry	Motion-off or catalyst-matched non-motile control
Catalase	H_2O_2 consumption, O_2 generation, and mucus modification	Catalase-containing non-motile control
Urease	pH/ammonia changes and urease activity	Inactive-urease or chemistry-matched non-motile control

This distinction provides a basis for a more rigorous evaluation of micro/nanorobotic drug delivery and highlights the need for future studies to prioritize matched passive controls, quantitative transport measurements, mechanistic controls, and direct links between active transport and therapeutic outcomes.

DISCUSSION

Does active motion truly improve drug delivery?

The evidence evaluated in this review indicates that active motion can improve drug transport, but this effect is neither universal nor automatically attributable to propulsion. The principal advantage of active motion appears to emerge when a biological transport bottleneck limits the performance of passive carriers. Under such conditions, propulsion can provide an additional transport mechanism that increases the probability of reaching, penetrating, or interacting with a target.

However, the presence of active motion alone should not be interpreted as evidence of improved drug delivery. A substantial proportion of reported micro/nanorobotic systems combine propulsion with additional biological, chemical, or physical functions. Consequently, the observed delivery enhancement often represents the integrated performance of a multifunctional platform rather than the isolated contribution of locomotion.

The central question should therefore not be whether a micro/nanorobot can move, but whether its movement produces an incremental delivery benefit that would not be obtained from an otherwise comparable non-motile system.

Soft-robotic design features and active transport

The focus on soft micro-/meso-/nanorobots is particularly relevant to the causal question addressed in this review because compliant and biohybrid platforms can couple locomotion with adaptation to complex biological environments. Deformability, adaptive contact, wireless actuation, and biohybrid motility may alter how a carrier interacts with mucus, vessel walls, extracellular matrix, or tumor tissue. These properties can therefore create a

functional delivery advantage while simultaneously making propulsion-specific attribution more difficult.

For soft robotic drug delivery, active motion should consequently be evaluated together with the mechanical and biological features that enable that motion. A useful comparison should report not only propulsion mode and speed, but also the degree of deformability or shape adaptation, actuation modality, operating environment, cargo retention, navigation or steering capability, and the relevant biological endpoint. Where possible, matched non-motile or actuation-off controls should preserve the material, surface, cargo, and biological properties of the active system while removing the motion-generating input.

This perspective also clarifies the translational relevance of soft robotic systems. The objective is not simply to maximize locomotion, but to determine whether compliance, adaptive locomotion, or wireless control solves a defined transport bottleneck that is difficult to address with passive carriers. Evidence for clinical relevance therefore becomes stronger when robotic motion is connected to quantitative delivery, tissue interaction, therapeutic exposure, safety, reproducibility, and controllability in physiologically relevant models.

Active motion as a solution to transport bottlenecks

From a transport-physics perspective, the relevant question is not simply whether a carrier has a measurable velocity, but whether active motion contributes materially to transport relative to diffusion and physiological convection. A useful dimensionless descriptor is the Péclet number, Pe = UL/D, where U is a characteristic transport velocity, L a characteristic length scale, and D the effective diffusivity. Although biological tissues are more complex than this simple scaling relation, the framework emphasizes why propulsion should be interpreted in the context of particle size, diffusivity, tissue permeability, and local flow rather than as an isolated speed metric.

The potential value of active propulsion is highly dependent on the transport environment. In relatively unconstrained media, passive nanoparticles may already achieve sufficient

distribution through diffusion and convection, reducing the potential benefit of active motion. In contrast, environments characterized by strong physiological flow, dense extracellular matrices, mucus, abnormal tumor vasculature, or elevated interstitial pressure may create transport limitations that passive carriers cannot efficiently overcome.

This suggests that the therapeutic value of active motion is likely to be context-dependent rather than intrinsic. The more severe the transport bottleneck, the greater the theoretical opportunity for propulsion to provide an advantage.

This interpretation is consistent with experimental observations showing particularly strong improvements in systems designed to cross mucus, penetrate dense tumor tissue, or navigate under physiological flow. These environments impose physical constraints that directly interact with the mechanical capabilities of actively propelled carriers.

Accordingly, future evaluation of micro/nanorobotic drug delivery should identify the specific transport bottleneck that propulsion is intended to overcome. A claim of improved delivery is substantially more meaningful when the experimental design demonstrates that active motion directly addresses a defined limitation of passive transport.

The problem of causal attribution

One of the most important challenges identified across the literature is distinguishing correlation between motion and delivery from causation.

An actively propelled carrier may exhibit higher tumor accumulation, increased cellular uptake, or deeper tissue penetration than a passive carrier. However, these differences may result from changes in surface chemistry, enzyme activity, particle morphology, targeting ligands, local chemical gradients, or other properties that accompany propulsion.

This problem is particularly important for enzyme-powered systems. Enzymatic propulsion can simultaneously generate mechanical motion and modify the surrounding biological environment. Urease, catalase, glucose oxidase, and other catalytic components may alter

local chemical conditions, generate reaction products, consume substrates, or produce reactive species. These effects can independently influence tissue penetration, cellular uptake, and therapeutic activity.

Therefore, a stronger causal claim requires experimental controls that isolate propulsion from the accompanying chemical mechanism. Without such controls, the most appropriate interpretation is that the multifunctional active system improves delivery, while the independent contribution of motion remains uncertain.

Why multifunctionality is both an advantage and a limitation

Multifunctionality represents one of the major strengths of micro/nanorobotic drug-delivery platforms. Combining propulsion with targeting, imaging, controlled release, barrier degradation, hyperthermia, photothermal activity, or catalytic therapy can produce highly sophisticated therapeutic systems.

From an engineering perspective, this integration is advantageous because biological delivery is itself a multistep process. A carrier may need to navigate toward a target, overcome a physical barrier, release its cargo, enter cells, and produce a therapeutic effect. Combining several functions within a single platform can therefore increase overall performance.

From an evidence perspective, however, multifunctionality complicates attribution. If several mechanisms are activated simultaneously, the therapeutic outcome cannot automatically be assigned to any single component.

This creates an important distinction between two questions:

Does the multifunctional active system improve drug delivery?

and

Does active motion itself account for the improvement?

The first question can often be answered positively using existing experimental evidence. The second requires substantially stronger experimental controls.

Passive controls as the critical experimental standard

The quality of passive controls is one of the most important determinants of causal confidence. An appropriate passive control should reproduce, as closely as possible, the properties of the actively propelled system while lacking the ability to undergo active motion.

Ideally, the active and passive systems should be matched in particle size, morphology, surface chemistry, drug loading, targeting functionality, and other relevant characteristics. The principal difference should be the presence or absence of active propulsion.

This design allows the measured difference in delivery to be more confidently interpreted as a consequence of active motion.

In contrast, comparisons between an actively propelled multifunctional system and an unrelated conventional nanoparticle provide weaker evidence. Such experiments may demonstrate that the robotic system is superior to the comparator, but they cannot determine whether the improvement resulted from propulsion, targeting, barrier modification, or another difference between the platforms.

The absence of rigorous passive controls is therefore one of the major limitations preventing stronger causal conclusions in the current literature.

Quantitative advantage is more informative than qualitative demonstration

Another important observation is the difference between demonstrating improved behavior and quantifying the magnitude of improvement.

Statements such as “enhanced penetration”, “improved targeting”, or “increased uptake” are useful for establishing proof of concept but provide limited information about the practical contribution of active motion. Quantitative measurements, such as fold changes in

drug accumulation, penetration depth, cellular uptake, transport efficiency, retention time, or therapeutic response, provide substantially stronger evidence.

Nevertheless, quantitative magnitude should not be interpreted in isolation. A large fold improvement obtained using an inappropriate control may be less informative than a smaller improvement obtained using a rigorously matched passive system.

The interpretation of effect size should therefore always consider both the magnitude of the reported improvement and the quality of the experimental comparison.

From transport enhancement to therapeutic relevance

A major challenge in the field is establishing whether improvements in transport translate into meaningful therapeutic benefits.

Enhanced penetration does not necessarily result in improved treatment. A carrier may penetrate deeper into a tumor but release its drug inefficiently, fail to achieve intracellular delivery, or produce insufficient pharmacological activity. Similarly, increased tumor accumulation does not necessarily indicate increased therapeutic efficacy.

The strongest evidence therefore requires a continuous connection between transport and therapeutic outcome. Ideally, studies should demonstrate that active motion increases delivery, that increased delivery results in greater intracellular or tissue-level drug exposure, and that this increase produces a measurable improvement in therapeutic efficacy.

Studies demonstrating this complete sequence provide the most compelling evidence for the translational value of active transport.

***In vitro* versus *in vivo* evidence**

The biological complexity of *in vivo* systems creates an important distinction between *in vitro* proof of concept and therapeutic validation.

Microfluidic devices, cell cultures, and three-dimensional tumor spheroids provide valuable experimental platforms for evaluating propulsion, navigation, penetration, and cellular interactions under controlled conditions[15,17,20,25-30]. They are particularly useful for isolating individual mechanisms and comparing active and passive transport.

However, *in vivo* environments introduce additional variables, including blood flow, immune clearance, protein corona formation, tissue heterogeneity, enzymatic degradation, physiological barriers, and complex pharmacokinetics. A propulsion mechanism that produces a substantial advantage in a simplified model may therefore provide a smaller or qualitatively different benefit *in vivo*.

Consequently, evidence from three-dimensional models and animal studies should be considered particularly important when assessing the biological relevance of active transport. At the same time, *in vivo* therapeutic improvement should not eliminate the need for mechanistic controls because multiple system components can contribute simultaneously to the final outcome.

Which propulsion mechanisms offer the strongest evidence?

No single propulsion mechanism can be considered universally superior based solely on the current evidence. Instead, different propulsion strategies offer different experimental advantages and limitations.

Magnetic propulsion provides precise external control and does not necessarily require a chemical fuel within the biological environment. This makes magnetic systems particularly attractive for controlled navigation and targeted transport. However, magnetic actuation may require specialized equipment and may be difficult to implement uniformly at deep tissue sites.

Enzyme-powered propulsion can exploit endogenous or externally supplied substrates and is particularly attractive for biological environments in which the relevant chemical

reactions can occur. However, the associated enzymatic activity may itself modify the biological environment, creating substantial causal confounding.

Light-driven propulsion provides temporal and spatial control and can be combined with photothermal or photochemical effects. However, tissue penetration of the activating light and the possibility of simultaneous photothermal or photochemical activity complicate interpretation of therapeutic effects.

Acoustic propulsion can provide remote actuation and is potentially compatible with deeper tissue applications. Nevertheless, acoustic stimulation may itself influence biological structures or drug release, requiring careful controls.

Biohybrid propulsion is particularly promising because living cells or microorganisms can provide intrinsic motility, biological interactions, and tissue-specific behavior. At the same time, these intrinsic biological properties make it especially difficult to isolate locomotion as an independent variable.

Thus, the optimal propulsion mechanism should be selected according to the biological transport problem rather than according to propulsion speed alone.

Propulsion speed is not equivalent to delivery efficiency

A recurring conceptual problem in the field is the implicit assumption that faster motion necessarily produces better drug delivery.

Although propulsion speed is an important engineering parameter, delivery efficiency depends on several additional factors. These include trajectory control, residence time, cargo retention, tissue interaction, barrier permeability, targeting specificity, drug release kinetics, cellular uptake, and biological clearance.

A very rapidly moving particle may traverse a target region without establishing sufficient interaction with the tissue. Conversely, a slower carrier with efficient targeting or prolonged retention may achieve greater therapeutic delivery.

Therefore, propulsion speed should be considered a mechanistic parameter rather than a surrogate endpoint for therapeutic performance.

A related consideration is cargo retention. Active transport is beneficial only if the carrier retains its payload long enough to reach the intended compartment and releases it at an appropriate rate. Premature leakage, mechanically induced release, or excessively rapid release can decouple carrier motion from effective drug exposure. Delivery efficiency should therefore be considered as a coupled outcome of propulsion, cargo retention, release kinetics, localization, and cellular uptake.

Future studies should increasingly report delivery-related endpoints alongside propulsion characteristics to determine whether improvements in motion actually translate into meaningful improvements in drug transport.

The evidence gap between proof of concept and translation

The operational cost of propulsion should also be considered. Chemical fuels, substrates, light, ultrasound, or magnetic fields introduce requirements for energy delivery, fuel availability, equipment, dose control, or tissue penetration. A transport gain should therefore ultimately be evaluated together with the energy or operational input required to obtain it, as well as the associated safety and manufacturing burden.

The current literature demonstrates considerable progress from simple proof-of-concept nanomotors toward multifunctional systems capable of active delivery in complex biological models and animals. However, a substantial gap remains between experimental demonstration and clinical translation.

Important translational questions include long-term biocompatibility, biodegradation, immune interactions, manufacturing reproducibility, propulsion control in heterogeneous tissues, fuel availability, external-field penetration, pharmacokinetics, clearance, and safety. These considerations are particularly relevant because the same properties that enable active transport may introduce new biological risks. Catalytic reactions, persistent inorganic components, external energy sources, or complex biohybrid architectures may complicate regulatory evaluation.

Therefore, future progress should not be measured exclusively by increasing propulsion speed, penetration depth, or therapeutic efficacy in animal models. A more meaningful development pathway should simultaneously improve mechanistic understanding, control, safety, reproducibility, and causal evidence.

A proposed standard for future studies

Based on the evidence analyzed in this review, future studies evaluating active drug delivery should incorporate several experimental principles.

First, an appropriately matched passive or non-motile control should be included whenever technically feasible.

Second, delivery enhancement should be quantified using predefined and biologically meaningful endpoints.

Third, propulsion should be characterized independently from cargo release and therapeutic activity.

Fourth, potential confounding mechanisms should be experimentally controlled whenever propulsion is coupled with enzymatic, photothermal, catalytic, magnetic, or biological effects.

Fifth, transport measurements should be connected to downstream biological outcomes, including cellular uptake, tissue drug concentration, pharmacodynamic response, and therapeutic efficacy.

Sixth, studies should distinguish between system-level therapeutic efficacy and propulsion-specific efficacy.

Finally, reporting should allow independent assessment of evidence level, data quality, and causal confidence.

Such standardization would make comparisons between different micro/nanorobotic platforms substantially more meaningful and would help determine whether improvements arise from active motion, from auxiliary functionalities, or from their combination.

Overall interpretation

Taken together, the available evidence supports a nuanced conclusion. Active motion is capable of improving drug transport, particularly in biological environments where passive diffusion is strongly restricted. The strongest demonstrations occur when active propulsion is used to overcome defined transport barriers and when quantitative comparisons with passive systems are available.

However, the current evidence does not justify treating propulsion as an inherently superior drug-delivery mechanism. Many of the most successful systems achieve their effects through a combination of locomotion and additional functionalities. As a result, system-level therapeutic efficacy is generally better established than propulsion-specific therapeutic efficacy.

The most important conceptual distinction emerging from this review is therefore:
An active platform can improve drug delivery, but improved delivery does not by itself prove that active motion caused the improvement.

The future development of biomedical micro/nanorobotic drug delivery should consequently move beyond demonstrating that a system can move and instead focus on demonstrating when, where, and by how much active motion provides an incremental advantage over passive transport.

Such an evidence-based approach may ultimately identify the biological conditions in which active propulsion is genuinely necessary, rather than merely technologically possible, for achieving superior drug delivery.

CONCLUSIONS AND FUTURE PERSPECTIVES

Scope and translational alignment

The evidence synthesis is aligned with biomedical soft robotics through its focus on active drug transport, wireless or externally controlled actuation, biohybrid and stimuli-responsive systems, navigation, biological-barrier interaction, and translational constraints. Across these domains, the review treats active motion as an enabling mechanism whose value must be demonstrated against an appropriate passive or non-motile comparator.

Conclusions

Micro- and nanorobotic drug-delivery systems have demonstrated the ability to actively transport therapeutic cargo, navigate complex environments, overcome biological barriers, enhance tissue penetration, and improve therapeutic outcomes in selected experimental models. These findings establish active propulsion as a technically feasible strategy for addressing transport limitations that cannot always be efficiently overcome by passive drug-delivery systems.

However, the evidence evaluated in this review indicates that the presence of active motion should not be considered synonymous with improved drug delivery. The strongest evidence for an active-delivery advantage is obtained when actively propelled systems are directly compared with appropriately matched passive or non-motile controls and when the resulting difference is quantified using meaningful delivery endpoints.

The analysis further demonstrates that the contribution of propulsion is frequently difficult to isolate because micro/nanorobotic platforms are commonly multifunctional. Enzymatic barrier degradation, targeting interactions, magnetic deformation, photothermal effects, catalytic activity, stimulus-responsive release, and biohybrid properties may operate simultaneously with active motion. Consequently, many studies provide convincing evidence for the efficacy of the overall active platform while providing less definitive evidence for the independent contribution of propulsion.

The endpoint framework used in this review separates motion and cargo-transport observations from direct barrier-crossing evidence, quantified comparison with passive or non-motile controls, and therapeutic outcomes. Barrier crossing and comparative advantage are distinct evidence dimensions; neither, on its own, establishes that propulsion caused a therapeutic improvement. Data quality and causal confidence are considered separately for this reason.

Overall, the available evidence supports a context-dependent role for active motion. Its greatest potential appears in biological environments where passive transport encounters a defined and substantial bottleneck, including physiological flow, mucus, dense extracellular matrix, tumor stroma, and other restrictive tissue architectures. Under these conditions, active propulsion may provide an additional transport mechanism capable of increasing localization, penetration, or cargo delivery.

The central conclusion is therefore not that active motion universally improves drug delivery, but that active motion can provide an incremental advantage under appropriate biological and experimental conditions. Demonstrating this advantage requires evidence beyond propulsion itself.

Future perspectives

Future research should prioritize the development of experimental designs capable of separating the contribution of active motion from that of other functionalities. The most important methodological priority is the inclusion of appropriately matched passive or non-

motile controls. Such controls should reproduce the major physicochemical and biological characteristics of the active system while differing primarily in their ability to undergo active propulsion.

Quantitative assessment should also become a standard component of micro/nanorobotic drug-delivery studies. Rather than relying primarily on qualitative descriptions of enhanced penetration or targeting, future studies should report measurable differences in drug accumulation, penetration depth, transport efficiency, cellular uptake, retention, tissue concentration, and therapeutic response.

An additional priority is the development of mechanistic controls for multifunctional systems. When propulsion is coupled with enzymatic activity, photothermal effects, reactive oxygen species generation, magnetic deformation, or other biological mechanisms, experiments should determine whether each component independently contributes to the observed delivery improvement. This would allow the field to distinguish propulsion-dependent effects from broader multifunctional effects.

Future studies should also place greater emphasis on the relationship between transport and therapeutic outcome. Increased penetration or tumor accumulation should ideally be connected to increased local drug exposure, intracellular delivery, pharmacodynamic activity, and ultimately therapeutic benefit. Establishing this complete sequence would provide stronger evidence that active transport produces a clinically meaningful advantage rather than merely improving an intermediate transport parameter.

Translation from simplified experimental models to physiologically relevant systems represents another major challenge. Microfluidic platforms, two-dimensional cultures, and three-dimensional spheroids remain valuable for mechanistic investigation, but they cannot fully reproduce the complexity of living tissues. Future work should therefore increasingly incorporate physiologically relevant flow, extracellular matrix composition, immune interactions, tissue heterogeneity, and clinically relevant disease models.

In vivo studies should also provide more comprehensive characterization of pharmacokinetics, biodistribution, clearance, biodegradation, immune interactions, and long-term safety. These parameters are essential for determining whether the benefits of active transport outweigh the additional complexity associated with robotic propulsion mechanisms.

The field would further benefit from standardized reporting of propulsion and delivery parameters. Important variables should include propulsion speed, directionality, fuel or energy requirements, operating duration, trajectory control, cargo retention, release kinetics, transport efficiency, tissue penetration, and therapeutic response. Reporting these parameters using consistent definitions would facilitate meaningful comparison between different robotic platforms.

Importantly, propulsion speed should not be treated as a surrogate for drug-delivery efficacy. A faster nanomotor is not necessarily a better drug-delivery system. Delivery performance depends on the interaction between propulsion, targeting, residence time, tissue architecture, cargo release, cellular uptake, and biological clearance. Future studies should therefore evaluate propulsion as one component of a broader transport process.

The development of computational and quantitative transport models may also improve mechanistic interpretation. Models integrating propulsion, diffusion, convection, tissue permeability, and biological interactions could help identify the conditions under which active motion is expected to provide a meaningful advantage over passive transport. Such approaches may eventually enable researchers to predict whether propulsion is necessary for a particular delivery problem before developing a complex robotic platform.

Another important direction is the design of simpler robotic systems specifically for causal testing. Instead of maximizing the number of integrated functions, some studies should deliberately minimize auxiliary functionalities so that the independent contribution of motion can be determined experimentally. This reductionist approach could complement the development of highly multifunctional therapeutic systems.

Biohybrid systems represent a particularly promising but challenging direction. Their intrinsic biological motility, tissue interactions, and targeting capabilities may provide advantages that are difficult to reproduce using purely synthetic systems. At the same time, these properties make causal attribution more complex. Future biohybrid studies should therefore distinguish between the contribution of biological recognition, cellular activity, and locomotion.

For clinical translation, the field must ultimately address issues beyond transport performance. Manufacturing reproducibility, scalability, storage stability, sterilization, batch-to-batch consistency, biocompatibility, degradation, immune response, controllability, and regulatory requirements will strongly influence the feasibility of robotic drug-delivery platforms.

A particularly important future objective should therefore be the establishment of standardized benchmarks for active drug delivery. Such benchmarks could include matched passive controls, predefined quantitative delivery metrics, standardized biological models, explicit mechanistic controls, and reporting of both transport and therapeutic endpoints. A standardized framework would make it possible to determine whether different robotic platforms provide comparable benefits and under which biological conditions those benefits are reproducible.

Limitations of the evidence synthesis

Several limitations should be considered when interpreting this synthesis. The included studies are heterogeneous in propulsion mechanism, carrier architecture, cargo, biological model, comparator design, and delivery endpoint; reported numeric outcomes therefore cannot be pooled or compared as if they were common effect sizes. Causal attribution is constrained when propulsion is coupled to enzymatic, photothermal, catalytic, magnetic, targeting, or biohybrid effects. The E0-E5 categories and data-quality labels are author-proposed tools and are not externally validated; causal-confidence labels are qualitative author judgments rather than a numerical composite score. The manuscript does not report

independent dual screening or inter-rater reliability. It also does not provide a database-by-database search log, a final search date, record counts, or domain-by-domain assessment records for each study; the selection process and categorical ratings therefore cannot be fully reproduced from the manuscript alone. This work should be understood as a structured critical evidence synthesis, not a formal systematic review or quantitative meta-analysis. Exact fold differences for bladder-spheroid internalization and the in vivo fluorescence ratio for the NIR-driven MMS/Pt system are omitted where they could not be independently reproduced from the published figure-level data or supporting information; the corresponding qualitative outcomes are retained.

Final perspective

The development of biomedical micro- and nanorobotic drug-delivery systems represents an important evolution in therapeutic transport. Active propulsion introduces the possibility of addressing physical and biological barriers that limit conventional passive carriers. Nevertheless, technological sophistication alone does not establish therapeutic superiority.

The evidence reviewed here suggests that active motion is most valuable when it directly addresses a defined transport limitation and when its contribution can be experimentally distinguished from other functions of the delivery platform. The most convincing studies are therefore those that combine active-versus-passive comparisons, quantitative delivery measurements, mechanistic controls, and demonstrable therapeutic benefit.

In this context, the future success of micro/nanorobotic drug delivery will depend not only on making robots faster, smaller, or more multifunctional, but on establishing clear evidence for when active motion is genuinely necessary and when it provides a meaningful advantage over passive transport.

The ultimate goal should be to move from the statement that “the robot can move” to the much more consequential conclusion that “the movement improves drug delivery, the magnitude of the improvement is measurable, and the improvement can be causally attributed to active transport.”

This evidence-based distinction may provide a more rigorous foundation for evaluating the true therapeutic value and translational potential of micro/nanorobotic drug-delivery technologies.

DECLARATIONS

Authors' contributions

Seyed Masih Abtahi Naeini: conceptualization, methodology, literature analysis, evidence synthesis, writing—original draft, and writing—review and editing.

Availability of data and materials

No new datasets were generated or analyzed in this study. The review is based on information available in the cited published literature.

AI and AI-assisted tools statement

During the preparation of this manuscript, OpenAI ChatGPT was used for language editing, structural organization, and drafting assistance. The author independently reviewed, verified, edited, and approved the manuscript content and takes full responsibility for the final text.

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