Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

INTERPRETABLE MULTIMODAL MODELS FOR NANOCARRIER BIODISTRIBUTION USING PHYSICOCHEMICAL AND IMAGING DATA

Hassan Ali[1], Mariam Farooq[1]*, Usman Shah[2]

1. ***Department of AI Pharmaceutical Engineering, Faculty of Pharmacy, University of Lahore, Lahore, Pakistan.***
2. ***Department of Computational Drug Systems, Faculty of Engineering, National University of Sciences and Technology, Islamabad, Pakistan.***

ARTICLE INFO

Received:
10 October 2025
Received in revised form:
12 January 2026
Accepted:
15 January 2026
Available online:
28 February 2026

Keywords: Explainable AI, Nanocarrier biodistribution, Multimodal learning, Physicochemical descriptors, Molecular imaging, SHAP

ABSTRACT

Achieving predictable and favorable biodistribution is a central goal in nanomedicine. However, the relationships among nanoparticle design, imaging biomarkers, biological barriers, and organ accumulation remain complex and difficult to generalize. Current predictive approaches often operate as black boxes or depend on narrow feature sets. This makes it difficult for nanocarrier engineers to identify which modifiable particle properties drive undesirable uptake in clearance organs. This article proposes an interpretable multimodal machine learning framework for predicting organ-level nanocarrier biodistribution. The model is designed to connect physicochemical descriptors and imaging-derived features with transparent, organ-specific explanations. A multimodal architecture would combine an encoder for physicochemical features with an imaging-feature encoder. Explainability would be provided through post-hoc SHAP analysis or built-in attention mechanisms that decompose organ-uptake predictions into contributions from individual particle properties and imaging readouts.
Conceptually, the model could forecast liver, spleen, tumor, and kidney accumulation while highlighting the dominant drivers for each organ. For example, high liver uptake could be explained by low PEG density, positive zeta potential, or imaging signatures consistent with nonspecific reticuloendothelial accumulation. An interpretable multimodal approach could help close the feedback loop between prediction and nanocarrier redesign. By linking organ-level biodistribution patterns to actionable formulation variables, it could support more rational development of targeted nanomedicines.

To Cite This Article: Ali H, Farooq M, Shah U. Interpretable Multimodal Models for Nanocarrier Biodistribution Using Physicochemical and Imaging Data. Pharmacophore. 2026;17(1):12-21. https://doi.org/10.51847/BACFkkXGAS

Introduction

Nanocarriers offer a compelling route for improving drug delivery by altering circulation, tissue exposure, and cellular access, yet their clinical translation continues to be constrained by off-target organ accumulation. Biodistribution studies consistently show that liver, spleen, kidney, tumor, and blood exposure are shaped by both particle design and host biology, making organ-level fate difficult to predict from intuition alone [1]. Pharmacokinetic reanalyses of nanomedicine delivery further suggest that simple assumptions about tumor targeting can obscure substantial variability in organ exposure [2]. These challenges motivate computational frameworks that can represent biodistribution as a multi-organ prediction problem rather than a single targeting endpoint [3].

Traditional nanocarrier design has relied heavily on empirical formulation rules, iterative synthesis, and trial-and-error testing. Machine learning approaches have begun to predict nanoparticle delivery patterns from curated physicochemical and experimental descriptors, but many remain limited in how directly they explain why one formulation is favored for tumor delivery while another is redirected toward clearance organs [4]. Artificial-intelligence-assisted pharmacokinetic modeling has shown how mechanistic structure and data-driven learning can be combined, yet interpretability must be strengthened for formulation scientists who need design-level guidance [5]. Without feature-attributed reasoning, a prediction of high liver or spleen uptake may be informative but not readily actionable.

Corresponding Author: Mariam Farooq; Department of AI Pharmaceutical Engineering, Faculty of Pharmacy, University of Lahore, Lahore, Pakistan. E-mail: mariam.farooq@outlook.com.

The convergence of physicochemical characterization, quantitative molecular imaging, and explainable AI creates an opportunity to model biodistribution in a more transparent way. Imaging can reveal spatial and temporal patterns of nanocarrier accumulation, while particle descriptors such as size, charge, composition, and surface chemistry can encode the modifiable causes of those patterns [6]. Multimodal biomedical AI has already emphasized the value of combining complementary data streams, especially when image-derived and structured variables contain different but mutually informative signals [7]. In nanomedicine, this integration could allow predictions to be accompanied by explanations that distinguish image evidence from formulation-driven mechanisms.

This manuscript presents a conceptual interpretable multimodal model for nanocarrier biodistribution prediction. The proposed framework would learn from both physicochemical properties and imaging-derived features, then output organ-level uptake estimates together with feature-attributed explanations. Prior nanoparticle delivery studies using machine learning and pharmacokinetic modeling provide the foundation for such a framework [8], while broader medical XAI methods offer tools for translating model behavior into human-interpretable evidence [9]. The central thesis is that explainable multimodal prediction could move nanocarrier design from retrospective interpretation toward prospective, mechanism-aware formulation refinement.

Background

Determinants of Nanocarrier Biodistribution

Nanocarrier biodistribution is governed by interacting physicochemical factors, including hydrodynamic size, surface charge, shape, composition, stiffness, PEGylation, ligand density, and the formation of a protein corona. Studies of particle size, charge, shape, disease state, and sex emphasize that organ accumulation is not determined by a single descriptor, but by coupled design and biological variables [10]. Protein corona and blood interactions further modify the biological identity of nanoparticles, influencing mononuclear phagocyte system recognition and uptake by clearance organs [11]. For interpretable modeling, these determinants should be encoded as mechanistically meaningful features rather than anonymous numerical inputs.

Imaging Modalities for Biodistribution Quantification

Molecular and anatomical imaging modalities provide complementary routes for estimating organ-level nanocarrier distribution. PET and SPECT can provide activity-based readouts, MRI can capture contrast-related signal behavior, optical imaging can support ex vivo and whole-body visualization, and CT can contribute structural or contrast-associated information. Single-cell-resolution whole-body nanocarrier imaging illustrates how imaging can connect organism-level distribution with finer spatial patterns, even when a predictive model ultimately summarizes uptake at the organ level [12]. Machine learning in nanoparticle-based imaging also highlights the potential for image-derived features to inform rational design and precision diagnosis [13].

Multimodal Machine Learning in Drug Delivery

Multimodal machine learning is well suited to nanocarrier development because formulation descriptors and imaging measurements describe different aspects of the same biological process. In drug delivery, computational pharmaceutics has framed predictive modeling as a way to integrate formulation, process, and biological variables into model-guided decision-making [14]. Multimodal medical AI provides related architectural principles for combining tabular records, images, and derived biomarkers into unified representations [7]. For nanocarrier biodistribution, this suggests a fusion architecture that treats physicochemical data and imaging features as complementary evidence streams rather than competing alternatives.

Explainable AI for Nanoparticle Design

Explainable AI can make nanocarrier prediction more useful by identifying which particle properties or imaging signatures drive a model's organ-level outputs. SHAP-based nanoparticle models have demonstrated how feature attribution can connect delivery predictions to interpretable design variables [8]. Broader reviews of explainable AI in medicine emphasize the need to distinguish explanation methods that support trust, debugging, scientific insight, and decision support [9]. In nanocarrier biodistribution, the key gap is not merely predicting uptake, but generating explanations that align with known structure–biodistribution relationships while remaining useful for particle redesign.

Datasets and Benchmarks for Nanocarrier Biodistribution

Biodistribution benchmarks require paired information on nanoparticle design, experimental context, and organ-specific accumulation. Meta-analyses of nanoparticle delivery to tumors and major organs have begun to organize heterogeneous literature data into forms that support modeling across liver, spleen, tumor, and other compartments [1]. Physiologically based pharmacokinetic modeling provides another benchmark structure by linking predicted organ exposure to mechanistic assumptions about transport, distribution, and clearance [3]. Evaluation should therefore consider prediction accuracy, organ-specific calibration, comparison with unimodal baselines, and the biological plausibility of the model's explanations without relying on unsupported performance claims.

Model Development Overview

High-Level Prediction Pipeline

The proposed prediction pipeline would jointly process physicochemical descriptors and imaging-derived features to estimate a biodistribution vector across relevant organs. Prior machine learning studies have already framed nanoparticle delivery as a predictive task, including tumor delivery estimation from nanoparticle and biological descriptors [4]. An interpretable multimodal extension would add organ-specific explanation layers so that each predicted liver, spleen, tumor, or kidney output is accompanied by SHAP or attention-based attribution. This design turns biodistribution prediction into both a forecasting task and a formulation-reasoning task.

Core Input Features

The physicochemical input space would include hydrodynamic diameter, polydispersity, zeta potential, shape factor, PEG density, targeting ligand density, stiffness, composition, and surface chemistry. These variables reflect known determinants of blood interaction, organ retention, and clearance, as emphasized by studies of nanoparticle-blood interactions and particle design effects [11]. Imaging inputs would include region-of-interest summaries such as PET-derived uptake measures, SPECT activity patterns, MRI signal features, CT contrast-associated features, optical intensity summaries, or radiomics-style texture descriptors where appropriate. Radiomics-based nanomedicine modeling supports the idea that routine imaging-derived features can help predict nanomedicine accumulation when linked carefully to biological interpretation [15].

Design Principles

The model should be multimodal, explainable, robust to incomplete inputs, and aligned with experimental validation rather than optimized as an opaque statistical artifact. AI-assisted pharmacokinetic modeling shows that data-driven prediction can be strengthened when it remains connected to interpretable biological compartments and exposure processes [5]. Multi-view learning approaches for nanoparticle pharmacokinetics similarly suggest that different feature views can provide complementary information about systemic behavior [16]. In this framework, missing imaging data should be handled explicitly so that predictions remain transparent about whether they are driven mainly by formulation descriptors or by observed distribution signatures.

Data Sources and Feature Engineering

Compilation of Nanocarrier Biodistribution Datasets

A conceptual biodistribution database would combine literature-derived studies, institutional datasets, and imaging-linked experiments that report organ uptake alongside complete physicochemical characterization. Meta-analytic work on nanoparticle distribution in tumors and major organs provides a template for harmonizing study-level evidence across heterogeneous nanocarrier systems [1]. Machine learning studies of tissue distribution and tumor delivery also demonstrate the importance of organizing formulation, animal, tumor, and organ endpoints into model-ready data structures [17]. Because this article proposes no new experiments, dataset compilation is framed as a design requirement for future implementation rather than as a completed empirical resource.

Encoding Physicochemical Features

Physicochemical feature engineering should preserve mechanistic meaning while allowing flexible nonlinear learning. Continuous features such as size, zeta potential, PEG density, ligand density, stiffness, and polydispersity would be normalized, while categorical variables such as composition, morphology, and targeting strategy would be encoded in a way that retains formulation interpretability. Predictive nanoinformatics work emphasizes that nanomaterials require careful representation and description because incomplete or inconsistent descriptors can undermine model validity [18]. Simulation-derived descriptors for monolayer-protected gold nanoparticles further show how engineered features can connect nanoscale structure with biological or physicochemical behavior [19].

Harmonizing Multi-Modal Imaging Data

Imaging-derived features must be harmonized across modalities before they can be fused with physicochemical descriptors. PET and SPECT measures can be mapped to organ-level activity summaries, MRI and CT can contribute intensity or contrast-derived features, and optical imaging can provide whole-body or ex vivo distribution summaries when standardized region definitions are available. Machine learning applications in magnetic particle imaging illustrate how imaging models can extract distribution-relevant information from modality-specific signal properties [20]. A harmonized representation would not erase modality differences, but would encode them alongside organ, time point, and acquisition context so that explanations remain scientifically interpretable.

Table 1 organizes the proposed feature space according to its mechanistic meaning, organ-level prediction relevance, explanation value, and potential formulation-redesign implications.

Table 1. Mechanistic Feature-to-Organ Interpretation Framework for Interpretable Nanocarrier Biodistribution Modeling

Feature domain	Representative variables	Biological or experimental meaning	Primary organ-level prediction relevance	Explanation value for nanocarrier designers	Redesign implication

Particle size and dispersity	Hydrodynamic diameter, polydispersity index, size distribution width	Captures circulation behavior, extravasation potential, filtration tendency, and heterogeneity of the administered formulation	Liver, spleen, tumor, kidney, blood exposure	Indicates whether organ accumulation is being driven by physical transport constraints rather than ligand-mediated targeting	Adjust particle size distribution, reduce aggregation, or narrow batch heterogeneity
Surface charge	Zeta potential, charge density, pH-dependent charge behavior	Reflects interaction with serum proteins, cell membranes, opsonization processes, and clearance recognition	Liver, spleen, kidney	Clarifies whether predicted clearance-organ uptake is associated with electrostatic interaction patterns	Reduce strong positive charge, modify ionizable groups, or increase shielding
Surface shielding	PEG density, PEG chain length, zwitterionic coating, stealth-layer descriptors	Represents protection from protein adsorption and mononuclear phagocyte recognition	Liver, spleen, blood exposure	Helps distinguish insufficient surface shielding from other causes of liver or spleen retention	Increase PEG density, optimize coating architecture, or test alternative anti-fouling surfaces
Targeting architecture	Ligand density, ligand type, receptor-targeting strategy, multivalency	Encodes active targeting intent and potential receptor-mediated accumulation	Tumor, diseased tissue, off-target organs	Shows whether predicted tumor accumulation is supported by targeting features or dominated by passive distribution signals	Tune ligand density, alter ligand chemistry, or deprioritize ineffective targeting designs
Composition and matrix structure	Lipid, polymer, inorganic core, hybrid composition, degradation behavior	Reflects material-dependent stability, degradation, immune recognition, and clearance route	Liver, spleen, kidney, circulation	Identifies whether uptake patterns are linked to material class rather than modifiable surface variables alone	Change carrier matrix, modify polymer grade, or compare alternative nanocarrier platforms
Shape and mechanical properties	Aspect ratio, morphology, stiffness, deformability	Captures vascular transport, margination, filtration, and tissue penetration behavior	Spleen, tumor, kidney, blood exposure	Makes visible whether structural or mechanical properties contribute to organ-specific retention	Modify morphology, stiffness, or fabrication conditions
Protein-corona and blood-interaction descriptors	Corona composition, serum-binding proxies, opsonization markers	Represents biological identity after exposure to blood, not only the synthetic particle identity	Liver, spleen, circulation	Helps determine whether unexpected clearance is consistent with blood-interaction behavior	Modify surface chemistry or pre-screen corona formation under relevant biological conditions
Imaging uptake summaries	PET/SPECT activity, optical intensity, MRI/CT signal features, organ ROI values	Provides observed biodistribution evidence from experimental or preclinical imaging	Liver, spleen, tumor, kidney	Separates direct imaging evidence from formulation-derived inference	Use imaging feedback to validate or revise predicted accumulation mechanisms
Imaging texture and spatial features	Radiomics texture, heterogeneity, regional signal distribution, spatial clustering	Captures intra-organ or tumor-region distribution patterns beyond bulk uptake	Tumor, liver, spleen	Reveals whether predicted uptake is spatially uniform, heterogeneous, or regionally concentrated	Refine carrier design for penetration, retention, or reduced nonspecific accumulation
Study and acquisition context	Dose, time point, animal model, disease model, imaging modality, segmentation protocol	Captures experimental conditions that influence comparability across studies	All organ outputs	Prevents explanations from attributing study-context effects incorrectly to particle design	Standardize reporting, stratify interpretation, and avoid overgeneralizing across incompatible datasets

Interpretable Multimodal Architecture

Modality-Specific Encoders

The architecture would begin with modality-specific encoders that transform structured particle descriptors and imaging-derived features into compatible latent representations. A feed-forward encoder could process tabular physicochemical variables, while an imaging encoder could process radiomics, region-of-interest statistics, attention maps, or spatial image features when available. Multimodal biomedical AI supports this separation because each modality often carries distinct noise structure, resolution, and semantic meaning [7]. In nanocarrier imaging, modality-aware modeling is especially important because image features may reflect both true particle accumulation and modality-specific acquisition effects [13].

Fusion and Prediction Heads

After modality-specific encoding, the model would fuse physicochemical and imaging representations through late concatenation, gated fusion, or cross-attention. The fused representation would feed separate organ-specific prediction heads for liver, spleen, tumor, kidney, and other relevant compartments, allowing shared learning while preserving organ-level interpretation. Deep learning fusion of imaging and structured health records has shown that multimodal architectures require careful alignment of feature timing, scale, and clinical meaning [21]. For nanocarrier biodistribution, the same principle implies that imaging features should be fused with particle descriptors only after organ, time, and experimental context have been consistently encoded.

Figure 1 presents the proposed interpretable multimodal architecture linking nanocarrier physicochemical descriptors, imaging-derived biodistribution features, organ-specific prediction heads, explainability outputs, and formulation-redesign guidance.

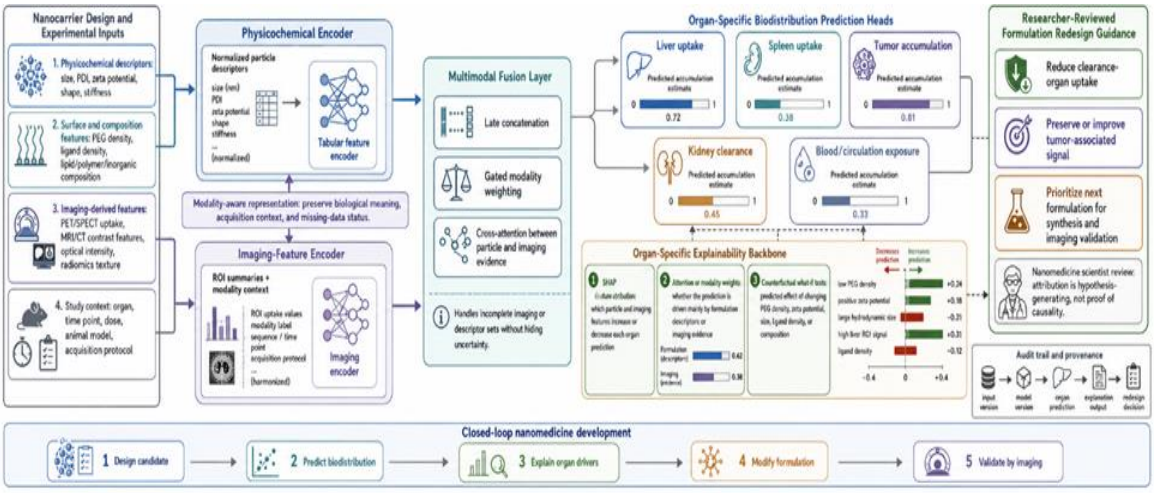

Figure 1. Interpretable Multimodal Architecture for Nanocarrier Biodistribution Prediction and Design Feedback

Explainability Backbone

The explainability backbone would provide organ-specific feature attributions rather than a single global explanation for the entire model. SHAP values could decompose each organ prediction into additive contributions from particle properties and imaging readouts, while attention weights could indicate which modality or organ-specific signal influenced a prediction most strongly. Reviews of explainable deep learning emphasize that attribution methods must be interpreted carefully and linked to the intended scientific question rather than treated as automatic mechanistic proof.

Explaining Organ-Level Uptake and Mechanistic Insights

Global Feature Importance for Biodistribution

Global explanation outputs would summarize which physicochemical and imaging features most consistently influence predicted organ uptake across the modeled formulation space. For liver accumulation, the model might identify PEG density, zeta potential, hydrodynamic size, and nonspecific imaging signal as dominant contributors, which would be consistent with literature linking surface chemistry and charge to blood interactions and clearance-organ recognition [11]. Data-driven prediction of nanoparticle biodistribution from physicochemical descriptors also supports the expectation that interpretable global patterns can be extracted from standardized feature representations [22]. These explanations should be interpreted as model-derived summaries that require biological review rather than as direct experimental proof of causality.

Local Explanation of a Single Nanocarrier's Organ Profile

Local explanations would help a designer understand why one specific nanocarrier is predicted to show a particular organ profile. For example, a SHAP waterfall plot could indicate that predicted spleen accumulation is driven more strongly by size and composition than by targeting ligand density, echoing evidence that particle size, charge, shape, disease state, and biological context can jointly alter organ distribution [10]. Machine learning models for tissue distribution and tumor delivery provide a relevant precedent for linking formulation-level descriptors to organ-specific outcomes [17]. In practice, the local explanation would be used to propose a redesign hypothesis, such as changing size or surface shielding, rather than to claim confirmed biological mechanism.

Interaction between Physicochemical and Imaging Features

A central advantage of multimodal explainability is the ability to examine interactions between particle descriptors and imaging-derived signals. SHAP interaction values or attention maps could suggest that the effect of PEG density on predicted liver uptake depends on size, while a high liver imaging signal increases the model's reliance on surface-property features during prediction. Multimodal radiomics approaches for predicting nanomedicine accumulation show how image-derived

features can complement non-imaging descriptors when estimating biological delivery patterns [15]. Such interaction explanations would be especially useful when imaging reveals an organ-specific pattern that is not fully explained by physicochemical data alone.

Counterfactual Design: "What-If" Modifications

Counterfactual explanations would allow the model to ask how a predicted organ profile might change if a modifiable design feature were altered. For instance, the model could conceptually evaluate whether increasing PEG density, reducing positive surface charge, or changing composition would be expected to reduce predicted liver uptake while preserving tumor-associated signal. Machine learning for brain-targeting delivery system design demonstrates how lab-in-the-loop strategies can connect computational predictions with iterative formulation choices [23]. In the proposed biodistribution model, counterfactuals would serve as transparent design suggestions that must be tested experimentally before being treated as valid optimization outcomes.

Explainability Methods for Nanocarrier Designers

Interactive Visualisation of Feature Contributions

An interactive visualization layer would translate organ-specific feature attributions into a format that formulation scientists can inspect without reading model internals. A dashboard could overlay SHAP contributions on a nanocarrier schematic, showing whether size, charge, PEG density, ligand density, stiffness, composition, or imaging features are increasing or decreasing predicted uptake in each organ. XAI surveys in medical applications emphasize that explanations should be matched to user needs, because a researcher debugging a model and a designer selecting a formulation may require different explanation formats [9]. Visualization would therefore be designed as a decision-support interface rather than as a decorative output.

Natural-Language Explanations

Natural-language explanations would convert attribution patterns into concise, design-oriented statements. For example, the model could state that predicted liver uptake is mainly supported by positive zeta potential and low surface shielding, while the imaging encoder contributes additional evidence from liver-region signal. Integration of artificial intelligence and nanotechnology for precision cancer medicine highlights the need for computational tools that can connect complex model outputs to actionable biomedical reasoning [24]. In this framework, generated explanations should remain cautious, using language such as "is consistent with" or "would be expected to," because attribution does not by itself establish experimental causality.

Benchmarking against Known Structure-Property Relationships

The credibility of model explanations should be benchmarked against established structure–property and structure–biodistribution relationships. If the model repeatedly attributes high liver accumulation to features inconsistent with known particle-blood interactions or mononuclear phagocyte system recognition, the explanation layer would require review even if prediction behavior appears plausible [11]. Nanoinformatics work on representing and describing nanomaterials reinforces that explanation quality depends strongly on descriptor quality and semantic consistency [18]. Benchmarking would therefore evaluate whether global and local explanations align with established nanocarrier biology while still allowing the model to reveal new testable associations.

Audit Trail and Model Governance

A governance layer would record each prediction, input feature set, explanation output, model version, and user action taken after the recommendation. Such an audit trail would be important because interpretable predictions may influence formulation priorities before synthesis or before additional imaging studies are performed. Computational pharmaceutics has emphasized the growing role of model-guided decisions in drug delivery, which makes traceability and review increasingly important [14]. For nanocarrier biodistribution, governance should document not only the predicted organ profile but also the explanation that motivated any proposed particle redesign.

Integration Into Nanomedicine Development

Pre-Synthesis Screening of Candidate Formulations

Before synthesis, the model could be used to screen virtual nanocarrier libraries and deprioritize designs predicted to show unfavorable liver, spleen, or kidney accumulation. Machine learning-guided ionizable lipid discovery illustrates how computational prioritization can accelerate formulation exploration when candidate chemistry and delivery behavior are connected through predictive modeling [25]. Similar pre-synthesis screening for biodistribution would not replace experimental validation, but it could narrow the design space toward candidates with more favorable predicted organ profiles. The explanation layer would add value by identifying which design variables are responsible for excluding or prioritizing each candidate. **Figure 2** illustrates how computational screening can narrow virtual nanocarrier formulation libraries before synthesis by prioritizing candidates with favorable predicted organ-distribution profiles and explaining the formulation variables driving inclusion or exclusion decisions.

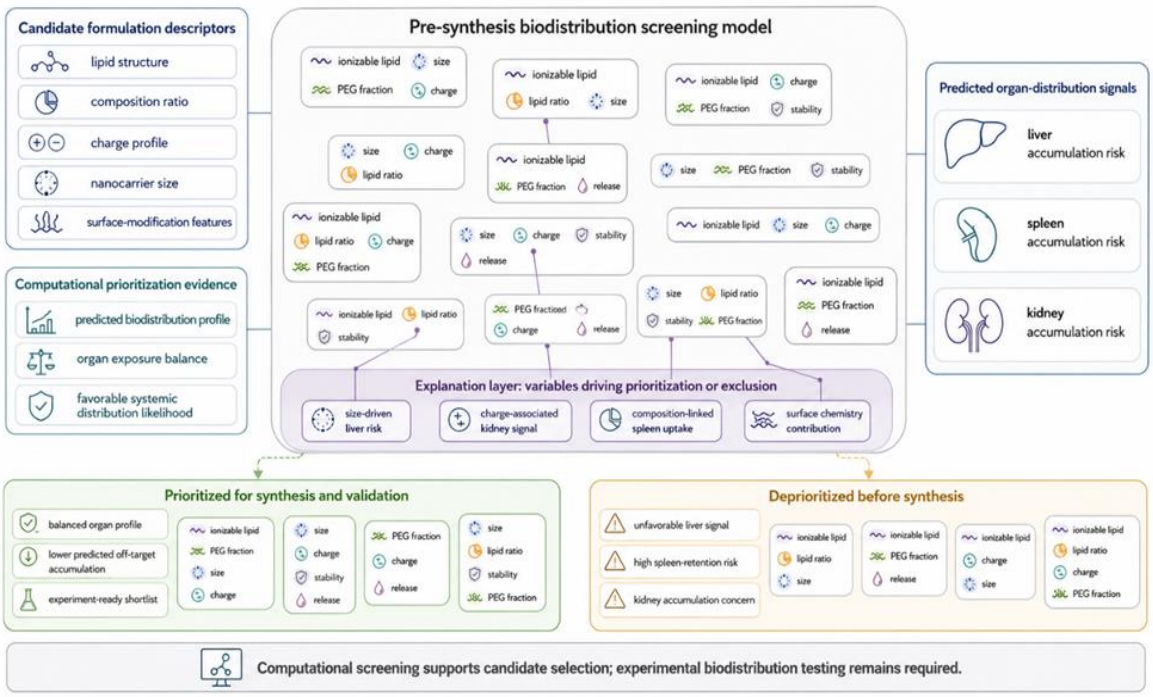

Figure 2. Pre-Synthesis Screening of Nanocarrier Formulations Using Predictive Biodistribution Evidence

Closing the Loop with Experimental Imaging

After a synthesized nanocarrier is evaluated by PET, SPECT, MRI, optical imaging, CT, or related biodistribution assays, the resulting imaging-derived features could be fed back into the model. Whole-body nanocarrier imaging at high spatial resolution demonstrates how imaging can enrich understanding of distribution beyond simple bulk organ measurements [12]. AI-assisted pharmacokinetic modeling further supports iterative refinement in which new observations update predictions and improve biological consistency [5]. This creates a design–predict–image–explain loop in which each round of imaging informs both the next prediction and the next formulation hypothesis.

Evaluation Strategy

Prediction Accuracy

Prediction accuracy should be evaluated conceptually through organ-specific error metrics, calibration behavior, and comparison with unimodal baselines, without overstating unverified numerical performance. Prior studies of nanoparticle delivery prediction and tissue distribution modeling show that model evaluation should distinguish tumor delivery, clearance-organ uptake, and systemic exposure rather than relying on a single aggregate endpoint [4, 17]. For the proposed multimodal model, physicochemical-only, imaging-only, and fused models would be compared to determine whether multimodal learning provides meaningful conceptual benefit. Any reported evaluation in a future implementation should be tied to held-out experimental evidence rather than inferred from prior literature.

Explanation Quality and Consistency

Explanation quality should be assessed by examining whether feature attributions are stable, biologically plausible, and useful for formulation decisions. Interpretable nanoparticle delivery models using XGBoost-SHAP show how attribution methods can connect predicted delivery behavior to input features, but the same principle should be extended cautiously to organ-level biodistribution [8]. Reviews of explainable deep learning emphasize that explanation fidelity and explanation usefulness are distinct, so a visually persuasive attribution map may still require formal checks against model behavior. Expert review by nanomedicine researchers would therefore evaluate whether explanations align with known biology and whether they suggest reasonable design modifications.

Utility in a Live Nanocarrier Optimization Project

Practical utility should be evaluated in a prospective or simulated optimization workflow where the model recommends design modifications intended to improve an organ-level biodistribution profile. An AI-driven targeted nanoparticle design framework that uses component-level chemical structural information supports the idea that predictive models can guide formulation exploration when inputs are sufficiently interpretable [26]. Studies applying machine learning to nanoparticle drug delivery also indicate that design guidance is most valuable when it can be connected to specific formulation variables rather than only to abstract model scores [27, 28]. In a live project, the key question would be whether model explanations help researchers choose more rational next formulations, not whether the model merely produces plausible predictions.

Table 2 defines a model-evaluation and governance framework that separates predictive accuracy, explanation quality, multimodal added value, prospective design utility, and auditability.

Table 2. Evaluation and Governance Matrix for Explainable Multimodal Biodistribution Models

Evaluation dimension	Core question	Recommended analytical approach	What successful performance would demonstrate	Main failure mode	Governance or validation safeguard
Organ-specific prediction accuracy	Does the model estimate liver, spleen, tumor, kidney, and circulation exposure with acceptable error?	Evaluate each organ separately using held-out experimental datasets and organ-specific error metrics	The model captures distinct biodistribution patterns rather than optimizing only a global average endpoint	Good aggregate accuracy hides poor performance in clinically or biologically important organs	Report organ-level metrics separately and avoid single-score model claims
Calibration of predicted uptake	Are predicted values proportional to observed organ accumulation?	Use calibration curves, prediction intervals, and uncertainty estimates by organ and modality	Predictions can be interpreted as reliable estimates rather than only rank-order scores	Overconfident predictions encourage premature formulation decisions	Display uncertainty with every organ prediction
Multimodal added value	Does fusion improve prediction beyond physicochemical-only or imaging-only models?	Compare physicochemical-only, imaging-only, and fused architectures under identical validation splits	Multimodal learning adds complementary information rather than unnecessary complexity	Fusion model performs similarly to simpler baselines while being harder to interpret	Require baseline comparison before claiming multimodal advantage
Missing-data robustness	Does the model behave transparently when imaging or descriptor fields are incomplete?	Conduct controlled feature-masking experiments and compare prediction shifts	The model identifies when predictions rely mainly on one modality and communicates reduced confidence	Missing data are silently imputed and produce misleading explanations	Record missingness status and expose modality reliance in the output
Global explanation plausibility	Do global feature-importance patterns align with known nanocarrier biology?	Compare SHAP rankings or attention summaries with established structure–biodistribution relationships	The model highlights biologically plausible drivers such as size, charge, PEG density, and imaging uptake patterns	The model attributes uptake to spurious study or acquisition variables	Require expert review of global explanations before deployment
Local explanation usefulness	Can a researcher understand why a single nanocarrier is predicted to accumulate in a specific organ?	Use SHAP waterfall plots, feature-contribution summaries, and natural-language explanation templates	Local explanations identify actionable design variables for the specific formulation	Explanation appears plausible but does not correspond to the model's actual decision logic	Pair local explanations with fidelity checks and counterfactual testing
Counterfactual design validity	Do "what-if" modifications produce biologically reasonable prediction changes?	Simulate changes to modifiable features such as PEG density, zeta potential, size, and ligand density	Counterfactuals generate experimentally testable redesign hypotheses	Counterfactuals recommend impossible or chemically incompatible modifications	Constrain counterfactuals to feasible formulation ranges
Imaging-feature interpretability	Are imaging-derived predictors understandable to nanomedicine researchers?	Map imaging features to organ ROI, modality, time point, and acquisition context	Imaging features support biological interpretation rather than acting as opaque numerical artifacts	Radiomics or texture features drive predictions without interpretable linkage	Require feature dictionaries and modality-specific documentation
Prospective design utility	Does the model improve formulation prioritization in a real or simulated development workflow?	Compare researcher decisions with and without model explanations in pre-synthesis or post-imaging redesign tasks	The model improves rational selection of next formulations for synthesis or imaging validation	Accurate predictions do not change design decisions or experimental planning	Evaluate user-facing decision impact, not only model metrics
Auditability and accountability	Can predictions, explanations, and redesign decisions be traced?	Log input version, model version, prediction output, explanation output, reviewer identity, and action taken	Each model-supported formulation decision can be reviewed retrospectively	Predictions influence development choices without traceable rationale	Maintain an audit trail for every prediction and redesign recommendation

Limitations

Data Scarcity and Standardization

A major limitation is that biodistribution data are generated under heterogeneous conditions, including differences in animal models, dosing, sampling time, imaging modality, organ segmentation, and particle characterization protocols. Meta-analytic studies help organize this heterogeneity, but they also reveal the difficulty of comparing organ uptake across studies that were not designed for unified modeling [1, 3]. Missing descriptors, inconsistent PEGylation reporting, variable imaging calibration, and incomplete negative results could all bias the learned relationships. As a result, the proposed model should be treated as a transparent decision-support system rather than as a universally generalizable predictor.

Partial Biological Scope

The model focuses on organ-level accumulation, which is useful for formulation screening but incomplete for understanding therapeutic efficacy and toxicity. Nanocarrier behavior can differ across vascular, interstitial, cellular, and subcellular compartments, and organ-level summaries may miss these biologically important distributions. Studies using high-resolution imaging and micrometastasis analysis show that spatial heterogeneity can be central to nanoparticle delivery even when bulk organ metrics appear favorable [6, 12]. Future extensions should therefore connect organ-level predictions with cellular and regional imaging features when such data are available.

Conclusion

An interpretable multimodal model for nanocarrier biodistribution would connect physicochemical design variables and imaging-derived features to organ-level uptake predictions. By producing explanations alongside predicted biodistribution profiles, the framework would make model behavior more transparent to nanomedicine researchers.

Its main strength is the translation of complex biodistribution data into design-relevant reasoning. Instead of providing only a predicted organ profile, the model would indicate which particle properties and imaging signatures most strongly support that prediction.

Important challenges remain before such a framework could be used confidently in real nanomedicine development. Data heterogeneity, inconsistent reporting, limited standardization, and the need for prospective validation all constrain the reliability of model-guided formulation decisions.

Progress will depend on collaborative data-sharing initiatives, harmonized biodistribution reporting, and integration of interpretable modeling into routine nanoparticle development workflows. With careful validation, explainable multimodal AI could support a more rational and transparent path from nanocarrier design to organ-specific delivery behavior.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

References

1. Chen Q, Yuan L, Chou WC, Cheng YH, He C, Monteiro-Riviere NA, et al. Meta-analysis of nanoparticle distribution in tumors and major organs in tumor-bearing mice. ACS Nano. 2023;17(20):19810-31.
2. Price LS, Stern ST, Deal AM, Kabanov AV, Zamboni WC. A reanalysis of nanoparticle tumor delivery using classical pharmacokinetic metrics. Sci Adv. 2020;6(29):eaay9249.
3. Cheng YH, He C, Riviere JE, Monteiro-Riviere NA, Lin Z. Meta-analysis of nanoparticle delivery to tumors using a physiologically based pharmacokinetic modeling and simulation approach. ACS Nano. 2020;14(3):3075-95.
4. Lin Z, Chou WC, Cheng YH, He C, Monteiro-Riviere NA, Riviere JE. Predicting nanoparticle delivery to tumors using machine learning and artificial intelligence approaches. Int J Nanomedicine. 2022;17:1365-79.
5. Chou WC, Chen Q, Yuan L, Cheng YH, He C, Monteiro-Riviere NA, et al. An artificial intelligence-assisted physiologically-based pharmacokinetic model to predict nanoparticle delivery to tumors in mice. J Control Release. 2023;361:53-63.
6. Kingston BR, Syed AM, Ngai J, Sindhwani S, Chan WC. Assessing micrometastases as a target for nanoparticles using 3D microscopy and machine learning. Proc Natl Acad Sci USA. 2019;116(30):14937-46.
7. Acosta JN, Falcone GJ, Rajpurkar P, Topol EJ. Multimodal biomedical AI. Nat Med. 2022;28(9):1773-84.
8. Ma X, Tang Y, Wang C, Li Y, Zhang J, Luo Y, et al. Interpretable XGBoost-SHAP model predicts nanoparticles delivery efficiency based on tumor genomic mutations and nanoparticle properties. ACS Appl Bio Mater. 2023;6(10):4326-35.
9. Tjoa E, Guan C. A survey on explainable artificial intelligence (xai): Toward medical xai. IEEE Trans Neural Netw Learn Syst. 2020;32(11):4793-813.

10. Ledford BT, Wyatt TG, Vang J, Weiss J, Tsihlis ND, Kibbe MR. Effects of particle size, charge, shape, animal disease state, and sex on the biodistribution of intravenously administered nanoparticles. Part Part Syst Charact. 2023;40(7):2300001.
11. Guha P, Heatherton KR, O'Connell KP, Alexander IS, Katz SC. Assessing the future of solid tumor immunotherapy. Biomedicines. 2022;10(3):655.
12. Luo J, Molbay M, Chen Y, Horvath I, Kadletz K, Kick B, et al. Nanocarrier imaging at single-cell resolution across entire mouse bodies with deep learning. Nat Biotechnol. 2025;43(12):2009-22.
13. Kang N, Li Z, Tan F, Liu Z, Yang Y, Qian X, et al. Machine learning for nanoparticle-based imaging: From rational design to precision diagnosis. Adv Colloid Interface Sci. 2025;337:103773.
14. Wang W, Ye Z, Gao H, Ouyang D. Computational pharmaceutics-A new paradigm of drug delivery. J Control Release. 2021;338:119-36.
15. Tang J, Zhang J, Li Y, Hu Y, He D, Ni H, et al. Interpretable radiomics model predicts nanomedicine tumor accumulation using routine medical imaging. Adv Mater. 2025;37(12):2416696.
16. Khakpour A, Florescu L, Tilley R, Jiang H, Iyer KS, Carneiro G. AI-powered prediction of nanoparticle pharmacokinetics: a multi-view learning approach. Mater Today Commun. 2025;46:113742.
17. Mi K, Chou WC, Chen Q, Yuan L, Kamineni VN, Kuchimanchi Y, et al. Predicting tissue distribution and tumor delivery of nanoparticles in mice using machine learning models. J Control Release. 2024;374:219-29.
18. Wyrzykowska E, Mikolajczyk A, Lynch I, Jeliazkova N, Kochev N, Sarimveis H, et al. Representing and describing nanomaterials in predictive nanoinformatics. Nat Nanotechnol. 2022;17(9):924-32.
19. Chew AK, Pedersen JA, Van Lehn RC. Predicting the physicochemical properties and biological activities of monolayer-protected gold nanoparticles using simulation-derived descriptors. ACS Nano. 2022;16(4):6282-92.
20. Nigam S, Gjelaj E, Wang R, Wei GW, Wang P. Machine learning and deep learning applications in magnetic particle imaging. J Magn Reson Imaging. 2025;61(1):42-51.
21. Huang SC, Pareek A, Seyyedi S, Banerjee I, Lungren MP. Fusion of medical imaging and electronic health records using deep learning: a systematic review and implementation guidelines. NPJ Digit Med. 2020;3(1):136.
22. Wu J, Wick P, Nowack B. Data-driven prediction of nanoparticle biodistribution from physicochemical descriptors. ACS Nano. 2025;19(29):26425-37.
23. Qiu Q, Li S, Zhang J, Chen J, Ding X, Liu S, et al. Lab-in-the-loop machine learning for brain-targeting delivery system design. Cell Biomater. 2025;1(9):100045.
24. Adir O, Poley M, Chen G, Froim S, Krinsky N, Shklover J, et al. Integrating artificial intelligence and nanotechnology for precision cancer medicine. Adv Mater. 2020;32(13):1901989.
25. Li B, Raji IO, Gordon AG, Sun L, Raimondo TM, Oladimeji FA, et al. Accelerating ionizable lipid discovery for mRNA delivery using machine learning and combinatorial chemistry. Nat Mater. 2024;23(7):1002-8.
26. Wu H, Cheng Y, Ji Y. Unlocking component-level chemical structural information for AI-driven targeted nanoparticle design. J Control Release. 2026;392:114704.
27. Yousfan A, Al Rahwanji MJ, Hanano A, Al-Obaidi H. A comprehensive study on nanoparticle drug delivery to the brain: application of machine learning techniques. Mol Pharm. 2023;21(1):333-45.
28. Mahdi WA, Alhowyan A, Obaidullah AJ. Intelligence analysis of drug nanoparticles delivery efficiency to cancer tumor sites using machine learning models. Sci Rep. 2025;15(1):1017.