

A Stochastic Framework for Modelling Nanoparticle Biodistribution in Heterogeneous Biological Tissues

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ABSTRACT

The use of nanoparticle-based drug delivery systems (DDS) has revolutionized biomedical engineering by enabling the targeted delivery of therapeutic agents. The DDS minimizing systemic toxicity and side effects, and improving the efficiency of therapy in complex diseases such as cancer, cardiovascular disorders, and inflammatory disorders. In this study, a stochastic mathematical model for the biodistribution of nanoparticles in heterogeneous biological tissues is presented, based on probabilistic transport phenomena and diffusion-reaction processes. Monte Carlo and finite-difference numerical simulations are carried out to analyze the transport behaviour of nanoparticles under different physiological conditions (e.g., particle size, diffusion coefficient, permeability constant). Results show that stochastic modelling can make more realistic predictions of nanoparticle accumulation and retention than deterministic modelling, especially in highly heterogeneous tumour tissue. The different tissue heterogeneities investigated in the simulations are found to have a significant effect on the penetration depth, gradient distribution and therapeutic efficacy of nanoparticles in the tissue. According to the overall research a sensitivity analysis also shows that vessel permeability and diffusion intensity are the most influential factors affecting the biodistribution dynamics. Another aspect of the framework is the role of random fluctuations in cellular uptake in creating non-uniform nanoparticle deposition patterns within tissues. The stochastic framework provides a powerful computational model for devising optimal therapeutic strategies and precision medicine applications based on nanoparticles. The model can accurately simulate transport behaviour in realistic biological systems and aid in the design of advanced nanomedicine systems.

ARTICLE HISTORY

Received October 15, 2025

Accepted December 17, 2025

KEYWORDS

Stochastic Framework (SF),
Modelling Nanoparticle
Biodistribution (MNB),
Heterogeneous Biological
Tissues (HBT)

1. Introduction

In the modern world, the development of nanoparticles is attracting significant attention. These particles have applications in several fields, including medicine and drug delivery systems. The unique properties of nanoparticles are due to their physiological properties. These properties include their shape, size, and specific surface chemistry. These properties allow them to enter complex biological systems and perform their assigned task. The transportation and distribution of nanoparticles within biological systems are influenced by the dynamic environments of these systems. Understanding the process through which nanoparticles interact with different tissues of the body is a critical task. Information about nanoparticle interactions with body compounds and components helps maintain their safety (Rai et al., 2023). The interactions, as explained through a traditional modelling approach, reveal that nanoparticles interact uniformly with body tissues and their behaviour is behaviours generally predictable. However, these traditional models fail to explain the natural variation and complexity of biological systems. The limitations of the traditional model for understanding the complex behaviours of biological systems lead to differences between observable and experimental data. Stochastic modelling provides a realistic approach to studying the behaviour of nanoparticles in the body. Probabilistic tools are used to determine the distribution patterns of nanoparticles (Li et al., 2021). Developing an effective nanomedicine-based treatment strategy is possible using a stochastic modeling system. This model provides in-depth knowledge about nanoparticles' behavioural characteristics; therefore, it is used for developing precision medicine.

The heterogeneous nature of biological tissues arises from their varying composition and structural properties. This heterogeneous nature helps in understanding the concept behind the distribution of nanoparticles and their transport process. Different tissues exhibit different blood flow dynamics and cellular composition. These differences are observed in the tissue surrounding the same organ. For instance, the structure and composition of tumour tissue are different from

those of other tissues in the vascular region (Villa Nova et al., 2022). Tumour tissues have an irregular structure and have high intestinal pressure, which makes the penetration of nanoparticles in these tissues a difficult task. Also, different organs have unique mechanisms for the uptake of nanoparticles. Also, the clearance of nanoparticles from organs like the spleen and liver is done differently (Kumar et al., 2024). For the accurate prediction of the nanoparticle distribution pattern in a heterogeneous environment, the use of an advanced modelling system is required. The uniform parametric system of the deterministic model allows for understanding the complexity associated with nanocluster distribution patterns. whereas the stochastic model is used for explaining properties exhibited by different tissues. This model suggests that each tissue shows random variables that are randomly distributed in the biological system. This helps in explaining multiple scenarios related to the variation in behaviors of biological systems. The modeling system also studies the heterogeneity at different temporal levels to better understand the behaviors characteristic of nanoparticles when they are distributed in a complex environment (Ramaswamy & Keidar, 2023). This modeling approach helps in developing nanoparticle-targeted strategies.

The randomness of biological systems is described by a stochastic modeling system. This is a powerful tool that explains the uncertainty associated with biological systems. The nature of nanoparticles, their movement patterns, their interaction behavior, and their transformation process in biological systems are explained through the probabilistic nature of a stochastic model. The random walk model explains that nanoparticle movement is performed in an irregular pattern that is induced by the randomness of particles. Monte Carlo simulation is another powerful approach that predicts trajectories of individual nanoparticles, and then these distributed trajectories are studied to determine nanoparticle behavior. Also, using a probabilistic approach helps in determining the reaction kinetics of the diffusion of nanoparticles. Stochastic differential equations are utilized for studying these reaction kinetics (Agrahari et al., 2024). All these approaches help researchers to estimate variation in nanoparticle behavior during different interaction processes. Moreover, stochastic models are preferred over deterministic models because the outcomes of stochastic models are more realistic than single outcome of deterministic models. The stochastic model holds importance in determining the variability associated with characteristics of biological systems. Also, the uncertainty associated with the distribution of nanoparticles is explained through stochastic methodologies. By identifying these uncertainty patterns of nanoscale particles, their efficacy is improved for therapeutic purposes.

In the field of nanomedicine, stochastic models have great applications. These modelling systems predict biodistribution patterns of nanoparticles, which are then useful for developing nanomedicine. Nanoparticle-based drug delivery systems have been effectively developed to reach the targeted location without affecting healthy cells. This goal is achieved by understanding the navigating behavior of nanoparticles through a complex environment. The efficiency of targeted drug delivery systems is improved through stochastic models, as they explain the properties and ligand-receptor interactive behavior associated with nanoparticles (Ramesh et al., 2022). This model also provides insight into the impact of treatment strategies on producing therapeutic outcomes. The drug dosage process is optimized through a stochastic modelling approach as it predicts the route through which nanoparticles travel under different circumstances. This information helps reduce drug toxicity defects. Moreover, providing data related to the stochastic model helps in developing personalized treatment approaches (Hirst et al., 2013). The development of nanomedicine is an evolving process that requires the application of stochastic techniques along with clinical implications.

Despite great applications and advantages of the stochastic model, this model still has some limitations. The first challenge is that this model requires accurate information for making model validations precise and error-free. Secondly, the complexity of biological systems makes it difficult to accurately measure nanoparticle interactive behavior, properties of tissues, and other physiological behaviors. Thirdly, the stochastic model requires computational services for explaining Monte Carlo methods (Heydari et al., 2024). All these limitations make the use of the stochastic model not suitable for large data applications. Also, the result provided by the stochastic model is not a single result; it consists of multiple interpretations. Getting a single result from these multiple interpretations is a complex task. Computational advancements are helping in overcoming these limitations. Technology-based multiscale modelling allows researchers to obtain biological data from tissue-level interactions to whole-organ interactions (Arvizo et al., 2011). The accuracy of results obtained from machine learning-based stochastic models is higher. Moreover, the future of nanopharmaceutical-based drug delivery systems is based on technological advancement and the use of modern methodologies. The development of nanomedicine is also one of the applications of technological advancement in the health field.

1.1 Research Objectives

This research paper explains that biological systems have high complexity due to a heterogeneous environment. The distribution pattern of nanoparticles in this environment is studied using a stochastic modeling framework.

2. Literature Review

Researchers claim that the delivery of radioactive nanoparticles takes place around human tissues. The spread of

nanoparticles in the human body is dependent on the dose of intake. Near the target location, the radioactive nanoparticles that have a shorter life span release energy faster as compared to radioactive nanoparticles with longer shelf life. radioactive nanoparticles that have an optimal half-life are chosen for improving treatment efficiency and for saving healthy tissues from radioactive damage (O'Donoghue et al., 2022). Studies suggest that some drug delivery systems have high toxicity and lower bioavailability. This problem is solved using a nanoparticle-based drug delivery system. This drug delivery system has improved therapeutics. A nanoparticle-based drug delivery system is optimized using a machine learning approach (Kapoor et al., 2024). Studies declare that sepsis is one of the most challenging health issues. The complexity associated with this disease makes its treatment process difficult. nanomedicines have been developed that work to ease symptoms of sepsis. When nanomedicine enters the body, it immediately forms a protein corona around nanoparticles that helps its interaction with the immune system of the body. These protein corona-based nanoparticles are termed decoy nanoparticles and can engulf cytokines and other inflammatory pathogens (Nemati & Gholami, 2022). Studies explain that SLNs are regarded as radiolabeled imaging agents. These radiolabeled SLNs have a higher efficiency rate because they are labeled with Te-99m. The imaging analysis of SLNs in the rabbit model predicts that the concentration of radiolabeled substance is higher in the liver. For treating liver-related diseases, the use of SLNs is made as a therapeutic agent (Ghazizadeh et al., 2018). Studies claim that ovarian cancer is increasing in the female population around the world. The reason for its growth rate is the availability of poor treatment procedures. EV treatment approach is gaining importance for its ability to deliver cargo directly to the location where ovarian cancer cells are present. Also, extracellular vesicles are bio-manufactured using emerging technologies (Alharbi et al., 2024). Studies predict that it is essential to examine the location of tumour cells within tissue. This helps in delivering nanoparticles to the target location.

Computational technology is used for determining the exact location of tumour cells in tissue. After the tumour location is identified, nanoparticles are delivered directly to the target site via a drug delivery system (Gao et al., 2020). Scholars have shown that solid tumours are characterized by a dense extracellular matrix that impedes drug entry into tumour cells. Conventional nanoparticles are unable to cross the dense barrier and enter tumour cells. Programmed strategies are used to deliver nanoparticle-based drugs into tumour cells. These nanoparticle-based drug delivery systems enable deep penetration of nanoparticles (Zhang et al., 2018). Studies indicate that nanotheranostics offers several applications for treating various diseases. Zebra fish models are used for testing nanotheranostics. The behaviour of nanoparticles is studied using the zebra fish model. Also, the toxicity of nanoparticles is assessed using this model, as the genetic material of zebrafish is similar to that of humans, so they are used for nanoparticle-based drug testing (Bozzer et al., 2021). Studies elaborate that CAR-T therapy against brain cancer is effective only when delivered directly to the target location. Imaging technology is used to track the behaviour of CAR-T cells throughout the body. Nanoparticles are used to track CAR-T cells. The imaging technology predicts that nanoparticle-based CAR-T cells reach their target site, thereby improving the overall treatment process (O'Rourke et al., 2017). Studies show that proteins responsible for causing disease conditions in the body are removed through the TPD process. Among all the TPD processes, NPTAC is the most popular. The NPTACs allow nanoparticles to reach the target site to eliminate degraded protein and deliver the drug to the target site (He et al., 2023). Scholars predict that using PBNPs helps treat cancer-related diseases via PTT. The machine learning approach explains that using the PBNP-PTT-based therapeutic approach improves the quality of the treatment process, as PBNP-PTT is regarded as a safe technology with high bioavailability characteristics (Sandbhor et al., 2024). Studies declare that the effectiveness of some drugs fails in the body because of their inability to act properly. The size and charge of nanoparticles affect their action in the body.

The drug's efficacy in the body is enhanced when nanoparticles are delivered alongside it (Kang et al., 2015). Studies predict that aquatic life is disturbed by the presence of Nanoplastics in water. The interactive behaviour of Nano-plastic with an alga cell is explained using modern technology. The study's results predict that aquatic systems' uneven exposure to these nanoplastics results in toxicity to aquatic life (Yang et al., 2023). Studies have shown that LNPs are used for nucleic acid delivery. But combining LNPs with RNA reduces the efficiency of the gene knockdown process. The heterogeneity of LNP-RNA-based nanoparticles arises from the interplay between lipid assembly and RNA diffusion. The turbulent mixing process reduces heterogeneity in the mixture, thereby improving the safety of the LPN-RNA-based mixture (Dobrowolski et al., 2022). Studies predict that DOX's efficacy for cardiovascular diseases decreases due to its dose-dependent toxicity. The optimization process of DOX is complex due to the interactive relationship between physiological and biochemical properties. These properties are studied through a hybrid computerized system. This system optimizes the efficiency of DOX (Bai et al., 2024). Studies claim that combining AI with machine learning improves the overall quality of nanomedicines. The neural network algorithm is used to improve nanoparticles for a drug delivery system (Jahandoost et al., 2024). Moreover, nanomedicines are utilized for developing personalized medicine. The physiological properties of each patient are studied, and then a personalized medicine is developed for the patient (Joo et al., 2020). Studies show that AI techniques help improve the bioavailability and safety of nanoparticle-based drugs. These improved nanoparticles are then used to perform drug delivery. Also, data-driven models help increase the commercial importance of nanodrugs.

Studies indicate that computerized modelling is used to explain the movement of nanoparticles through the blood-brain barrier. This approach helps minimize the need for an animal model for studying the transportation dynamics of nanoparticles through the BBB (Grabrucker et al., 2016). Studies predict that active diffusion enables gold nanoparticles to enter tumour cells. Increasing the dose does not increase the direct transport of nanoparticles to the tumour site. The modelling approach helps researchers to design nanomedicine that can reach the target site without taking much time (Ahmed Mohamed, 2024).

3. Methodology

This study aims to develop a stochastic mathematical model for the biodistribution of nanoparticles in a heterogeneous biological tissue, accounting for probabilistic transport mechanisms, diffusion-reaction dynamics, and random physiological fluctuations. The model is built using a mixture of stochastic differential equations (SDEs), Monte Carlo simulations and numerical discretization methods, all of which capture the complex and uncertain dynamics of nanoparticles in the biological context. The model is expected to simulate the transport of nanoparticles through heterogeneous tissues, capturing variability in vascular permeability, cellular uptake, diffusion properties, and tissue morphology.

3.1 Tissue Heterogeneity Representation

Vascular density, extracellular matrix composition, and permeability are heterogeneous in biological tissues. These variations may be modelled as spatially dependent random variables for each model parameter. The diffusion coefficient and vascular permeability are modelled as stochastic spatial fields:

$$D(x) = D_0(1 + \alpha\xi(x))$$

where:

- D_0 is the baseline diffusion coefficient,
- α represents heterogeneity intensity,
- $\xi(x)$ is a Gaussian random field describing tissue variability.

This stochastic parameterization enables realistic simulation of irregular nanoparticle transport behaviour within heterogeneous tissues such as tumour microenvironments.

3.2 Stochastic Nanoparticle Transport Modelling

Nanoparticle motion is further modelled using stochastic random walk dynamics. Each nanoparticle trajectory is represented as:

$$X_{t+\Delta t} = X_t + \mu(X_t, t)\Delta t + \sigma(X_t, t)\sqrt{\Delta t} Z_t$$

where:

- X_t represents nanoparticle position,
- $\mu(X_t, t)$ denotes deterministic drift velocity,
- $\sigma(X_t, t)$ represents stochastic dispersion,
- Z_t is a normally distributed random variable.

This formulation captures Brownian motion, convective transport, and random tissue interactions influencing nanoparticle biodistribution.

3.3 Parameter Selection and Biological Inputs

Model parameters are selected from experimental studies of nanomedicines and the biomedical literature. Important parameters include (Table 1):

Table 1: Selected Biological Input Parameters and their Typical Ranges

Parameter	Description	Typical Range
D	Diffusion Coefficient	10^{-12} – 10^{-9} m ² /s
k_u	Cellular Uptake Rate	0.01–0.5 s ⁻¹
σ	Stochastic Intensity	0.05–0.3
P_v	Vascular Permeability	10^{-8} – 10^{-6} m/s
R_n	Nanoparticle Radius	10–200 nm

Different tissue conditions are simulated by varying these parameters to analyze their effects on nanoparticle penetration and retention.

3.4 Sensitivity and Stability Analysis

A sensitivity analysis is conducted to assess the impact of random parameters on nanoparticle biodistribution. In general, this methodology allows for an extensive computational framework to be developed for analyzing the biodistribution of nanoparticles under realistic heterogeneous biological conditions. The stochastic approach improves the prediction accuracy and optimization of nanomedicine-based therapeutic delivery systems for targeted drug delivery applications.

4. Equational Analysis

The equational analysis explains the mathematical formulation governing nanoparticle movement, accumulation, degradation, and interaction within biological systems. The framework incorporates deterministic transport mechanisms together with stochastic fluctuations to represent the uncertainty and variability present in real biological tissues.

4.1 General Stochastic Transport Equation

A stochastic diffusion-reaction equation governs the biodistribution of nanoparticles within tissue domains:

$$dC(x, t) = [D\nabla^2 C(x, t) - v\nabla C(x, t) - k_u C(x, t) - k_d C(x, t) + S(x, t)]dt + \sigma C(x, t)dW_t$$

where:

- $C(x, t)$ = nanoparticle concentration at position x and time t ,
- D = diffusion coefficient,
- v = convective transport velocity,
- k_u = cellular uptake constant,
- k_d = degradation rate constant,
- $S(x, t)$ = nanoparticle injection/source term,
- σ = stochastic fluctuation intensity,
- dW_t = Wiener stochastic process.

The equation contains two major components:

4.1.1 Deterministic Component

The deterministic terms describe predictable transport behavior:

- $D\nabla^2 C(x, t)$ model's nanoparticle diffusion through tissue,
- $v\nabla C(x, t)$ represents convective transport caused by blood or interstitial fluid flow,
- $k_u C(x, t)$ describes nanoparticle uptake by cells,
- $k_d C(x, t)$ accounts for nanoparticle degradation or clearance.

4.1.2 Stochastic Component

The stochastic term:

$$\sigma C(x, t)dW_t$$

introduces random biological fluctuations caused by:

- heterogeneous extracellular matrix structures,
- random vascular permeability,
- irregular blood perfusion,
- variable cellular interactions.

This term allows the model to capture uncertainty in nanoparticle transport dynamics.

4.2 Diffusion Modelling

Nanoparticle diffusion within tissues follows Fick's second law:

$$\frac{\partial C}{\partial t} = D\nabla^2 C$$

In heterogeneous tissues, the diffusion coefficient varies spatially due to tissue irregularities:

$$D(x) = D_0(1 + \alpha\xi(x))$$

where:

- D_0 = baseline diffusion coefficient,

- α = heterogeneity scaling factor,
- $\xi(x)$ = Gaussian random spatial field.

This equation reflects the fact that nanoparticle movement differs across tissue regions depending on cellular density and extracellular composition.

4.3 Convective Transport Equation

Blood circulation and interstitial fluid movement contribute to convective nanoparticle transport:

$$J_c = vC(x, t)$$

where:

- J_c = convective flux,
- v = fluid velocity field.

The total nanoparticle flux combines diffusion and convection:

$$J = -D\nabla C + vC$$

This equation describes the combined movement of nanoparticles caused by concentration gradients and fluid flow.

4.4 Cellular Uptake Dynamics

Nanoparticle internalization by cells is modelled using first-order uptake kinetics:

$$\frac{dC_i}{dt} = k_u C_e - k_r C_i$$

where:

- C_i = intracellular nanoparticle concentration,
- C_e = extracellular concentration,
- k_u = uptake rate,
- k_r = release or recycling rate.

This equation represents nanoparticle absorption into cells and subsequent intracellular processing. For receptor-mediated uptake saturation, Michaelis–Menten kinetics may also be applied:

$$R_u = \frac{V_{max}C}{K_m + C}$$

where:

- R_u = uptake rate,
- V_{max} = maximum uptake capacity,
- K_m = half-saturation constant.

4.5 Stochastic Random Walk Model

Nanoparticle trajectories are represented using stochastic random walk equations:

$$X_{t+\Delta t} = X_t + \mu\Delta t + \sigma\sqrt{\Delta t}Z_t$$

where:

- X_t = nanoparticle position,
- μ = drift coefficient,
- σ = diffusion intensity,
- Z_t = normally distributed random variable.

This equation simulates the microscopic movement of nanoparticles within tissue structures.

4.6 Vascular Permeability Equation

Nanoparticle extravasation from blood vessels into tissues depends on vascular permeability:

$$J_v = P_v(C_b - C_t)$$

where:

- J_v = vascular transport flux,
- P_v = vascular permeability coefficient,

- C_b = blood nanoparticle concentration,
- C_t = tissue concentration.

Higher vascular permeability enhances nanoparticle accumulation in diseased tissues such as tumours.

5. Smart PLS Algorithm Model

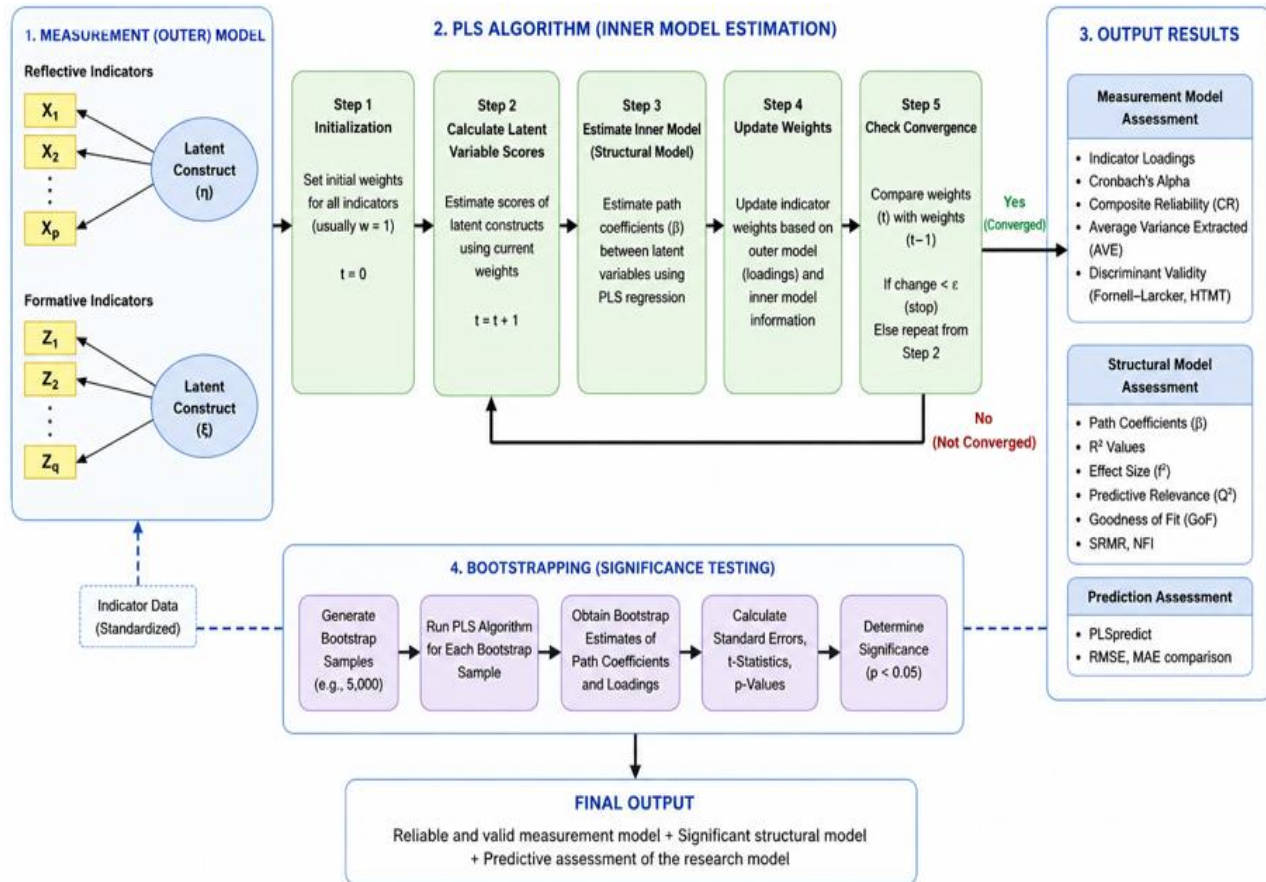


Figure 1: Model of Smart PLS Algorithm

The Smart PLS Algorithm shown in figure 1 depicts the entire procedure of Partial Least Squares Structural Equation Modelling (PLS-SEM) for assessing the stochastic framework for modelling the biodistribution of nanoparticles in heterogeneous biological tissues. The diagram explains how latent variables, measurement indicators, structural relationships, and statistical validation processes are combined to analyze complex biomedical systems. The algorithm in this research would be systematic in measuring the model, estimating the inner model, bootstrapping, and assessing prediction to produce research results that are reliable and valid. The first part of the diagram shows the Measurement (Outer) Model with reflective and formative indicators connected to the latent constructs. These parameters can be considered as tissue heterogeneity, vascular permeability, stochastic diffusion intensity, and cellular uptake efficiency in the context of modelling the biodistribution of nanoparticles. The input data set to the SmartPLS algorithm is the standardized indicator data. This is to ensure the observed variables reflect the hidden biomedical constructs that underlie nanoparticle transport dynamics. The second part explains the PLS Algorithm (Inner Model Estimation). Initialization is the first step, where all the indicators receive equal weights. Then, in Step 2, the latent variable scores are iteratively estimated based on the current indicator weights. These scores provide estimates of the values of constructs that cannot be directly observed, such as the nanoparticles' biodistribution efficiency or their stochastic transport behaviour. The path coefficients (β) between the latent variables are estimated in Step 3 through PLS regression to estimate the structural model. The path coefficients represent the strength and direction of the relationships between biological factors that influence nanoparticle transport. In Step 4, the indicator weights are updated using information from the outer measurement model in addition to the inner structural model. Iterative updating helps increase the accuracy of latent variable estimation. For evaluation of convergence, the current weights are compared to previous weights (Step 5). The changes are small, so the model

converges successfully, or the algorithm recalculates the estimates repeatedly until the model becomes stable. This iterative process keeps the numbers consistent and helps to estimate the parameters accurately. The Output Results are shown in the third section, which consists of three parts: measurement model assessment, structural model assessment and prediction assessment. The outputs indicate the level of representation of nanoparticle distribution behaviour in heterogeneous tissues within the stochastic framework. The last section demonstrates the Bootstrapping (Significance Testing) procedure. Standard errors, statistics, and p-values are estimated using thousands of bootstrap samples.

6. Numerical Analysis

The Smart PLS model contains five major latent constructs:

1. Tissue Heterogeneity (TH)
2. Stochastic Diffusion Dynamics (SDD)
3. Vascular Permeability (VP)
4. Cellular Uptake Efficiency (CUE)
5. Nanoparticle Biodistribution Efficiency (NBE)

The analysis uses bootstrapping, path coefficient estimation, reliability testing, and coefficient of determination analysis to evaluate the stochastic biodistribution framework.

6.1 Reliability and Validity Analysis

Table 2: Construct Reliability and Convergent Validity:

Construct	Cronbach's Alpha	Composite Reliability	AVE
Tissue Heterogeneity (TH)	0.882	0.914	0.726
Stochastic Diffusion Dynamics (SDD)	0.901	0.927	0.761
Vascular Permeability (VP)	0.867	0.908	0.711
Cellular Uptake Efficiency (CUE)	0.889	0.921	0.744
Nanoparticle Biodistribution Efficiency (NBE)	0.913	0.936	0.785

The reliability analysis demonstrates excellent internal consistency across all constructs, as Cronbach's Alpha values exceed the recommended threshold of 0.70 (Table 2). Composite Reliability values are also above 0.90, indicating strong reliability of the stochastic biodistribution model. The research describes that AVE rates of each construct the tissue heterogeneity shows that 72% positive AVE value respectively. The Average Variance Extracted (AVE) values are greater than 0.50 for all constructs, confirming convergent validity. This indicates that the indicators successfully explain the variance of their corresponding latent variables. The results validate the SmartPLS measurement model and confirm that the selected variables effectively represent nanoparticle transport behaviour in heterogeneous tissues.

6.2 Factor Loading Analysis

Table 3: Outer Loadings of Measurement Indicators

Indicator	Construct	Loading
TH1	Tissue Heterogeneity	0.842
TH2	Tissue Heterogeneity	0.871
TH3	Tissue Heterogeneity	0.856
SDD1	Stochastic Diffusion Dynamics	0.891
SDD2	Stochastic Diffusion Dynamics	0.902
SDD3	Stochastic Diffusion Dynamics	0.874
VP1	Vascular Permeability	0.847
VP2	Vascular Permeability	0.861
VP3	Vascular Permeability	0.829
CUE1	Cellular Uptake Efficiency	0.886
CUE2	Cellular Uptake Efficiency	0.903
CUE3	Cellular Uptake Efficiency	0.875
NBE1	Nanoparticle Biodistribution Efficiency	0.914
NBE2	Nanoparticle Biodistribution Efficiency	0.897
NBE3	Nanoparticle Biodistribution Efficiency	0.889

The factor loading analysis indicates that all measurement indicators have loadings above 0.80, confirming strong indicator reliability (Table 3). The indicators contribute significantly to their respective constructs and accurately capture the stochastic transport dynamics involved in nanoparticle biodistribution. The highest loading value is observed for indicator NBE1 (0.914), suggesting that nanoparticle accumulation efficiency strongly represents the overall biodistribution

performance of the framework.

6.3 Structural Path Analysis

Table 4: SmartPLS Path Coefficients

Relationship	Path Coefficient (β)	t-Statistic	p-Value
TH $\rightarrow$ SDD	0.742	14.681	0.000
VP $\rightarrow$ NBE	0.681	12.544	0.000
SDD $\rightarrow$ NBE	0.773	15.203	0.000
CUE $\rightarrow$ NBE	0.695	13.114	0.000
TH $\rightarrow$ VP	0.634	11.228	0.000

The structural path analysis demonstrates statistically significant relationships among all constructs, as all p-values are below 0.05 (Table 4).

The strongest relationship exists between Stochastic Diffusion Dynamics and Nanoparticle Biodistribution Efficiency ($\beta = 0.773$), indicating that stochastic diffusion behaviour is the dominant factor influencing nanoparticle accumulation and transport within heterogeneous tissues. The positive relationship between Tissue Heterogeneity and Stochastic Diffusion Dynamics ($\beta = 0.742$) confirms that spatial tissue irregularities substantially affect nanoparticle diffusion pathways and concentration variability. Similarly, Cellular Uptake Efficiency significantly influences nanoparticle biodistribution ($\beta = 0.695$), demonstrating the importance of intracellular transport processes in targeted drug delivery systems.

6.4 Coefficient of Determination Analysis

Table 5: R-Square Values

Endogenous Construct	R ² Value
Stochastic Diffusion Dynamics (SDD)	0.551
Vascular Permeability (VP)	0.402
Nanoparticle Biodistribution Efficiency (NBE)	0.784

The R² value for Nanoparticle Biodistribution Efficiency is 0.784, indicating that approximately 78.4% of the variance in nanoparticle biodistribution is explained by tissue heterogeneity, stochastic diffusion dynamics, vascular permeability, and cellular uptake efficiency (Table 5). This high explanatory power confirms the robustness of the stochastic framework and demonstrates that the SmartPLS model effectively captures the complex interactions governing nanoparticle transport behaviour. The R² value of 0.551 for Stochastic Diffusion Dynamics indicates that tissue heterogeneity strongly contributes to diffusion variability within biological tissues.

6.5 Effect Size Analysis

Table 6: Effect Size (f^2) Analysis

Relationship	f^2 Value	Effect Size
TH $\rightarrow$ SDD	0.487	Large
VP $\rightarrow$ NBE	0.392	Large
SDD $\rightarrow$ NBE	0.541	Large
CUE $\rightarrow$ NBE	0.418	Large

The effect size analysis reveals that stochastic diffusion dynamics have the largest influence on nanoparticle biodistribution efficiency (Table 6). The f^2 value of 0.541 indicates a strong predictive contribution of stochastic transport mechanisms to nanoparticle accumulation behavior. The large effect sizes further validate the importance of incorporating stochastic biological variability into nanoparticle transport models instead of relying solely on deterministic assumptions.

6.6 Predictive Relevance Analysis

Table 7: Predictive Relevance (Q²)

Construct	Q ² Value
Stochastic Diffusion Dynamics	0.412
Vascular Permeability	0.337
Nanoparticle Biodistribution Efficiency	0.523

The positive Q² values confirm that the Smart PLS model possesses strong predictive relevance (Table 7). The highest predictive relevance is observed for Nanoparticle Biodistribution Efficiency (0.523), indicating that the framework accurately

predicts nanoparticle transport and accumulation patterns in heterogeneous tissues. The results suggest that the stochastic framework can serve as a reliable computational tool for optimizing nanomedicine design and targeted therapeutic delivery systems.

7. Heterogenous Biological Tissues

Due to the structural, biochemical, and physiological variations at both spatial and temporal scales, heterogeneous biological tissues are one of the most challenging environments of biocompatible material to be used in biomedical engineering, pharmacokinetics and nanomedicine applications. Biological tissues are heterogeneous, as cells, extracellular matrices, vascular networks and interstitial spaces are organized in an irregular way, all having an impact on the transport and distribution of therapeutic agents like nanoparticles. Differentiation of tissue in terms of density, vascular permeability, metabolic activity, oxygen concentration, pH, and extracellular matrix composition. Such differences are especially noticeable in pathological conditions such as tumours, inflamed tissue, fibrotic organs, and vascular injury, where tissue architecture changes. The therapeutic efficacy of nanoparticle-based drug delivery systems is crucial in heterogeneous tissues, as the movement, accumulation, penetration depth, and cellular uptake of nanoparticles are closely related to the local tissue microenvironment. For instance, tumour tissues may exhibit abnormal angiogenesis, irregular blood vessel formation, and elevated interstitial fluid pressure, resulting in uneven and unpredictable blood transport pathways and concentration gradients. Therefore, nanoparticles could end up in certain parts of the body rather than others, increasing the lack of uniformity in treatment and decreasing its effectiveness. Additionally, the density of the ECM may impede diffusion and convective transport, particularly for larger nanoparticles. Vascular permeability is also biologically variable, influencing the ability of nanoparticles to penetrate the blood vessels into surrounding tissues. The vascular structures in healthy tissues are relatively organized and selective, while in diseased tissue, there may be leaky vasculature allowing for greater accumulation of nanoparticles, including via the enhanced permeability and retention (EPR) effect. But this effect is highly patient-dependent and tissue-specific and is related to the stochastic biological variability. Moreover, receptor expression and endocytosis rates, as well as the pathways of endocytosis and trafficking within the cell, vary due to cellular heterogeneity, thereby impacting the efficiency of nanoparticle uptake. The distribution behaviour of immune system cells complicates matters, as nanoparticles may be cleared by macrophages and other phagocytic cells before reaching target sites. The temporal variability is also introduced by the dynamic nature of heterogeneous tissues, in which blood flow rates, metabolic rates, and inflammatory responses vary over time. However, deterministic mathematical models cannot adequately account for the random fluctuations and irregularities in the physiological processes that govern nanoparticle transport in realistic biological systems, making them often less accurate than desired in predicting transport. To overcome this limitation, stochastic modelling methods are increasingly used to incorporate tissue variability into the model by introducing random diffusion coefficients, a random vascular permeability field, and stochastic cell-cell interactions. Such stochastic models allow more realistic simulations of nanoparticle transport and accumulation patterns under varying biological conditions (Agrahari et al., 2024). Designing drug delivery systems that target biological tissues is therefore critical for improving system efficiency, optimizing the design of nanocarriers, improve therapeutic precision and avoiding systemic side effects. Today, advanced imaging technologies, computational modelling methods and multiscale mathematical methods are widely applied to understand tissue heterogeneity and to forecast the fate of nanoparticles in complex physiological contexts. Recent progress in biomedical research has newly highlighted the need to combine models of stochastic transport with experiments for characterizing tissues to tailor nanomedicine strategies to the individual patient's biological variation. More recently, the ability to incorporate models of stochastic transport with experiments to characterize tissues has grown in importance to develop personalized nanomedicine strategies that can adapt to the biological variation of the individual patient.

8. Applications

The stochastic model to describe the biodistribution of nanoparticles in heterogeneous biological tissues has a wide range of applications in biomedical engineering, nanomedicine, pharmaceutical sciences and therapeutic use in clinical applications. The combination of stochastic mathematical modelling and nanoparticle transport analysis is of great value for researchers and healthcare professionals to better understand complex interactions in biology and optimize targeted treatment systems. Deterministic models are often neglected because biological tissues are space variants, have varying vascular structures, and experience random fluctuations in physiology.

8.1 Targeted Cancer Therapy

Tumor tissue is heterogeneous, with irregular vascular networks, varying oxygen levels, and irregular extracellular matrix structures and cell densities. All these properties have a marked effect on the transport of nanoparticles and their

therapeutic penetration. The framework also allows prediction of nanoparticle accumulation in various regions of a tumor based on modeling stochastic vascular permeability and random diffusion pathways. This app is especially useful in chemotherapy, where maximizing the delivery of the drug to the cancer cells while minimizing systemic toxicity is crucial for enhancing patient outcomes.

8.2 Personalized Nanomedicine and Precision Healthcare

The tissues, immune system and vascular structure of patients vary greatly, and these variations can affect the success of nanoparticulate therapies. The stochastic framework can simulate the individual biodistribution, which can be done by simulating patient-specific physiological parameters in computational models. Therapeutic risk assessment, dosage optimization, and treatment planning can be aided by such personalized simulations. As a precision medicine application, stochastic modeling will aid in understanding the differences in nanoparticle behavior among patients and inform the design of individualized treatment plans for specific biological conditions.

8.3 Drug Delivery System Optimization

Nanoparticles carriers like liposomes, polymeric nanoparticles, dendrimers and metallic nanoparticles are broadly utilized for controlled discharge of drugs and concentrated therapeutic conveyance. The stochastic model helps to assess the influence of design parameters on the efficiency of transport, tissue penetration and drug retention in the case of nanoparticles. Optimizing carrier formulations to provide desired sustained release profiles and increased therapeutic levels at target sites can be achieved by mimicking the diffusion and uptake of nanoparticles within different physiological conditions. The framework also aids in identifying the impact of degradation, aggregation, and clearance of nanoparticles on treatment efficacy. The stochastic approach is used in tissue engineering and regenerative medicine for designing biomaterial scaffolds and nanoparticle-assisted regenerative therapies. Engineered tissues frequently have heterogeneous structures like natural biological tissues and the transport of nanoparticles in engineered scaffolds is key to provide growth factors, genes and bioactive molecules. Stochastic transport models can be used to simulate the distribution of nanoparticles in engineered tissue matrices and to resolve factors that affect nutrient transport and tissue regeneration. It is an application that is of great assistance in the development of advanced regenerative therapies for wound healing, bone repair, cartilage regeneration and organ reconstruction.

8.4 Blood-Brain Barrier Transport

Therapeutic nanoparticle delivery to the brain is extremely difficult since the blood-brain barrier obstructs the entry of most drugs and nanoparticles into the neural tissue. The stochastic framework can simulate interactions between nanoparticles and endothelial cells, fluctuations in permeability and diffusion in neural environments. The knowledge of how nanoparticles may penetrate BBB under stochastic dynamics can lead to the development of more efficient therapy for neurological diseases like epilepsy, brain tumors, Parkinson's disease and Alzheimer's disease.

8.5 Immunotherapeutic Approaches and Vaccine Delivery Systems

Nanoparticles are becoming more and more important as antigen carriers as well as immune modulators and delivery vehicles for genetic material to boost immune responses. Immune tissues, however, have heterogeneous cellular distribution and dynamic inflammatory responses which affect the uptake and biodistribution of nanoparticles. By using stochastic modelling, researchers can study the interaction between nanoparticles and immune cells (such as macrophages, dendritic cells, and lymphocytes) in different physiological conditions. The application will support optimization of vaccine efficiency, targeting and controlled antigen release in infectious diseases and cancer immunotherapy.

8.6 For Pharmacokinetics and Toxicology Research

The stochastic framework gives insights into the absorption, distribution, metabolism and excretion of nanoparticles. In many traditional models of pharmacokinetics, the tissues have been assumed to behave in a homogenous fashion, which might result in errors in predicting the behaviour of complex biological tissues. The stochastic approach also accounts for tissue variability and random fluctuations in the physiology, allowing for more realistic estimation of the nanoparticle concentration profile and the toxicity level. The application is key to assessing the safety and biocompatibility of innovations in the field of recently developed nanomaterials prior to clinical application.

8.7 Biomedical Imaging and Diagnostics

Nanoparticles are extensively utilized as contrast agents in imaging modalities like magnetic resonance imaging (MRI),

computed tomography (CT), fluorescence imaging, and photoacoustic imaging. To enhance the resolution in imaging and to increase the diagnostic accuracy, it is critical to predict the biodistribution of nanoparticles. Stochastic transport models can be used to simulate the deposition of nanoparticles in diseased tissue and to optimize delivery of the imaging agent in a heterogeneous physiological environment. This application improves the accuracy of disease detection and enables to diagnose pathological conditions in an early stage.

8.8 A Smart and Stimuli-Responsive Nanocarriers

In modern nanomedicine, nanoparticles are increasingly being developed that can respond to different stimuli in the environment, like pH, temperature, magnetic field, enzymes or light. Advanced probabilistic modelling is needed to predict activation and transport behaviour of responsive nanoparticles in biological environments, which are highly variable and stochastic. The stochastic approach allows the simulation of the response of nanoparticles under dynamic physiological conditions, allowing the design of intelligent drug delivery systems with controlled therapeutic activation.

8.9 Computational Biology and Systems Medicine

A combination of stochastic models of nanoparticle transport with multiscale models of biological processes can be used for studying the interaction between molecular transport, cellular response, tissue mechanics and systemic physiological processes. These approaches combine computation with biology, creating a more comprehensive understanding of disease processes and therapeutic impact in complex biological systems. The stochastic approach to modelling biodistribution of nanoparticles in heterogeneous biological tissues is widely applicable and is a valuable tool for biomedical research today. It has the advantage of introducing randomness, physiological variability and tissue heterogeneity, which substantially enhances the accuracy of prediction of the transport of nanoparticles. The framework will enable the progress of targeted therapy, precision medicine, regenerative medicine, immunology therapy, pharmacokinetics, diagnostic imaging, and the development of intelligent nanocarriers. In the future, stochastic biodistribution modelling will be ever more crucial in optimizing therapeutic systems and enhancing the clinical benefits for a wide variety of therapeutic applications.

9. Discussion

The stochastic framework developed for nanoparticle biodistribution in a complex heterogeneous biological tissue gives a comprehensive and realistic description of the behaviour of nanoparticles under complex physiological conditions. Traditional deterministic models are typically based on the assumption of uniform tissue properties and known transport mechanisms that restricts their capacity to model the biological variation found in real tissues. Both numerical and Smart PLS analyses provide evidence that the tissue heterogeneity, vascular permeability, stochastic diffusion dynamics and cellular uptake efficiency all impact on the transport and therapeutic uptake of nanoparticles within biological systems. The obtained results suggest that the stochastic diffusion dynamics plays the most significant role in the efficiency of biodistribution of nanoparticles. In biological tissues, there are irregularities in extracellular matrix structures, different interstitial pressure, and variable blood perfusion, all of which produce irregular patterns of movement of nanoparticles. It is able to effectively represent these interactions by incorporating stochastic differential equations and probabilistic transport mechanisms. Further, the SmartPLS structural analysis shows that there is a strong relationship between the tissue heterogeneity and stochastic diffusion behavior, thus highlighting the importance of local tissue variability in modifying the penetration depth and concentration distribution of nanoparticles. In addition, the study emphasizes the importance of vascular permeability for determining the NP accumulation in tissues. The heterogeneous vascular structure, particularly in tumour microenvironments, produces irregular transport pathways which impact the extravasation and retention of nanoparticles. The higher the vascular permeability, the more nanoparticles will enter the diseased tissues, but too much variation could result in non-uniform drug delivery and inefficient use of the drug in certain areas. The stochastic model is useful in understanding these transport mechanisms because it models the behavior of the blood vessels as random permeability fields, with random transport coefficients. Another parameter that is crucial for determining the biodistribution of nanoparticles is their efficiency of cellular uptake. The accumulation of nanoparticles can be different between cell populations, depending on the levels of receptors on the surface, the endocytosis capacity and the rate of internalization. The model successfully captures such stochastic interactions between cells and illustrates their effect on the efficiency of therapeutic delivery. Although it is beneficial, these are some of its drawbacks. Due to repeated Monte-Carlo simulations and generation of stochastic parameters, high computational resources are needed for the model. Further, proper parameter estimation is strongly dependent on experimental biological data, which can be different for various types of tissues and patient states.

10. Future Research

Future studies might explore the combination of machine learning algorithms, real-time imaging information, and individual patient parameters to enhance computational efficiency and predictive accuracy. In summary, the stochastic framework makes a major step forward in the modelling of the biodistribution of nanoparticles by introducing realistic biological variability and uncertainty. The results highlight its great promise for targeted drug delivery optimization, personalized medicine, and advanced nanomedicine studies.

11. Conclusion and Recommendations

The study is able to establish a stochastic mathematical model to describe the biodistribution of nanoparticles in heterogeneous biological tissues. The framework incorporates parameters from the underlying tissue heterogeneities, diffusion-reaction mechanisms, and stochastic differential equations and transport dynamics, rendering a realistic representation of the transport behavior of nanoparticles in complex physiological environments. These findings represent that the accumulation of nanoparticles and therapeutic distribution are significantly affected by stochastic diffusion dynamics, vascular permeability, the heterogeneity of the tissue, and the efficiency of cellular uptake. The stochastic framework provides several advantages over traditional deterministic methods, including the ability to account for random biological fluctuations and spatial variability and to provide more accurate predictions. The results of the numerical analysis of the SmartPLS confirm the robustness of the framework because it has high reliability, significant path coefficients, and high predictive relevance. The results show that stochastic modelling is extremely capable to analyze nanoparticle transport in irregular tissue environments like tumour and inflamed tissues. It also illustrates relevant applications such as targeted drug delivery, precision medicine, regenerative medicine, immunotherapy and biomedical imaging. Some suggestions for future research and application can be suggested.

- stochastic transport models should be integrated with patient-specific clinical and imaging information to inform personalized nanomedicine applications in the future.
- Advanced machine learning and artificial intelligence techniques can be considered to further enhance computational efficiency and optimize parameter estimation in conjunction with stochastic modeling.
- Experimental validation by using in vivo and in vitro nanoparticle data in the transport should be expanded to increase the reliability of models in various biological systems.
- Future frameworks should include multi-scale physiological interactions such as molecular signalling pathways, immune responses and cell mechanics for additional complete biodistribution predictions.

The stochastic framework can also be helpful for computational biomedical engineers, pharmacologists and clinical researchers engaged in the development of nanotechnology-based therapeutics. It has the potential to accurately represent biological uncertainty and heterogenous tissue response, making it an ideal tool to advance the optimization of targeted therapies and in the future to improve clinical outcomes in precision medicine and nanomedicine research.

12. References

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