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Programmable Release under Pathological Heterogeneity through an Adaptive-Control Architecture for Stimuli-Responsive Nanomedicines across Unstable Disease Microenvironments

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ABSTRACT

Stimuli-responsive nanomedicines are often designed as if one pathological cue can reliably identify a disease site and authorize payload release. That assumption is fragile when biochemical signals, vascular access, cellular composition, intracellular trafficking, and treatment response vary among patients, lesions, tissue regions, and time points. This article proposes an adaptive-control architecture that treats programmable release as a partially observable control problem rather than a single material transition. Endogenous biochemical cues and externally applied physical signals are treated as complementary but fallible inputs. A proposed sensing–decision–release sequence combines transduction, context normalization, local-state estimation, multi-input logic, confidence qualification, thresholds, temporal persistence, hysteresis, and an independent safety interlock. Release is permitted only when the estimated state and safety conditions are concordant; otherwise, the system monitors, inhibits, or fails closed. Post-action measurements may support feedback only when independently validated as surrogates of a relevant state or pharmaceutical consequence, and adaptation is restricted to predefined parameters within a prospective operating envelope. Validation must challenge the architecture under spatially and temporally heterogeneous signals, variable carrier access, protein-corona formation, biological barriers, off-target conditions, and manufacturing variation. The contribution is an original non-empirical synthesis connecting responsive nanomaterials, pathological heterogeneity, logic-gated release, safety constraints, and bounded feedback. It does not establish universal thresholds, clinical benefit, regulatory acceptance, manufacturing readiness, or autonomous therapeutic operation.

Key words: *Nanomedicine, Targeted drug delivery, Biological barriers, Intracellular release, Biodistribution, Protein corona*

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INTRODUCTION

Nanomedicine can modify solubility, circulation, biodistribution, cellular interaction, and exposure, yet its performance remains constrained by biological complexity and difficult translation from controlled models to heterogeneous disease settings [1]. A carrier may be chemically stable and stimulus-responsive but still fail to reach the relevant region, encounter the intended signal, release at the appropriate time, or produce useful intracellular exposure. These problems are particularly important for responsive systems because release depends on the environment traversed by the carrier as well as its formulated composition.

Precision nanoparticle engineering therefore requires coordination between physicochemical design and biological interaction [2]. Size, shape, mechanics, surface chemistry, payload association, ligand presentation, and degradation influence behavior only through context-dependent relationships with vascular structure, immune recognition, extracellular transport, uptake, endosomal escape, and intracellular trafficking. Targeting, accumulation, uptake, intracellular delivery, and controlled release are related but non-equivalent stages. Success at one stage does not establish the next.

Smart nanomedicine has expanded responsive materials, multifunctional carriers, imaging functions, and externally actuated delivery, but responsiveness alone cannot determine where, when, or for whom activation is appropriate [3]. Acidity, enzymes, redox state, heat, light, magnetic fields, and ultrasound may be useful triggers, yet these cues can overlap with physiology, vary across regions, and change after treatment. A fixed transition can therefore activate in an unintended context or remain inactive in a relevant one.

This Original Adaptive-Control Architecture Article proposes a sensing–decision–release framework for incomplete and changing information. It integrates disease-state heterogeneity, carrier accessibility, endogenous and external inputs, state estimation, decision logic, safety interlocks, release actuation, qualified feedback, and bounded adaptation. The framework is a conceptual synthesis, not an empirical study or clinical recommendation. Its purpose is to make assumptions, failure states, validation requirements, and decision boundaries explicit.

Disease heterogeneity as a control problem

Pathological heterogeneity includes variation in composition, function, accessibility, and therapeutic susceptibility across patients, lesions, tissue regions, cellular populations, and time. Tumours may contain genetically, phenotypically, metabolically, and immunologically distinct states that respond differently and evolve under treatment pressure [4]. From a control perspective, the system to be influenced is not fixed. Its relevant state may change while a carrier circulates, extravasates, penetrates tissue, enters cells, or releases payload.

Heterogeneity also concerns access. Nanoparticle entry into solid tumours is nonuniform and may involve different vascular and transcellular pathways [5]. A valid signal can occur where the carrier is absent, while a carrier can accumulate where the selected signal is weak, transient, or unrelated to the intended target. Signal validity and actuator accessibility must therefore be represented separately.

Targeted delivery additionally requires passage through barriers affecting circulation, extravasation, penetration, uptake, endosomal escape, organelle trafficking, and target engagement [6]. These barriers can alter residence time, biological identity, signal exposure, and release context. They function not only as efficiency penalties but also as disturbances and constraints affecting what the carrier can observe and influence.

Accordingly, controllability depends jointly on evolving disease state, transport access, and target engagement rather than carrier responsiveness alone [4-6]. The proposed state representation includes biochemical conditions, cellular composition, vascular access, carrier abundance, intracellular location, and temporal persistence, while retaining uncertainty for unmeasured variables. This representation is analytical; it does not prove that every relevant state is observable or controllable.

Endogenous and externally applied release signals

Endogenous inputs arise from pathological or physiological biology and may include acidity, enzyme activity, redox imbalance, hypoxia, reactive species, metabolites, or inflammatory mediators [7]. They can drive cleavage, conformational change, degradation, charge switching, membrane destabilization, or pore opening. Their limitation is that disease association is not disease specificity. A cue may also occur in healthy tissue, vary within a lesion, or remain below a material response range despite important disease.

Within the architecture, an endogenous signal is information about possible state or location, not automatically a release command. It may serve as a state indicator, permissive input, corroborating input, inhibitor, or uncertainty marker. A biochemical cue can indicate an acidic compartment without proving that the carrier has reached the intended cell or intracellular destination.

External signals include ultrasound, light, magnetic fields, heat, and other applied physical inputs. Ultrasound-mediated delivery illustrates how external energy can influence carrier disruption, vascular transport, or local drug availability [8]. External control may improve timing or anatomical targeting, but attenuation, motion, positioning, heterogeneous exposure, and carrier distribution can separate a commanded input from the signal experienced locally.

Dual- and multi-responsive nanomedicines can combine endogenous and external inputs or require sequential conditions [9]. Added inputs may improve contextual discrimination while increasing material complexity,

analytical burden, interaction effects, and failure opportunities. Each signal therefore requires an explicit role, accessible measurement, intended context, and negative-condition test. No signal is presumed universally necessary, sufficient, stable, or specific.

Proposed sensing–decision–release architecture

Closed-loop drug delivery provides a precedent for connecting a biological measurement with therapeutic output [10]. The proposed architecture extends that relation by separating signal acquisition, transduction, context normalization, state estimation, decision logic, uncertainty qualification, safety interlocking, release actuation, post-action observation, and bounded adaptation. This separation exposes assumptions that otherwise remain embedded within a material response.

The sensing layer includes molecular, material, cellular, or device-associated elements that convert endogenous or external inputs into interpretable carrier states. Logic-gated nanovesicles demonstrate that conditional operations can regulate programmable payload release [11]. In this architecture, however, detection does not equal permission. Observations first undergo context normalization for baseline variation, interference, and cross-signal calibration, then contribute to a local-state estimate containing both an inferred state and uncertainty.

Nanoscale logic and biocomputing provide a formal basis for multi-input decisions [12]. The decision layer may use AND rules for concordant inputs, OR rules for alternative qualifying pathways, INHIBIT rules for contraindicating states, and temporal conditions for persistence or sequence. A distinct safety interlock can veto release even when primary logic qualifies. When confidence is insufficient, the permitted outputs are monitoring, inhibition, or fail-closed withholding.

Figure 1 presents the central closed-loop architecture. Heterogeneous disease conditions and external inputs feed sensing and transduction, followed by normalization, state estimation, logic, safety review, and release actuation. Biological barriers, biodistribution, intracellular trafficking, and acquired biological identity enter as constraints. A post-action observation can become feedback only after independent validation. Adaptation may modify selected parameters within predefined bounds but cannot create a new objective, dose, or release mechanism.

The actuator may use cleavage, pore opening, degradation, membrane disruption, deshielding, or phase transition. Actuation remains distinct from pharmaceutical consequence: release does not prove tissue retention, intracellular access, target modulation, efficacy, or safety. The architecture integrates mechanisms studied separately and does not establish an implemented controller, therapeutic superiority, autonomous clinical operation, or universal applicability.

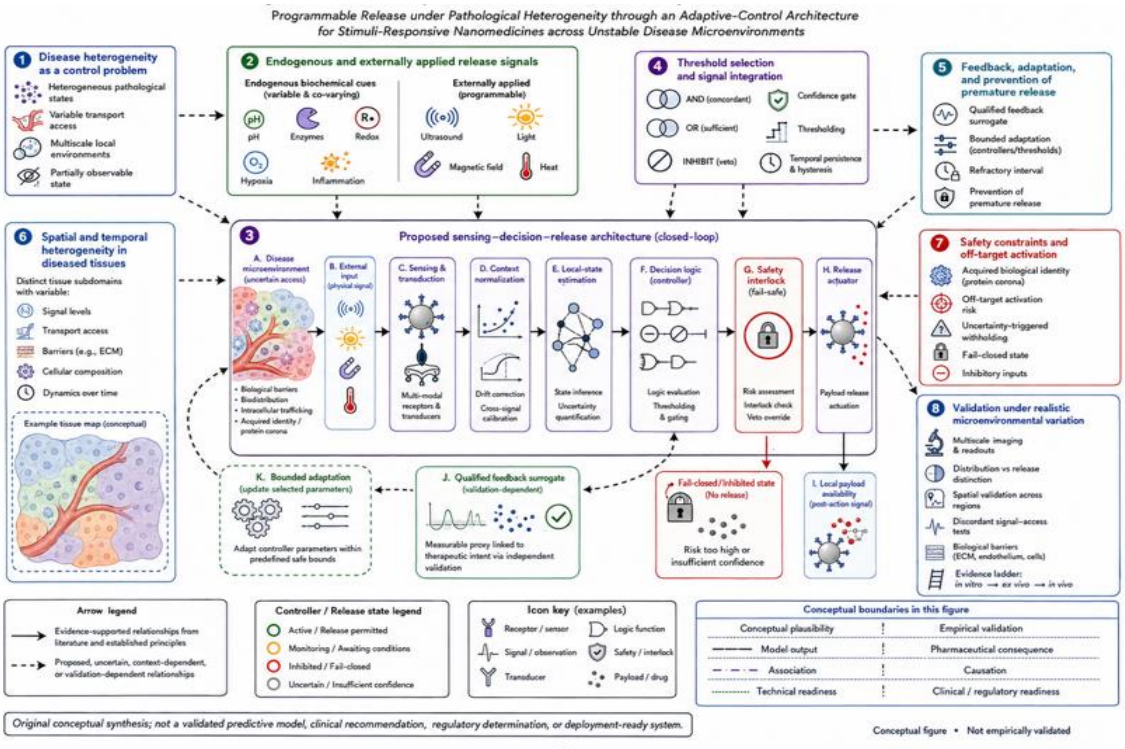

Figure 1. Closed-Loop Architecture for Stimuli-Responsive Nanomedicine

Endogenous cues and external physical inputs enter sensing and transduction, followed by proposed context normalization, local-state estimation, multi-input decision logic, and an independent safety interlock. A qualifying decision permits release actuation; uncertainty or contraindication produces monitoring, inhibition, or a fail-closed state. Biological barriers, biodistribution, intracellular trafficking, and protein-corona formation act as disturbances. A validated post-action surrogate may support bounded adjustment of selected thresholds or weights. Solid arrows denote evidence-supported mechanism classes; dashed arrows denote proposed, uncertain, context-dependent, or validation-dependent relations. The figure is an original conceptual synthesis, not a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

Threshold selection and signal integration

A release threshold is a decision boundary connecting an observed input to carrier-state change or permitted actuation. It differs from an analytical detection limit, material transition point, pharmacological effect threshold, and clinical decision threshold. Environment-reading nanocarriers show that combinations of molecular inputs can be processed as logic tasks [13]. They establish chemical feasibility but not which signals, weights, timing rules, or cut-offs are appropriate in vivo.

AND logic may reduce activation by isolated nonspecific cues, whereas OR logic permits alternative valid pathways and INHIBIT logic blocks release under contraindicating conditions. Molecular AND-gate probes demonstrate conditional discrimination between biological states [14]. Greater complexity, however, can also increase false withholding, component variability, incompatible kinetics, and opportunities for one input to fail.

Coupling endogenous and external inputs may separate biological permission from temporal authorization. A system combining matrix metalloproteinase activity with focused ultrasound illustrates joint biochemical and physical activation [15]. Such configurations remain product-specific and require evidence that both inputs reach the carrier at the required place and time.

Together, these studies support multi-input discrimination as a design principle, while not establishing any clinically valid threshold rule [13-15]. The architecture therefore proposes context-normalized thresholds, confidence gates, persistence requirements, and hysteresis. Activation and deactivation boundaries may differ to limit oscillation, while uncertainty triggers withholding. **Table 1** defines the principal components and boundaries.

Table 1. Definitions, components, relationships, and intended uses in adaptive-control release

Component	Problem addressed	Proposed relationship or function	Evidence required	Principal boundary
Pathological state	Disease varies across place and time	Represent relevant biochemical, cellular, structural, and temporal conditions	Spatial and longitudinal characterization [4]	A state vector cannot capture all biology
Transport-access state	Signal and carrier may not coincide	Separate signal validity from carrier and payload accessibility	Carrier, payload, and target-region mapping [5]	Access does not prove intracellular delivery
Endogenous input	Biological cues may be nonspecific	Use as indicator, permission, corroboration, or inhibitor	Target and non-target response testing [7]	Association is not specificity
External input	Timing may require operator control	Supply command, interrogation, or authorization	Exposure, registration, and safety testing [8]	Applied energy does not prove carrier presence
State estimator	Raw signals have multiple interpretations	Combine normalized observations with explicit uncertainty	Independent measurements of signals and tissue state	Estimate is not diagnosis
Decision logic	One input may be insufficient	Apply AND, OR, INHIBIT, sequence, persistence, and confidence rules	Comparative logic testing [14]	More logic is not necessarily better
Safety interlock	Qualified signals may still be unsafe	Veto actuation under contraindication or uncertainty	Prospective off-target and ambiguous-condition challenges	Interlock cannot replace toxicology
Release actuator	Decision must change payload availability	Execute cleavage, opening, degradation, or disruption	Leakage, kinetics, integrity, and repeatability [11]	Release does not prove benefit

Feedback surrogate	Therapeutic state may be unobservable	Admit feedback only after independent validation	Demonstrated surrogate–state relationship [10]	Convenient measurement is not valid feedback
Bounded adaptation	Fixed parameters may drift	Update selected parameters inside predefined limits	Prospective stability and domain-shift tests [10]	Autonomous self-modification is excluded

Feedback, adaptation, and prevention of premature release

Feedback requires information generated during or after action to influence a subsequent decision. This is narrower than stimulus responsiveness. Glucose-responsive insulin systems provide a useful precedent because sensed glucose, insulin output, and physiological state can be linked, while their translation exposes difficulties involving kinetics, stability, dose, and safety [16]. Most disease microenvironments lack an equally direct feedback variable.

A synthetic smart gel has demonstrated autonomous glucose-dependent insulin delivery in vivo [17]. Its relevance is architectural, not evidence that tumours, infections, inflammatory lesions, or fibrotic tissues supply equivalent controllable signals. Disease biomarkers may be indirect, intermittent, delayed, or persist after sufficient payload has already been released.

Administration route also changes responsive performance. Oral glucose-responsive delivery must negotiate gastrointestinal conditions, mucosal transport, and systemic physiology before its input–output relationship can be interpreted [18]. Intravenous, implanted, inhaled, and biohybrid carriers face different barriers that can delay sensing, alter material state, or separate the trigger from the desired release site.

Premature release may arise from baseline leakage, transient signals, cross-reactivity, non-target uptake, external-field misregistration, or repeated activation before earlier payload clears. Proposed protections include persistence checks, hysteresis, refractory intervals, maximum-release permissions, inhibitory inputs, and fail-closed behavior. Adaptation is limited to predefined parameters within a prospective operating envelope and cannot infer new therapeutic objectives or select unvalidated doses.

Spatial and temporal heterogeneity in diseased tissues

Spatial analyses demonstrate that pathological tissues contain organized local environments rather than equivalent mixtures. Multiplexed imaging has revealed structured tumour–immune neighbourhoods with distinct cellular relationships [19]. Responsive carriers may therefore encounter different biochemical cues, targets, barriers, and safety risks within adjacent regions. A bulk average may describe no actual local carrier experience.

Single-cell pathology likewise shows variation in cellular composition, phenotype, and tissue organization within and between tumours [20]. This creates separate questions about whether a carrier reaches a region, whether local cells produce the selected cue, and whether released payload can access the intended intracellular target. A correct signal classification can still lead to pharmacologically irrelevant release.

Clinical imaging has shown lesion-level and patient-level variation in nanoparticle uptake [21]. Such evidence does not establish a validated response predictor, but it supports measuring access rather than inferring it from formulation properties. Treatment can also change perfusion, inflammation, enzyme expression, permeability, cellular composition, and target abundance over time.

Spatial cellular organization, lesion-scale distribution, and patient-level uptake therefore define interacting sources of uncertainty [19-21]. Validation must include concordant and discordant combinations of disease signal, carrier access, target-cell presence, and temporal persistence rather than relying on homogeneous average conditions.

Safety constraints and off-target activation

Off-target activation differs from off-target biodistribution. A carrier may enter a non-target organ without releasing, or remain near the intended lesion while activating in the wrong cell type or compartment. Safety evaluation must therefore examine both location and the conditions under which payload becomes available.

Protein-corona formation introduces dynamic uncertainty because adsorbed biomolecules can alter nanoparticle identity, targeting, uptake, biodistribution, immune recognition, and toxicity [22]. A sensor characterized on the formulated surface may operate differently after exposure to biological fluids. Corona composition can vary with disease, patient, administration route, and time, affecting accessibility and signal interpretation.

Mechanistically informed safety assessment is required because endpoint testing may not reveal how material transformation, exposure, and biological interaction generate harm [23]. Relevant challenges include non-target

tissues containing partial trigger combinations, inflammatory environments, repeated activation, external-field exposure, degradation products, and biological fluids.

The proposed safety layer uses inhibitory inputs, uncertainty-triggered withholding, maximum-release permissions, and fail-closed states. These are design requirements, not validated guarantees. An interlock can fail because the contraindicating state is unobservable, the inhibitor is unstable, or the actuator leaks despite a withheld command. Toxicology, biodistribution, immunology, device safety, and pharmacology remain indispensable.

Validation under realistic microenvironmental variation

Validation must specify its claim. Analytical validation concerns input detection; material validation concerns carrier response; mechanistic validation concerns the proposed signal–decision–release relation; biological validation concerns function in relevant cells and tissues; and pharmaceutical validation concerns a consistent, safe product for an intended use. Evidence at one level cannot substitute for another.

Minimum-information principles for bio-nano studies emphasize material characteristics, biological conditions, protocol, dose, exposure, and measurement context [24]. Adaptive-control studies additionally require sensor calibration, input combinations, decision rules, activation history, negative conditions, uncertainty handling, actuator leakage, and any parameter update. Without these details, apparently similar systems may operate under incompatible domains.

Realistic validation must preserve spatial information. Multiscale imaging can distinguish the distributions of nanoparticle, drug, and tumour environment [25]. Tests should include regions with a valid cue but poor access, abundant carrier but weak cues, strong nonspecific signals, fluctuating boundaries, and treatment-induced temporal change. Carrier location, payload release, intracellular delivery, pharmacological action, and toxicity should remain separate readouts.

Figure 2 illustrates qualitative regional outcomes rather than measured performance. A low-signal region appropriately withholds release; an isolated nonspecific cue is inhibited; concordant cues with confirmed access permit release; a fluctuating boundary invokes persistence and hysteresis; an off-target region is vetoed; and a valid signal with poor access produces insufficient actuation. The lower comparison contrasts a simple threshold with a context-qualified rule.

A staged programme should progress from controlled inputs to mixed-signal matrices, fluctuating conditions, biological fluids, heterogeneous cultures, organotypic systems, and in-vivo spatial assessment. Computational analysis can test logical consistency and stability but cannot establish pharmaceutical consequence. **Table 2** states six falsifiable propositions and their evidence requirements. No universal sensitivity, release rate, threshold, or acceptance value is proposed.

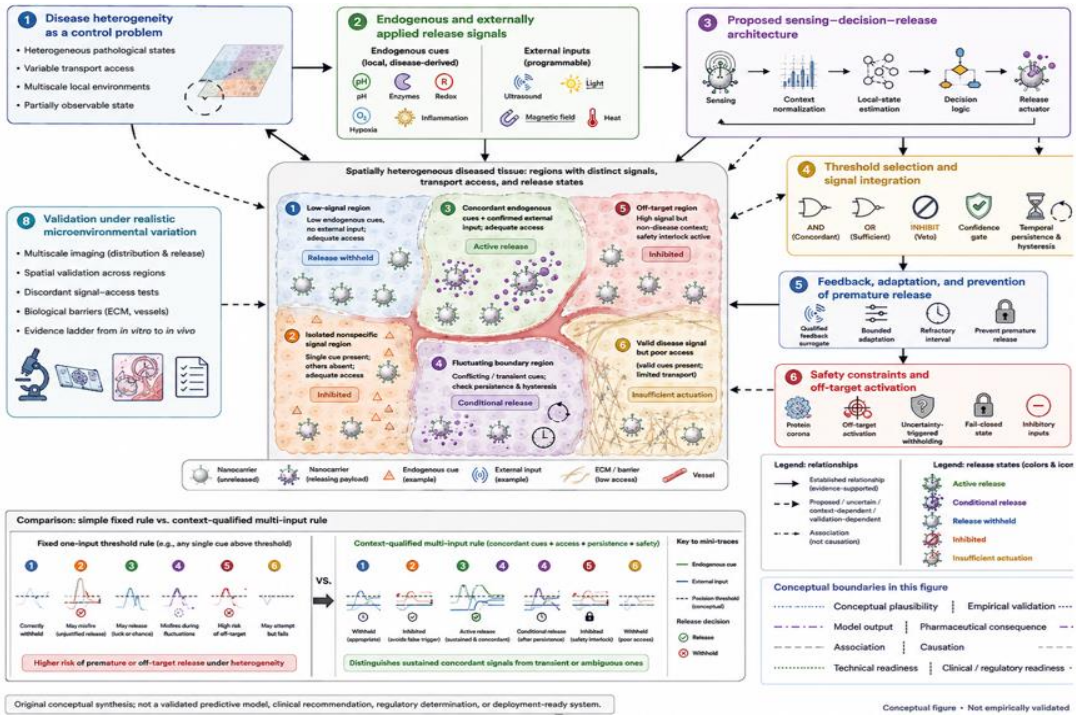

Figure 2. Release Behaviour under Spatially Heterogeneous Disease Signals

Spatial differences in pathological cues, nanocarrier access, external-input delivery, and off-target context produce distinct qualitative release states. A fixed one-input threshold can respond to a nonspecific cue, misclassify transient signals, or ignore absent carrier access. The proposed architecture instead considers signal concordance, persistence, spatial context, accessibility, uncertainty, and safety inhibition. States are shown as withheld, inhibited, conditional, active, or insufficiently actuated, without numerical release fractions. Solid arrows indicate evidence-supported relationships; dashed arrows indicate proposed or validation-dependent relations. This original conceptual synthesis does not display measured outcomes or a validated controller.

Table 2. Testable propositions and validation requirements

Proposition	Falsifiable expectation	Required challenge	Decision boundary
P1: Multi-input discrimination	Concordant-input logic outperforms its predefined one-input comparator within the same domain	Positive, isolated, discordant, and off-target signal combinations [9]	No generalization outside tested signals and models
P2: Temporal qualification	Persistence or hysteresis reduces transient activation without eliminating sustained response	Repeated threshold crossings and changing input sequences [17]	Delay and false withholding must also be measured
P3: Safety veto	Contraindicating or uncertain states withhold release despite a positive primary cue	Partial triggers, unsafe contexts, and missing observations [23]	Logical inhibition does not establish safety
P4: Spatial robustness	Region-specific failures are detectable rather than hidden by averages	Discordant maps of signal, access, target cells, and release [25]	Regional validity does not prove patient benefit
P5: Disturbance sensitivity	Barriers and corona measurably alter observations or actuation	Relevant fluids, extracellular barriers, uptake states, and trafficking [22]	Modeled disturbances cannot cover unknown biology
P6: Product consistency	Sensor, logic, interlock, and actuator behavior remain inside product-specific specifications	Batch, storage, handling, and process-change comparisons [24]	No universal manufacturing acceptance value is implied

Evaluation should also distinguish controller accuracy from pharmaceutical usefulness. A decision can be logically consistent while producing little value because the carrier is absent, the released drug cannot cross a cellular barrier, the payload is chemically damaged, or the relevant target has changed. Conversely, a pharmacological effect observed after administration does not prove that the proposed controller caused the effect, because passive leakage, nonspecific accumulation, or external stimulation alone may explain the outcome. Validation should therefore preserve causal ordering through matched controls for carrier presence, trigger exposure, logic qualification, interlock status, release, intracellular delivery, target engagement, and downstream response. Each stage should include negative and discordant conditions, and investigators should report when a stage cannot be measured directly. Repeated testing should examine whether prior activation changes later sensor response, actuator capacity, or tissue conditions, because history-dependent behavior may invalidate a nominally fixed rule. Studies should also predefine which errors are more consequential for the intended payload: false release, false withholding, delayed release, incomplete actuation, or prolonged exposure. These priorities cannot be inferred from material performance alone. They require disease-specific pharmacology, safety reasoning, and human oversight. Such claim-linked validation would allow the architecture to be simplified, revised, or rejected when added control functions do not yield interpretable benefit. It would also expose whether apparent robustness depends on one model, assay, operator, device, batch, or narrowly selected microenvironment.

Manufacturing and translational feasibility

Adaptive functionality increases the number of product attributes affecting performance. Sensor density, ligand accessibility, linker stability, material transition, payload association, leakage, kinetics, size, surface properties, and degradation may alter the effective input–output relation. Critical quality attributes must therefore connect composition and processing with claimed function [26]. Similar particle size and drug content do not establish equivalent sensing or release logic.

Scale-up may change mixing, assembly, encapsulation, surface presentation, sterilization tolerance, aggregation, residual solvents, or storage stability. In a multi-component system, small variation in one sensor or transducer

can alter the effective truth table. Manufacturing control should include functional assays covering intended signal combinations, negative states, leakage, and interlock behavior.

Translation requires alignment among disease biology, product design, manufacturing, preclinical evidence, clinical strategy, and practical delivery [27]. The intended use must specify the state to be recognized, where release is permitted, expected input combinations, consequences of false activation and false withholding, and circumstances disabling adaptation. Device-dependent systems require coordinated carrier and energy-delivery characterization.

Manufacturability should constrain architecture selection early. A simpler two-input fail-closed system may be more defensible than a highly adaptive network whose functions cannot be measured independently. The architecture does not establish successful co-formulation, sterilization, storage, scale-up, reproducibility, clinical usability, or regulatory acceptance.

Limitations and research agenda

The architecture is limited by partial observability. Important disease states may not be directly measurable, while available cues can be indirect, nonspecific, delayed, or treatment-dependent. Translation remains constrained by biological, manufacturing, clinical, and implementation hurdles that logic cannot solve alone [28]. State estimation can organize uncertainty but cannot reconstruct absent information or make inaccessible targets controllable.

Clinical experience with cancer nanomedicines indicates that no isolated feature—circulation, accumulation, ligand targeting, responsiveness, or formulation novelty—guarantees translation [29]. The framework is therefore not a universal design recipe. Its value depends on whether it improves claim clarity, experimental falsifiability, error analysis, and alignment between material function and intended use.

Research priorities include observability, cross-reactivity, threshold drift, sensor degradation, corona-mediated identity change, actuator leakage, spatial undersampling, feedback-surrogate validity, and scale-dependent function. Studies should determine when multi-input logic offers a measurable advantage over simpler rules and when complexity only creates additional untestable dependencies.

Table 3 links major failure modes to detection, safeguards, and decision responsibility. Progress should be governed by claim-specific evidence and multidisciplinary review rather than architecture sophistication. Resolving the listed questions could refine or reject the proposal but would not automatically establish efficacy, regulatory acceptance, commercial viability, or deployment readiness.

Table 3. Failure modes, safeguards, and governance needs

Failure mode	Consequence	Detection or evidence need	Proposed safeguard and decision gate	Residual boundary
Signal cross-reactivity	Unjustified release	Relevant non-target and partial-input tests [7]	Conjunction, inhibition, or narrower intended use; biology and safety review	Unknown overlaps may remain
Threshold drift	Unstable decisions over time	Longitudinal calibration and fluctuating-input tests [16]	Bounded recalibration or fixed fallback; analytical change control	Feedback may not reveal the cause
Transient activation	Premature or oscillatory release	Time-resolved repeated crossings [17]	Persistence, hysteresis, refractory interval; formulation review	Protection may delay valid release
Corona-mediated identity change	Altered uptake, sensing, or toxicity	Recharacterization in relevant fluids [22]	Uncertainty gate and biointerface testing; safety review	Patient-specific states remain difficult to model
External-input misregistration	Off-target or insufficient actuation	Spatial exposure and carrier mapping [8]	Registration and exposure interlocks; device review	Motion and attenuation remain variable
Premature leakage	Release without permission	Baseline, storage, and repeated-cycle assays [11]	Leakage specification and fail-closed design; quality gate	Zero leakage may be unattainable
Spatial undersampling	Local failure hidden by averages	Multiregion and multiscale measurements [25]	Spatial validation plan; imaging and pathology review	Sampling cannot capture every region

Batch-dependent logic change	Different effective decisions among batches	Functional signal-combination comparability [26]	Critical quality attributes; manufacturing review	Complex interactions may evade routine assays
Clinical-context mismatch	Technically correct but unusable function	Intended-use and external-validity assessment [27]	Restrict claims or redesign strategy; translational review	Clinical benefit remains unproven
Unobservable feedback	Adaptation follows an irrelevant marker	Independent surrogate validation [10]	Retain nonadaptive operation; pharmacology review	Useful feedback may remain unavailable

CONCLUSION

Programmable release under pathological heterogeneity requires more than coupling a responsive bond or transition to a nanocarrier. The proposed architecture reframes release as a sequence involving incomplete sensing, context normalization, local-state estimation, multi-input decisions, safety interlocks, actuation, qualified feedback, and bounded adaptation. It connects heterogeneous biology, barriers, endogenous and external triggers, nanoscale logic, spatial validation, and translation within one testable conceptual structure.

The framework makes withholding a legitimate controller output and separates signal detection, carrier access, payload release, intracellular delivery, pharmacological effect, and clinical consequence. A strong pathological cue may occur where carriers cannot penetrate; a carrier may reach a lesion without accessing target cells; and released payload may remain ineffective or unsafe. Uncertainty and contraindicating information must therefore influence decisions explicitly.

The architecture remains non-empirical and conditional on intended use. It provides no universal signal threshold, validated estimator, guaranteed protection, or proof that adaptive control outperforms simpler formulations. It does not establish manufacturing reproducibility, clinical benefit, regulatory acceptability, or autonomous operation. Its value will depend on whether future studies can falsify its propositions under realistic biological, spatial, temporal, and product-level variation while showing that additional complexity produces interpretable advantages within a bounded evidence domain.

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