

Tumor-Targeted Nanoparticle Delivery Prediction Using Machine Learning

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Abstract—Because of its rising incidence and mortality rates, cancer is a major public health issue worldwide. Although one of the most common cancer treatments is chemotherapy, the method can cause serious side effects by damaging normal cells along with cancer cells. Nanomedicine is a promising field with significant potential to reduce the harmful effects of chemotherapy and increase the effectiveness of the treatment process. On the other hand, the effective delivery of nanoparticles to solid tumors continues to be a substantial obstacle in the clinical application of cancer nanomedicine. This study involved the development and comparison of six machine learning models to predict the tumor delivery efficiency of nanoparticles. The models were developed using the Nano-Tumor Database, comprising 376 samples and four target variables (DE_24, DE_168, DE_Max, DE_Tlast). After data preprocessing and hyperparameter tuning, the XGBoost model achieved the lowest error values on the test set, with root mean square error values of 2.87, 1.43, and 3.42 for the DE_24, DE_168, and DE_Max target variables, respectively. The Random Forest model achieved the lowest error values on the test set, with a root mean square error value of 2.83 for the DE_Tlast target variable. The findings suggested that machine learning approaches have significant potential in the field of cancer nanomedicine.

Keywords—artificial intelligence; machine learning; nanomedicine; nanotechnology; drug delivery

I. INTRODUCTION

Cancer remains one of the leading global public health concerns, attributable to its high incidence and mortality rates [1]. According to global cancer statistics for 2022, there were approximately 20 million new cases and nearly 9.7 million cancer-related deaths worldwide [2]. Chemotherapy is a widely used cancer treatment method. Conventional chemotherapy can damage tumors and healthy cells, causing gastrointestinal reactions, bone marrow suppression, and hair loss. These side effects reduce treatment efficacy and dose tolerance, lowering quality of life [3]. Targeted drug delivery systems are being developed to diminish these obstacles. These systems target chemotherapeutic agents directly to the tumor site to reduce drug toxicity and improve treatment efficacy [4]. Liposomes, polymeric nanoparticles, dendrimers, and metal nanoparticles are commonly used in this field of nanotechnology [5, 6].

Nanomedicine is a valuable field in biomedical research in search of safer and more effective cancer chemotherapies [7, 8].

On the other hand, the limited delivery efficiency (DE) of nanoparticles (NPs) to solid tumors remains a significant obstacle to the clinical translation of cancer nanomedicine [9, 10]. The percentage of systemically administered nanoparticles that localize in tumor tissue is called DE. This metric quantifies the total accumulation of NPs in the tumor at a specific time point [11].

Wilhelm et al. [11] carried out a detailed literature review to assess the DE of NPs to solid tumors. They reported that a median of 0.7% of the injected dose (ID) of nanoparticles reached the tumor based on the literature analysis. Furthermore, they highlighted that DE varied depending on various factors, including physicochemical properties of the NP (type, core material, size, zeta potential, and shape), targeting strategy, tumor model, and cancer type. Recent studies have leveraged machine learning (ML) and artificial intelligence (AI)-assisted physiologically based pharmacokinetic (PBPK) approaches to predict nanoparticle delivery [12, 13], and our work extends these studies by comparing multiple ML models.

In the present study, we developed and compared different ML models to predict the tumor DE of NPs. These ML-based prediction models were based on diverse factors, including NPs' physicochemical properties, targeting strategy, and tumor-related parameters, using the Nano-Tumor Database, which comprises 376 samples. Our findings suggest that ML-based approaches, particularly when integrated with PBPK modeling, may provide valuable insights for advances in cancer nanomedicine.

II. MATERIALS AND METHODS

A. Dataset and Data Preprocessing

Within the scope of this study, “Nano-Tumor Database” [9] was used to develop ML models. The dataset included 376 samples sourced from 200 studies, covering a diverse array of cancer nanomedicine research published between 2005 and 2018. The dataset comprised various parameters associated with physicochemical properties of NP, targeting strategy, cancer type, tumor size, tumor weight, tumor model, injected dose, and body weight of subject. In addition, the dataset comprises four target variables derived from the PBPK model [9]. More comprehensive information about the dataset is presented in Table 1.

TABLE I. OVERVIEW OF VARIABLES AND THEIR CATEGORIES/VALUES USED IN THE MACHINE LEARNING MODELS

Feature	Unit	Category / Value Range
Nanoparticle type	–	Inorganic, Organic, Hybrid
Nanoparticle's core material	–	Polymeric, Gold, Other OM, Liposomes, Silica, Hydrogels, Dendrimers, Other IM, Iron Oxide, Silica-Liposomes, Iron Oxide-Polymeric, Other HM, Silica-PDA, Zinc Protein-Hydrogels
Nanoparticle shape	–	Spherical, Rod, Plate or Flake, Other
Hydrodynamic diameter	nm	[5, 456.6]
Zeta potential	mV	[-59.4, 71.3]
Targeting strategy	–	Passive, Active
Cancer type	–	Brain, Breast, Cervix, Colon, Liver, Lung, Ovary, Pancreas, Prostate, Skin, Stomach, Kidney, Other
Tumor model	–	Allograft Heterotopic, Allograft Orthotopic, Xenograft Heterotopic, Xenograft Orthotopic, Other
Tumor weight	g	[0.02, 5.09]
Tumor size	cm ³	[0.02, 1.8]
Administered dose	mg/kg	[0, 1220]
Subject Body weight	g	[16, 35]
DE at 24 hours	%ID	[0.008, 50.03]
DE at 168 hours	%ID	[0.003, 23.83]
Maximum DE	%ID	[0.008, 56.89]
DE at the last sampling time point	%ID	[0.009, 29.80]

In data preprocessing, to detect outliers, the interquartile range (IQR) method was used. After this step, the K-Nearest Neighbors (KNN) imputation method was employed to impute missing values. The distribution of rare categories was subsequently examined, and their target variable means were compared with those of other categories. Following this, some rare categories were merged. Afterwards, one-hot encoding was employed to transform categorical variables into numerical data. Following these steps, the dataset was split into train and test sets, allocating 80% for training and 20% for testing. Finally, z-score normalization, which is feature scaling, was applied to the numerical variables to rescale.

B. Model Development

A total of six ML algorithms were used to develop models that predict the DE of the NPs in this study. The ML algorithms included Linear Regression (LR) [14], KNN [15], Support Vector Machines (SVM) [16], Classification and Regression Trees (CART) [17], Random Forests (RF) [18], and eXtreme Gradient Boosting (XGBoost) [19]. Hyperparameter tuning was performed using the grid search method to develop an ML model that predicts the target variable with minimal error. Following the hyperparameter tuning, the top 25 features were selected based on their importance scores derived from RF models trained independently for each dependent variable. After feature selection, hyperparameter tuning was performed once more for each model, and the models were rebuilt.

C. Model Performance Evaluation

Two different performance metrics, root mean square error (RMSE) and coefficient of determination (R^2), were employed to assess and compare the developed models. The model's

performance was evaluated using the training set, on which 5-fold cross-validation (CV) was applied as internal validation, and the test set for external validation.

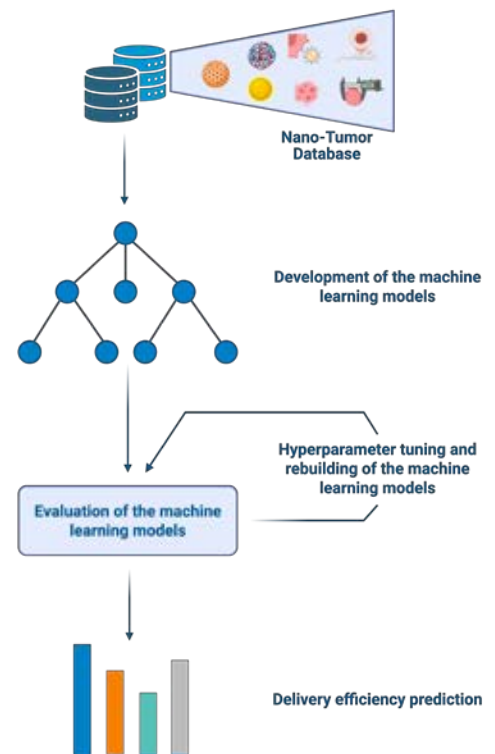
D. Implementation Environment

Data preprocessing methods, development of ML models, hyperparameter tuning, and performance evaluation of the models were implemented in Python 3.12.7 in conjunction with the NumPy, Pandas, Scikit-Learn, XGBoost, GridSearchCV, SciPy, and scikit-posthocs libraries. Jupyter Notebook was used as an Integrated Development Environment (IDE). The computational setup consisted of a macOS operating system and 16 GB of RAM.

III. RESULTS

A. Model Development and Evaluation Overview

The Nano-Tumor Database [9] was used in this study. This dataset included 12 features, such as cancer treatment scenarios, NP characteristics, and tumor-related features. The study also included four target variables: DE_24, DE_168, DE_Max, and DE_Tlast. These target variables were estimated by Chen et al. in previous studies [9] using PBPK models based on the Nano-Tumor Database. Six ML algorithms were used for each target variable, and a total of 24 models were developed following data preprocessing, which involved detection of outliers, imputation of missing values, analysis of rare categories, feature selection, and scaling. The optimized hyperparameters for the ML models were determined by 5-fold CV. The final models were evaluated using both the training and test datasets. RMSE and R^2 were employed to evaluate the models' performance. The study workflow is illustrated in Figure 1.


 Fig. 1. Overview of the study framework to develop ML models to predict nanoparticle DE to the tumor site in mice. Created in <https://BioRender.com>.

B. Training and Testing Results of Machine Learning Models

Following data preprocessing, the ML algorithms were trained. The prediction performance of the ML models was evaluated utilizing R^2 and RMSE metrics. To assess the consistency of model performance, 5-fold CV was conducted on the training set. The models' final performance was determined according to the test set results, which reflect the model's generalization capability. Among the developed ML models, XGBoost achieved superior predictions with higher R^2 and lower RMSE values for the DE_24, DE_168, and DE_Max target variables, while the RF model achieved better predictions with higher R^2 and lower RMSE for the DE_Tlast target variable. In the test dataset, the R^2 and RMSE values for the XGBoost model ranged from 0.31 to 0.56 and from 1.43 to 3.42, respectively, across all target variables. In the test dataset, the R^2 and RMSE values for the RF model ranged from 0.43 to 0.52 and from 1.45 to 3.45, respectively, across all target variables. Conversely, the LR and CART models showed the poorest performance. In the test dataset, the R^2 and RMSE values for the LR model ranged from 0.02 to 0.25 and from 1.68 to 4.83, respectively, across all target variables. In the test dataset, the R^2 and RMSE values for the CART model ranged from 0.00 to 0.36 and from 1.72 to 4.08, respectively, across all target variables. The results of the performance metrics for these models are detailed in Table 2.

TABLE II. 5-FOLD CV AND TESTING RESULTS FOR TUMOR DE USING VARIOUS ML MODELS

	DE_24		DE_168		DE_Max		DE_Tlast	
Model	5-fold CV	Test	5-fold CV	Test	5-fold CV	Test	5-fold CV	Test
LR	RMSE	2.65	4.02	1.49	1.68	4.23	4.83	2.99
	σ	± 0.42		± 0.24		± 0.64		± 0.84
	R^2	0.08	0.13	0.33	0.25	0.13	0.03	0.08
KNN	RMSE	2.38	3.82	1.50	1.57	3.85	3.73	2.96
	σ	± 0.33		± 0.28		± 0.65		± 0.87
	R^2	0.25	0.21	0.31	0.34	0.29	0.42	0.09
SVM	RMSE	2.43	4.14	1.47	1.60	4.26	4.47	2.79
	σ	± 0.35		± 0.25		± 0.86		± 1.02
	R^2	0.23	0.08	0.34	0.32	0.15	0.17	0.23
CART	RMSE	2.61	4.08	1.55	1.72	4.21	3.92	3.08
	σ	± 0.30		± 0.36		± 0.77		± 0.75
	R^2	0.09	0.10	0.27	0.20	0.15	0.36	0.00
RF	RMSE	2.19	2.98	1.29	1.45	3.27	3.45	2.58
	σ	± 0.36		± 0.24		± 0.65		± 0.92
	R^2	0.36	0.52	0.49	0.44	0.49	0.50	0.33
XGBoost	RMSE	2.21	2.87	1.28	1.43	3.46	3.42	2.57
	σ	± 0.31		± 0.24		± 0.69		± 0.87
	R^2	0.34	0.56	0.49	0.46	0.42	0.51	0.34

C. Feature Importance

The feature importance values were extracted from the RF model to evaluate the impact of input features on model predictions [18]. As depicted in Figure 2, zeta potential, NP size, injected dose, tumor weight, and tumor size had the greatest impact on all target variables. Even if the significance levels of these five variables varied across target variables, they contributed more to the final models than other variables.

Overall, the cumulative predictive contribution of these variables to the target variables ranged from 52% to 61%.

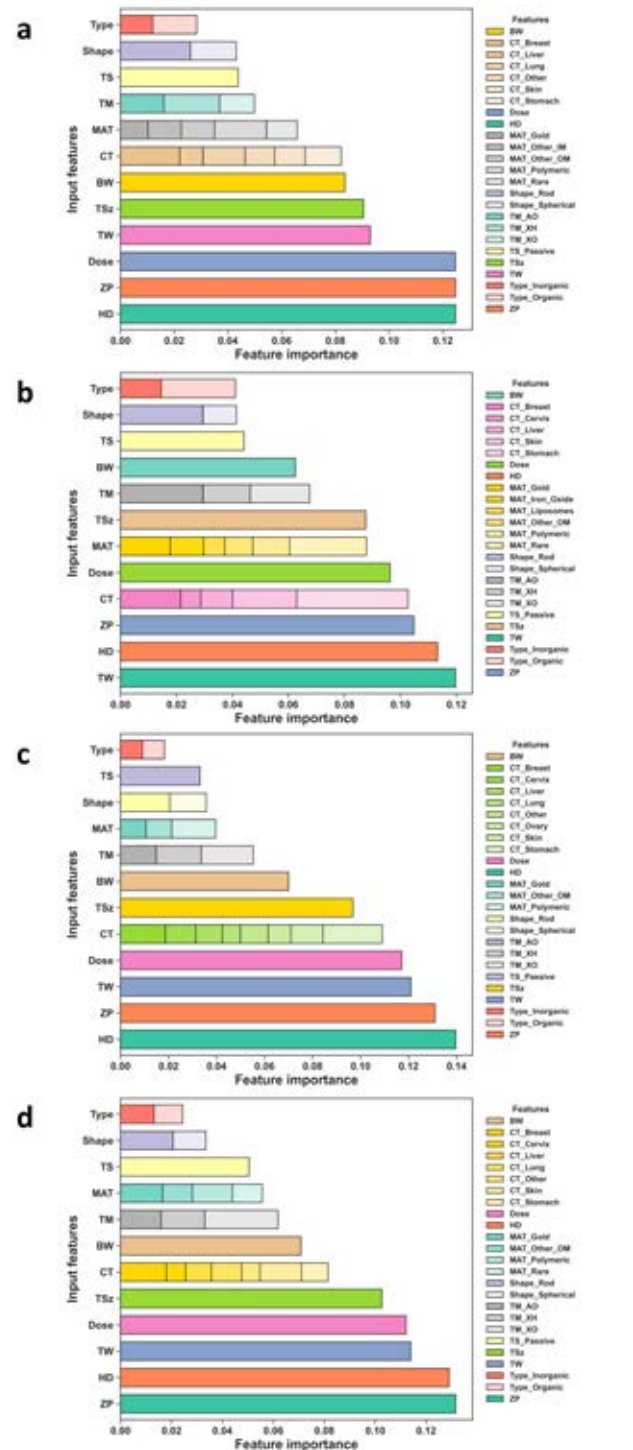


Fig. 2. Importance percentage in the RF model for each feature variable. (a-d) represent results for the feature variable of DE_24, DE_168, DE_Max, and DE_Tlast, respectively. Individual importance is represented by colors in the stacked bars. Abbreviations: ZP, zeta potential; Type, type of nanoparticles; TS, targeting strategy; TM, tumor model; HD, hydrodynamic size; Shape, shape of nanoparticles; MAT, core material of nanoparticles; CT, cancer type; AO, allograft orthotopic; XH, xenograft heterotopic; XO, xenograft orthotopic; Dose, injected dose; TSz, tumor size; TW, tumor weight; BW, subject body weight.

IV. DISCUSSION

This study presents a PBPK-based ML model that can predict the DE of NPs to tumors in mice, relying on various parameters, including the cancer type, the tumor model, and the physicochemical properties of NPs. The model's predictive performance has room for improvement. Nevertheless, the findings indicate that it has the potential to be an instrument that can help the development of novel NP-based drug formulations for cancer therapy. This tool could, in the future, be developed to avoid including nanoparticles with low tumor DE in preclinical studies, thus facilitating the advancement of nanomedicine research and reducing the need for animal experiments. This study additionally demonstrates the integration of ML approaches with PBPK modeling in the cancer nanomedicine field.

The enhanced delivery of NPs has the potential to mitigate adverse effects in non-target tissues and to reduce the total dose required for treatment [20]. However, the low DE of NPs to tumors poses a significant obstacle in cancer nanomedicine. Previous studies revealed the existence of critical factors affecting DE [11]. Studies were performed to ascertain the relationship between physicochemical properties of NP and tumor DE. Multiple regression analysis [11], ML, and artificial neural networks were used in these studies [12]. In the present study, we developed six ML models for each target variable and compared their predictive performance (Table 2). Among these, the RF and XGBoost models, both of which are tree-based algorithms, demonstrated better performance compared to the other models. These findings reveal that tree-based ensemble models can more successfully predict tumor DE based on physicochemical and tumor-related properties in this dataset. This superiority may be attributed to their ability to capture nonlinear relationships and model complex feature interactions more effectively than linear or single-tree methods; however, the performance and generalizability of the models remain constrained because of the relatively small sample size of the dataset, which may also introduce potential biases.

This study, in line with existing literature [12, 13], suggests that integrating ML approaches with PBPK modeling can significantly enhance nanomedicine research. Given the widespread use of PBPK modeling in various biomedical applications [12], including drug discovery and development, this study could serve as an example for similar integrative approaches. These findings also highlight a potential contribution to the clinical translation of nanomedicine through prioritizing nanoparticle formulations with higher tumor delivery efficiency.

V. CONCLUSION

In this study, the ML model was developed to predict the tumor DE of NPs. This study points out the potential of using ML-based approaches with PBPK models to enhance cancer nanomedicine research. In future studies, the dataset can be expanded to improve the model's generalization ability and achieve better results. Additionally, deep neural network models can be developed to capture subtle patterns that tree-based ensemble machine learning models might miss, thereby improving prediction performance. In conclusion, such multidisciplinary approaches can help determine which NP

candidates are promising in the preclinical stage and improve design processes in nanomedicine applications. Thus, (i) the number of experimental studies can be reduced, (ii) animal experiments can be better prioritized, and (iii) the efficiency of translational research can be increased.

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