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Predicting Nanoparticle Behavior in Biological Systems: A Machine Learning Approach

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Abstract

Commercial use of nanoparticles is on the rise, but our understanding of how these particles behave in living organisms is still in its infancy. Their worth, and their potential danger, stem from the fact that the characteristics of the nanophase are very different from the bulk properties of the same material. Nanoparticle uptake, distribution, modification, and potential toxicity must all be investigated experimentally. Predictive models would be very helpful, especially for helping regulators reduce health and environmental hazards, but they are expensive and time-consuming to develop. Three datasets were modelled, one of which contained nanoparticles, with the use of sparse machine learning algorithms and bayesian neural networks (BNN). In the initial phase of experimentation, researchers employed: Pancreatic cancer cells, human umbilical vein endothelial cells (HUVEC) and three macrophage or macrophage-like cell lines. These cells were exposed to iron oxide nanoparticles coated with a diverse set of 108 compounds, coatings, fifty-two nanoparticles with different core materials, and surface changes were added. These nanoparticles underwent comprehensive analysis using four parameters, including size, relaxivity, and zeta potential. Additionally, their impact on cell lines was evaluated through a total of eight measurements, comprising four biological assessments per cell line, each conducted at four different dosage levels. In the third batch of data, 80 different small compounds were used to modify gold nanoparticles and study their biological effects. The biological outcomes that were modelled were binding to AChE and nonspecific binding. Nanoparticles' biological impacts were modelled with help from chemical descriptors for the substances that covered their surfaces. Most biological outcomes were modelled with high statistical quality. These proof-of-concept models demonstrate that it is feasible, with the help of current modelling techniques, to simulate the impacts of nanomaterials on living organisms.

Keywords

Bayesian methods, Nanomaterials, Machine learning, QSAR, Modelling and prediction, Adverse biological effects

Introduction

In the past decade, nanomaterials have attracted a significant lot of scientific attention because of the unusual properties they show, particularly because of their extremely large surface areas. Because of their unique characteristics,

nanoparticles have quickly found their way into consumer goods. Nanoparticles have been present in the Earth's atmosphere since the beginning of life. Nanoparticles can be produced naturally by a variety of means. Natural nanoparticles are often well tolerated because they are processed by processes that have developed over millions of years to deal with them. As a result, it's feasible that many nanoparticles created intentionally or accidentally during industrial processes can be processed by living organisms with minimal effect. Certain nanoparticles are known to be extremely hazardous, however [1]. Exposure to nanoparticles has been linked to several severe disorders. Asbestos and silica nanoparticles both have well-understood harmful effects pathways, but for many other nanoparticles, this is not the case. The materials are very new, and the necessary trials have not yet been conducted, thus it is unclear what, if any, negative biological consequences they may have on humans and the environment [2].

Nanomaterials' characteristics may be modelled computationally, allowing for the prediction of their biological consequences. The latest machine learning and feature selection techniques are powerful and broadly applicable. Very quickly, computational models may generate predictions about materials that haven't even been used or produced yet. Their methods will hopefully allow governments to ensure the safe regulation of nanomaterials without limiting their economic growth.

The following are some of the benefits of using computational models [3]:

- The huge scale at which nano-products are produced makes it impractical and expensive to conduct adequate experimental testing of chemicals for physicochemical, toxicological, and environmental problems.
- There is mounting demand to drastically cut back on or end all animal experimentation.
- The application of computational methodologies like QSAR for the evaluation of industrial chemicals has gained traction among regulators in recent years.
- The use of computer modelling to analyse the biological effects of nanoparticles will complement, rather than replace, the use of experimental assessment. Nonetheless, information is vital, necessitating high-throughput nanoparticle manufacturing and evaluation techniques.

Recently, a workshop was held to discuss the use of QSAR techniques for modelling and prediction in the context of nanomaterial control. This cost-sponsored workshop aimed to pinpoint the most pressing areas for research and development in science and computing that may facilitate the fast development of models of nanomaterials' biological impacts.

Nanoparticles' impacts on living things are notoriously challenging to model. An intricate corona surrounds the particle due to its interactions with the fluids of animals and humans, as well as the environment. Another issue is that scientists don't yet fully understand how cells absorb nanoparticles. As opposed to pure organic substances, nanoparticles tend to collect or agglomerate, have significant interactions with and are modified by their surroundings, and are heterogeneous and poorly defined. Nanoparticles lack the vast biochemical and pharmacological understanding of the interactions of tiny organic molecules with life systems. Nonetheless, decision support tools for nanomaterials are necessary for regulators [4].

Machine learning and QSAR-based modelling methodologies are the sole options because there is presently no mechanistic information of how nanoparticles interact with biological systems [5, 6].

Data-driven, supervised modelling approaches that don't require a detailed understanding of the interaction processes can capture the molecular (microscopic), physicochemical, and biological (macroscopic) aspects of nanomaterials.

$$Biological\ response\ (BR) = F(molecular\ properties) \quad (1)$$

The absence of nano-specific descriptors and huge data sets for training models is a challenge for this method, but it also presents the greatest opportunity. Combinatorial and high-throughput materials experiments are becoming increasingly popular, which bodes well for a quick resolution to the second issue. An essential area of study is the formulation of nano-specific descriptors. With the help of recent advances in feature selection and nonlinear regression, as well as appropriate descriptors. Predictive models for these difficult materials may be developed with the help of these powerful pattern recognition techniques.

Since its inception 50 years ago, the QSAR approach has amassed a plethora of knowledge and resources that may be used to predict nanomaterial characteristics and material properties in general [7]. Using three case studies, we show how QSAR machine learning algorithms may be used to simulate nanoparticles' biological impacts.

Materials and Methods

Researchers have employed iron oxide nanoparticles with diameters of 40 nm and aspect ratios close to 1 to examine apoptosis and cellular uptake in smooth muscle. Dextran (CLIO, cross-linked iron oxide) were used as coatings, and then minute organic molecules were covalently attached to their surfaces to provide the desired functionality [8, 9]. Author [10] describes nanoparticle compositions, coatings, functionalization, and measured characteristics. Thirdly, we have evidence on gold nanoparticles with tiny organic molecules attached to their surfaces [11]. The gold nanoparticles had sizes of around 5-6 nm and were well diffused in water with minimal agglomeration. The surface chemistry of gold nanoparticles is summarized in figure 1.

Initially, the nanoparticle's surface chemistry was adjusted such that it would be drawn to cell types for study or therapy. Small molecule coatings are much better than those found on other nanoparticles, and that's why these materials were chosen. Biological information was retrieved from the journals or revised considering more current research.

Fifty different nanoparticles were tested for their impact on four different cell lines in this study, including endothelial cells, smooth muscle cells, monocytes, and hepatocytes. Four

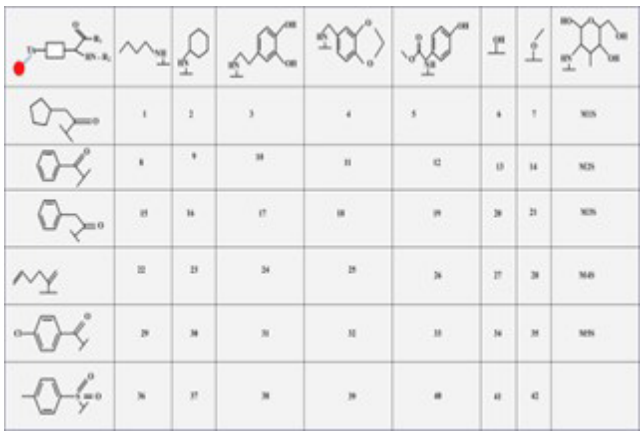

Figure 1: Functionalization of the surface of gold nanoparticles.

different concentrations of these nanoparticles were examined. Measurements of ATP content, reducing equivalents, caspase-mediated apoptosis, and mitochondrial membrane potential were used as four of the biological tests. For each of the 50 nanoparticles, a biological response variable was recorded, which fell within the range of 0 to 64. This resulted in a dataset comprising a total of 3200 data points.

Interestingly, in the analysis, the researchers used the dose-response slope, which is essentially equivalent to the Hill slope, as the dependent variable. This choice was made because they encountered challenges in deriving an EC50 (half-maximal effective concentration) or a comparable parameter from the data. Using k-means clustering, we built models using either the full dataset or subsets consisting of 26 and 6 nanoparticles for training and testing, respectively.

Fluorescent nanoparticles with a core of superparamagnetic iron oxide (SPIO) and a covering of dextran were the focus of this investigation. These nanoparticles had unique collections of small molecules attached to their surfaces, as documented in a previous study [12]. The researchers investigated the uptake of these nanoparticles by various cell types, including:

- HUVEC.
- Primary resting human macrophages (Rest Mph).
- Granulocyte macrophage colony-stimulating factor (GM-CSF) stimulated human macrophages (GM-Mph).
- The U937 human macrophage-like cell line.
- Human pancreatic ductal adenocarcinoma cells ($PaCa_2$).

For their analysis, the researchers divided the experimental data into a training set and a test set. Specifically, they used the logarithm (log10) of the experimental data. The training set comprised data from 87 different molecules, while the test set included data from 21 molecules. This division represented approximately 80% of the total data set, allowing for comprehensive training and evaluation of their experimental results. The z-scored data were utilized to evaluate the biological information content of the experiments, with zNP = (NP-PBS)/PBS denoting tests performed in the presence of NPs and zPBS denoting PBS buffer control assays. Most dose-response curves in an assay were regarded to have shown a non-significant impact if they were within a z-score of ± 2.

Tryptophans, tyrosine's, and phenylalanines are aromatic surface residues that were used to quantify protein adsorption by detecting their fluorescence quenching [13]. The extent to which acetylcholinesterase activity was inhibited was indicative of specific binding.

Our employment of generic, resilient, sparse linear and nonlinear modelling techniques was necessitated by the high degree of complexity present in both the materials and the settings in which they were deployed. By using sparse Bayesian linear and nonlinear feature selection techniques, we were able to further simplify and increase the precision of our models. In our study, sophisticated techniques were employed to conduct feature selection and regression analysis.

Expectation minimization with sparse (Laplacian): An expectation minimization technique was used with a sparse Laplacian prior to performing linear feature selection and regression in a sparse mode. This approach allowed us to identify and prioritize relevant features in our data [14].

Bayesian regularized neural network with Gaussian or Laplacian: To capture nonlinear relationships between variables, a Bayesian regularized neural network was used. This neural network model enabled us to select sparse nonlinear features. Gaussian or Laplacian priors to guide the selection process was used. Weight pruning was also applied in combination with nonlinear feature selection to create models that were both sparse and highly predictive [15].

Neural network architecture: Our neural network models were structured with three layers: input, hidden, and output. Depending on the specifics of the issue at hand, the number of nodes was set in each successive layer. Typically, there were as many nodes in the input layer as there were descriptors in the dataset, two or three nodes in the hidden layer, and one node in the output layer for each characteristic sought to describe. While sigmoidal functions were utilized during training for the hidden layer, linear transfer functions were used for the input and output nodes.

Training optimization: To maximize the Bayesian evidence during network training, we employed the Levenberg-Marquardt technique. This technique helps fine-tune the model's parameters for better predictive performance.

No validation set required: While traditional backpropagation neural networks require an additional validation set to determine when training should end, our Bayesian regularized networks did not. The optimization procedure is made easier by this independence from the number of modes present in the hidden layers.

Choice of descriptors: In our models for cellular uptake and protein adsorption, we used DRAGON descriptors rather than those obtained from 3D space and quantum chemistry. The nanoparticles' chemical variety, the mystery of the protein corona's composition, and the absence of mechanistic data on absorption all played a role in the decision to choose these descriptions. The complexity of the biological system makes it

very challenging to create a QSAR model that is both predictive and interpretable in terms of molecular interactions [16].

Results and Discussion

The authors [17, 18] released data on cellular uptake of 109 superparamagnetic, dextran-coated nanoparticles bearing a variety of small compounds. There was no statistically significant difference in uptake between unmodified and modified surfaces for any of the five examined cell lines. All three macrophage and macrophage-like cell lines have very comparable uptake surface chemistry.

The findings of DRAGON descriptor-based linear and nonlinear QSAR models for forecasting nanoparticle uptake in PaCa and HUVEC cell lines are shown in table 1. Both the linear and the nonlinear models have comparable predictive accuracy [19].

To an accuracy of within a factor of 2, we were able to predict the absorption of nanoparticles by HUVEC and PaCa2 cells (Table 1 and figure 2).

It's possible that the HUVEC model's 11 and the PaCa2 model's 19 characteristics correspond to two distinct uptake mechanisms. There may not have been much of a reaction from macrophages and macrophage-like cells because of the nanoparticle's small size (30 nm). Macrophages are universal phagocytes that can identify a wide variety of different particles, including proteins. It has been observed that absorption of iron oxide nanoparticles considerably increases at diameters over 300 nm (Figure 3) [20]. It is also possible, though not proven, that altering the nanoparticles' surface chemistry will affect their absorption by macrophages.

In a study involving 47 surface-modified gold nanoparticles, researchers evaluated their nonspecific adsorption and their ability to inhibit acetylcholinesterase (AChE) [21]. To model AChE inhibition or nonspecific adsorption, the researchers employed both linear and nonlinear models, utilizing a total of 14 DRAGON descriptors.

For predicting AChE inhibition, multiple linear regression (MLR) with specific parameters yielded the most accurate results. The model achieved the following performance metrics:

- Training set coefficient of determination (r2train): 0.91.
- Standard Error of Estimation (SEE): 5.1.
- The test set coefficient of determination (r2test): 0.81.
- Standard error prediction (SEP): 5.6.
- The test set used for validation comprised 20% of the data.

In contrast, the optimal BNN model for the same task featured a simple architecture, consisting of only two nodes in the hidden layer and 14 effective weights. This model achieved the following performance metrics:

- Training set coefficient of determination (r2train): 0.84.
- Standard Error of Estimation (SEE): 3.7.

Table 1: Quantitative analysis of the nanoparticle uptake QSAR models.

Type of cell	Model	r2test	SEP	r2train	SEE	No. descriptors
HUVEC	Linear	0.64	0.37	0.75	0.35	11
PaCa2		0.80	0.25	0.77	0.20	19
PaCa2	Nonlinear	0.67	0.34	0.71	0.31	11
HUVEC		0.55	0.29	0.78	0.16	19

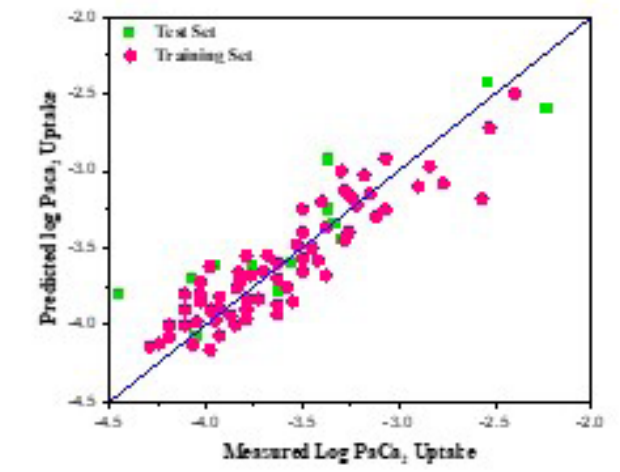

Figure 2: Comparing predicted to measured log nanoparticle uptake in PaCa cells.

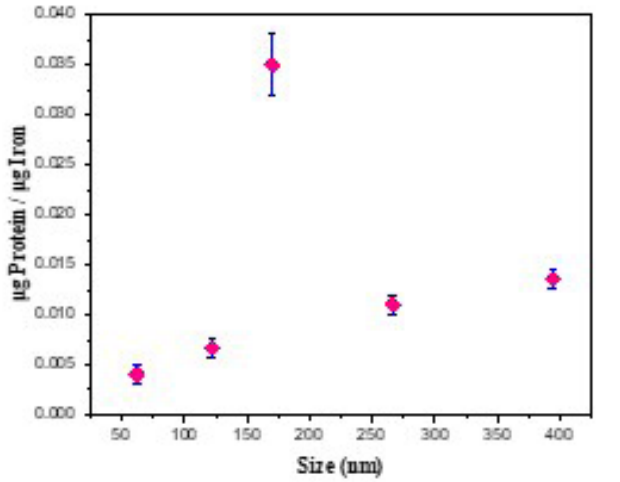

Figure 3: Size-dependent uptake of ion nanoparticles by macrophages.

- The test set coefficient of determination (r2test): 0.80.
- Standard error prediction (SEP): 5.2.

These results demonstrate the effectiveness of both the MLR and BNN models in predicting AChE inhibition, with the BNN offering a more parsimonious model structure with comparable predictive performance. Figure 4 illustrates the model's performance graphically.

In the modeling process, 10% of the test set data was utilized along with DRAGON descriptors for studying nonspecific protein binding. The performance metrics for the top multiple linear regression (MLR) model were as follows:

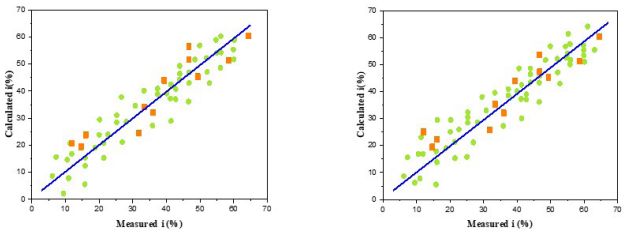

Figure 4: Measured and predicted AChE inhibition by surface modified gold nanoparticles for linear model (left), and nonlinear model (right). Training set (circles), test set (squares).

- Training set coefficient of determination (r2train): 0.93.
- Standard error estimation (SEE): 0.88.
- Test set coefficient of determination (r2test): 0.93.
- Standard error prediction (SEP): 0.75.

The optimal nonlinear BNN model, on the other hand, demonstrated the following performance metrics:

- Training set coefficient of determination (r2train): 0.96.
- Standard error estimation (SEE): 0.43.
- Test set coefficient of determination (r2test): 0.94.
- Standard error prediction (SEP): 0.75.

This BNN model included 15 effective weights and featured 2 hidden-layer nodes. It achieved impressive predictive accuracy, especially on the training set.

Figure 5 refers to a visual representation or chart that illustrates the model's performance or some aspect of the analysis, but without the actual image or context, it's challenging to provide further details.

Multiple biological impacts of surface-functionalized nanoparticles might be modelled satisfactorily using these machine learning approaches. They were able to predict the biological effects of nanoparticles with the same precision in test sets as they did in the training set. Models are complementary to measurements since they are data-driven and cannot replace the necessity for experimentation. Although these techniques are simple to use, they are not capable of producing accurate prediction models when working with little data, data of low quality, or inadequate descriptors. The independent test set compound property predictions were accurate; however, caution should be exercised when making additional predictions outside of the original property space. The chemical variety utilized to train the models, the ranges of the molecular descriptors, and the biological response data all put limits on this space. It would be difficult to exaggerate the value of trustworthy data.

Predictive models need to be put through experimental testing to show regulators and other scientists their value. For the reasons stated above, these models frequently lack access to molecular specifics of the mechanism of action. When it comes to nanoparticles interacting with biology, however, it is likely that various mechanisms of action will predominate; yet QSAR approaches can capture these complexities.

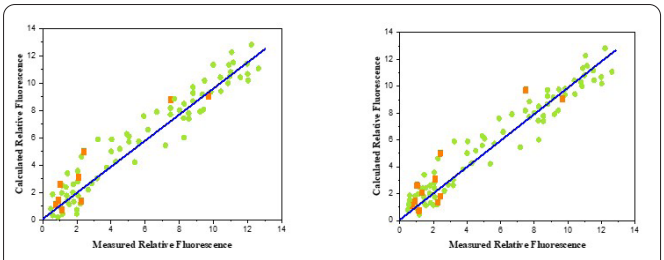

Figure 5: Nonspecific protein binding was observed and predicted for the **(a)** Linear model and **(b)** The nonlinear model.

Dose-response connections were seen only in the apoptosis experiments, whereas the nanoparticles induced effects that were not statistically significant in the other biological studies. The models with the highest statistical significance were found in the smooth muscle cell apoptosis experiment. Smooth muscle apoptosis was affected by the nanoparticle's core substance (Fe_2O_3 vs Fe_3O_4), coating type, and surface charge. Surface functionality, coating type (coded as +1 for dextran, 0 for other coatings), and core nature (coded as +1 for Fe_2O_3, 0 for Fe_3O_4) were all included as indicator variables in the models built for these characteristics [22].

This resulted in a straightforward QSAR equation that accurately predicted metal oxide nanoparticle-induced smooth muscle apoptosis (SMA):

$$SMA + 2.26(\pm 0.720 - 10.73(\pm 1.05)I_{Fe2O3} - 5.57(\pm 0.98)I_{dextran} - 3.53(\pm 0.54)I_{charge} \quad (2)$$

The model has the following statistical properties: r2train = 0.81, r2test = 0.86, SEE = 3.6, SEP = 3.3, r2train = 0.81, and r2test = 0.86 for the training set and the test set, respectively. The model statistics of r2train = 0.80, r2test = 0.90, SEE = 2.8, and SEP = 2.9 demonstrate the statistical significance of the nonlinear models we built. The model with six effective weights was shown to have lower prediction errors compared to the linear model on both the training and test data [23].

These straightforward models may find practical applications in the field of biology. The adsorption of a protein corona in plasma or serum is likely responsible for the small impact of cell apoptosis on the zeta potential of particles, which reflects their surface charge. It's not surprising that properties related to the surface charge of pure nanoparticles are less critical to these models, given that the protein coat or corona effectively maintains a relatively constant zeta potential ranging from -10 to -20 mV.

The fact that the core material of the nanoparticles had the most significant impact on SMA (presumably, a measure related to the biological response) suggests that iron oxide nanoparticles played a pivotal role in the observed effects. It's worth noting that iron oxide nanoparticles can exist in different forms, such as Fe_2O_3 and Fe_3O_4, and this difference in core composition likely contributed to most of the observed effects.

Conclusion

Researchers have successfully demonstrated the application of machine learning techniques for creating robust predictive models that can assess the diverse biological

effects of nanoparticles and other materials. These techniques prove invaluable in modeling complex structure-activity relationships of materials, but they necessitate the development of specialized descriptors tailored to the unique characteristics of nanomaterials.

The described methodologies are exceptionally well-suited for the rapidly growing field of high-throughput nanomaterials, which encompasses various stages like synthesis, characterization, and testing. Machine learning models are particularly effective in this domain due to their ability to process vast amounts of data quickly and efficiently.

Like their role in predicting the biological effects of industrial chemicals, these models will assume a pivotal role in foreseeing the potential biological consequences of nanomaterials. They will prove invaluable in assisting regulatory bodies in developing guidelines aimed at safeguarding the health and well-being of workers, the public, and the environment against potential risks associated with nanomaterials.

Significantly, these efforts seek to strike a delicate balance between ensuring the protection of health and the environment on one hand and enabling innovation and the responsible economic utilization of nanomaterials on the other. This balance is essential for fostering both scientific progress and sustainable development in the field of nanotechnology.

Acknowledgements

None.

Conflict of Interest

None.

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