Nanotoxicity prediction using computational modelling - review and future directions

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Abstract: Nanomaterials has stimulated various outlooks for future in a number of industries and scientific ventures. A number of applications such as cosmetics, medicines, and electronics are employing nanomaterials due to their various compelling properties. The unending growth of nanomaterials usage in our daily life has escalated the health and environmental risks. Early nanotoxicity recognition is a big challenge. Various researches are going on in the field of nanotoxicity, which comprised of several problems such as inadequacy of proper datasets, lack of appropriate rules and characterization of nanomaterials. Computational modelling would be beneficial asset for nanomaterials researchers because it can foresee the toxicity, rest on previous experimental data. In this study, we have reviewed sufficient work demonstrating a proper pathway to proceed with QSAR analysis of Nanomaterials for toxicity modelling. The paper aims at providing comprehensive insight of Nano QSAR, various theories, tools and approaches used, along with an outline for future research directions to work on.

1. Introduction
The intensely microscopic size of nanomaterials helps the cells to penetrate more easily, as well as models different chemical, physical, biological properties. These peculiarities of nanoparticles draw in the various industries to employ these particles in various applications such as cosmetics, pharmaceuticals, electronics etc. Nanomaterials can also be engineered for particular functionalities such as improving strength, catalyst nature, electrical and thermal conductivity etc. As the properties of nanomaterials are not always well characterized, they call for risk assessment of possible exposures arising during their manufacture and use.

Nanotoxicology is a branch of toxicology, which analyses the toxicity of nanomaterials. The study directs that to what extent the toxic effects of nanoparticles can impair the human health as well as environment. It is of vital importance to have knowledge of subsequent toxic effects of nanomaterials before utilizing it in applications. Every nanoparticle does not bring about the detrimental health effects, although there are various aspects on which the toxicity of nanoparticles depends such as size, configuration, surface functionality, particle ageing etc. \[1\][2].

The composition and size of nanomaterials plays a definite role in cellular response. In [3], the author has justified that the same material can generate different Intracellular responses and potential mechanism of toxicity depending on the exposed cell type. The compositions of nanomaterials get varied according to the products and brands. Table 1 shows some of the most commonly used nanomaterials along with their compositions, used in different items. This data has been collected from the Household Products Database of the National Library of Medicine which is based on the Consumer Product Information Database (NLM). The data of the table shows the average compositions used, but this does not prove helpful in defining the threshold values of these
nanoparticles for toxicity check. This is due to the variation in the amount of the particles utilized in products. As mentioned in the table, different materials are used in different amounts for different products. The toxic effects of these materials come into existence after a regular use for a long time. The author in [4] formed a list of distinct cosmetics manufactured in different countries. It shows that composition again gets vary with the variation in manufacturing countries. The standards followed by various countries manufacturers and brands are different, due to which it is difficult to set a fixed usage value for these materials.

Table 1. Nanomaterials composition used in household products

| Nanoparticle     | Usage                        | Composition               |
|------------------|------------------------------|---------------------------|
| Titanium Dioxide | Sunscreen (SPF 15)          | 1.0 – 5.0                 |
| Titanium Dioxide | Paint                        | 5.0 – 30.0                |
| Zinc Oxide       | Sunscreen (SPF 30, 36)      | Concentration up to 25%   |
|                  |                              | (Safe)                    |
| Zinc Oxide       | Personal Care (Cream)        | 10.0 – 20.0               |
| Silicon Dioxide  | Sunblock lotion or cream SPF (30,45,55) | 1.0 – 5.0 |
| Silicon Dioxide  | Personal Care (In form of paste or gel) | 10.0 – 30.0 |
| Silicon Dioxide  | Personal Care (In form of liquid or solid) | 0.1 - 1 |

Experimental data are critical to accelerate the insight of various properties of nanoparticles as well as for predictive analysis. The data, metadata and outcome of various experiments are present in different formats. Depicting such mix up data, requires a standard approach for compilation and communication. For most of the nano domain experts having mere informatics assistance, it will be really troublesome to programmatically execute it. The broad diversification and categorization of NM makes the toxicity interpretation more complicated. A minor change in the nanostructure properties, indicates the variation in their biological response, which again escalates the efforts to figure out the cause. For this, it is required to again go through each NM. The only feasible method to predict toxicity without experiment is to use their structural properties. QSAR (Quantitative Structure Activity Relationship) is a computational approach which endeavour to predict the biological functioning of a compound on the basis of their physiochemical properties and theoretical molecular descriptors. The next section discusses the physicochemical properties and descriptors which were studied and evaluated previously for toxicity prediction.

2. Properties affecting nanotoxicity

2.1. Physicochemical properties
Nanomaterials toxic effects are brought about by their various properties. For building up the toxicity prediction model, the first and foremost phase is to recognize the properties of nanoparticles which accelerate the toxic nature. The OECD group working on Nanomaterials had provided an extensive list of significant physicochemical properties, appropriate for toxicological studies [5]. Along with these basic properties, QSAR needs quantifier data to prevent incorrect interpretation. Table 1 index the elementary properties of nanoparticles (also known as physicochemical descriptors) and their quantifiers, which were analysed earlier for toxicity prediction. In [6][7][8][9] particle size was taken as base parameter and quantifiers as particle size and size distribution to find out toxicity level of TiO2 and Nanosilver. The study predicts that smaller size nanoparticles are more prone to toxicity as compared to larger size nanoparticles. Here the size distribution data gives better prediction results as compared to average size value. Therefore all the possible quantifiers need to be checked out while proceeding with QSAR approach. Table 2 displays the details of the analysis done in past, based on various properties such as shape, crystal structure, surface charge, surface functionality and aggregate phase. Other than these, there exist few more physicochemical properties such as purity, chemical composition, solubility, hydrophobicity, porosity, dustiness, production process and many
more on which the toxic nature of a compound depends. [7][10]. More experimental data as well as research efforts are required to explore QSAR modelling based on the physicochemical properties of nanomaterials.

**Table 2.** Physicochemical properties affecting toxicity

| Nanoparticles Properties | Quantification | Examples | Observations               |
|--------------------------|----------------|----------|----------------------------|
| Size                     | Particle size  | TiO2, Nano-silver | Smaller size exhibit high toxicity |
| [6][7][8][9]             | Size Distribution |           |                            |
| Shape                    | Spherical, Rectangle, Long, Short, Rod Like | Carbon-Nanotubes (CNT), Silver NPs | Long CNT signify more toxicity as compared to short CNT |
| [8][11][12]             |                  |          |                            |
| Crystal Structure        | Tetragonal, Orthorhombic, Monoclinic | TiO2, Nano Silica | Toxicity may alter contingent upon structure |
| [2][13]                 |                  |          |                            |
| Surface Charge           | Positive, Negative, Weakly Negative, neutral | Silicon NPs, Silica NPs | Negatively charge NPs are more toxic as compared to neutral and positively charged NP |
| [14][15]                |                  |          |                            |
| Surface Functionality    | Coating, Customization | Ag-NPs | NP Surface can be functionalized deliberately which can alter the toxic nature. |
| [16][17][18][19][20]   |                  |          |                            |
| Aggregate Phase          | Solid, dry, liquid, suspension | NPs impulse to contact each other and form chunks | Collective nature affects various critical properties, so it needs to be considered. |
| [21][22][23][24]       |                  |          |                            |

2.2. *Nano descriptors*

For designing a proper computational model, only physicochemical properties are not sufficient. As nano features differ a lot, there is a need to look upon the nano descriptors (NP Descriptors). NP Descriptors can be defined as peculiar characteristic or consolidation of various characteristics of a materials. Table 3 exhibit some of the NP Descriptors used in the past [25][26][27] took microscopic images as NP descriptors. These microscopic images are the blend of various characteristics such as surface scope, aspect ratio, shape, roughness, pixels, RGB codes and chemical ordering. On the basis of these features’ values, the level of harmfulness can be predicted.

**Table 3.** NP descriptors affecting toxicity

| NP-Descriptors | Characteristics |
|----------------|-----------------|
| Microscopic Images [26] | Surface scope, aspect ratio, shape, roughness, chemical ordering |
| Microscopic Images [27] | Pixels, RGB codes, Grayscale |
| Biological Surface Absorption Index [28] | Polarity, lone pair electron, hydrogen bond acceptor and donor |
| Spectra Category [25] | Infrared, Ultraviolet |
| Procedure Followed [29] | Development, Combination and Transformation methods used |
Similarly, other NP descriptors were defined as the combination of various characteristics of nanomaterials. Not only properties, but the procedures followed during development, combination and transformation of compound used as the initial data to explore the toxicity level. These descriptors data may not be in appropriate form to apply on computational models, so it needs to be refined. One of the main issue is to translate these theoretical descriptors into computer language for computation. The complication and heterogeneity of NM make it difficult to transform initial data into standard formats. Some standard methods and formats are required to refine these raw data into computer accessible format. Next section discusses the previous work done on collection of nanomaterials data from various resources as well as on processing it into a common format.

3. Nanodata collection and format conversion
In order to pull together with this diversified nanomaterials study, some formats and standards are required for extensive communication of the data. Several associations are working in this directions. This section gives the overview of the past work done in this area.

A framework was introduced i.e. ISA-TAB Nano (Investigation – Study – Assay – Material Tab delimited) [3]. ISA-TabNano is an extension of ISA-Tab, which is a general purpose framework introduced for proper collection and communication of experimental data. ISA-Tab Nano utilizes a sequence of technologies which collect and transmit complex nanomaterial data in a standard way. It accepts the data into four files namely investigation file, study file, assay file and materials file which are further divided into specific fields or columns. This data manually accumulated from the literature on predefined templates and various business rules are also applied. Additionally, a python program is present to convert resulting ISA-Tab nano files to text files delimited using tab. This output file assist the progress of computational analysis and database compliance. The issues associated with it includes the need of revision of various recorded data such as reaction rate, chemical compositions as well as template design. Another problem is that this scheme does not suit well for all type of experimental data and vivo toxicology study. The data collected is not good enough for further analysis. It needs to be redefine, to get utilized in predictive modelling.

In [30] the author had footnoted the requirement for more quality efforts in collecting the suitable and quality nano data as well as to develop prediction models for nanotoxicity check. The authors included few NanoQsar examples applied in past, to explain the prediction model development process. However, this analysis is not sufficient to provide a pathway in this area.

As fitting high quality dataset is one of the key prerequisite in the area of nanomaterials research, lemin xiao et al. tried to solve this dilemma by developing an information extraction system [31]. This extraction system performs carried out ontology-based entity extraction and rule-based attribute extraction on publications relevant to nanotoxicity. Further the extracted data is stored into a table accordance with relations among the data. As this system is based on ontology, it is not adequate to discover new entity instances. Machine learning methods can prove beneficial in determining new instances and inflate the dictionary.

4. Computational techniques
The past segment talks about the different approaches to gather and arrange the test information. To investigate the accessible information, different computational or information mining systems are required to smooth the assessment procedure. In [4][32][33], the authors have reviewed the QSAR approaches applied in the past. The following segment examines the most generally utilized strategies for the prediction of nanotoxicity.

Regression: Regression analysis is widely used in prediction and forecasting. It explains the variation occurs in value of dependent variables with respect to independent variable. The most widely used linear regression algorithms include multiple linear regression (MLR), Partial least square regression (PLR) and Principle component regression (PCR) [34][35][36][37]. The PLS regression is used when there is inter correlation between certain descriptors. These strategies demonstrates advantageous when different reactions should have been displayed simultaneously. The foremost advantage of linear regression methods is their transparency to provide relevant significance information of
physicochemical descriptors. Once in a while these models turn out to be ineffectively performed as a result of the nearness of information factors which are other than the yield. Consequently to expel these different measurement lessening strategies, for example, PCA (Principle Component Analysis) is utilized. Different past examinations had utilized PCA to enhance the result of their QSAR demonstrate. **Decision tree**: A decision tree is an efficient approach used in classification and regression. In QSAR, it can be used to predict toxicity on the basis of numerical and categorical data of biological activities [38][39]. The significant capabilities of decision tree which contribute the most in toxicity prediction includes automatic selection of input variables, removal of insignificant descriptors and to find worthwhile out of small, noisy and large datasets. **Support vector machine**: Various issues such as collinear descriptors, nonlinear relations, small and large datasets as well as over fitted models are handled by SVM. SVM proves to be an efficient approach for linear modelling which can manage both classification and regression problem [40][41]. The capability of SVM to give high precision and speculation making it an approach of intrigue. **Artificial neural network**: ANN is another approach utilized for nonlinear data relationship and large datasets. ANN approach has certain disadvantages such as choosing the ideal complexity, trouble of overfitting, high generalization sensitivity to variation in parameters and network topology and last but not the least, trouble in foreseeing the result [42][43].

5. QSAR (Quantitative structure activity relationship)  
Nastassja A. et al. had analysed the distinct informatics mechanisms that have been adapted in patent mining, nanomaterial device characterization, nanomedicine, and environmental risk assessment [44]. They single out the various natural language processing (NLP)-based tools such as NanoPort, NanoMapper, TechPerceptor, Nanodevice Analyser, Nanotoxicity Searcher, NEIMiner etc. Some of which are no longer available to use. The authors have endorsed for sharing NLP-related tools through online repositories to broaden participation in nanoinformatics.  
A new model GA-SVM, which works with the combination of two algorithms i.e. genetic algorithm and support vector machine was proposed [45]. The main aim of this paper is to classify the nanomaterials toxicity based on size, surface area and charge, chemical composition structure, reactivity and partitioning characteristics. The results obtained from experiments were satisfactory, but this model is applicable only when training data is available. While working with new set of experimental descriptors, it does not prove fruitful.  
Xiong Liu et al. proposed a prediction cube approach for nanotoxicity modelling [47]. Instead of using whole datasets (as done in traditional modelling), this data cube make use of subset modelling. It performs data exploration and predictive analytics which can help researchers in Slicing, dicing and drilling through nanotoxicity data and measure the quality of different subsets for building prediction models. Additionally, it stores prediction models and results in different cube cells. The inadequacy of proper experimental data and complications in acquiring that data, led to QSAR.  
QSAR (Quantitative structure-activity relationship) is defined as a mathematical model, which endeavour to generate a computable algorithm using various biological properties, compound structure and physico chemical features. As toxicity can be allied with such measurable properties, several QSARs models were proposed.  
The initial efforts to put QSAR in use for nanotoxicity computing was done by [46]. They checked for different toxicity sources using QSAR analysis, but due to unavailability of sufficient experimental data it did not turn out convincing.  
In [49], the author has come up with a QSAR model. The author has presented that various machine learning methods can generate promising predictive models for nanoparticles’ biological reactions. Three different datasets were taken as input that includes iron oxide nanoparticles, gold nanoparticles and other nanoparticles adorned with different molecules and are having different properties such as compositions, coating, concentration etc. Here Bayesian neural network along with linear and nonlinear machine learning techniques were adopted.  
Further various potential QSAR models were developed. In [29], the authors had proposed an effective statistical QSAR Model to anticipate the nanotoxicity. Moreover various classification based QSAR models were formed [48][50].
Natalia et al. have imparted a worthwhile review on QSAR approaches [4]. The paper focuses on inorganic NPs and provides an informative chemometrics data summary. As the lack of availability of proper datasets is one of the major issues in nanoinformatics, this review had tried to guide through the available and previously used datasets in QSAR, QSPR and chemometric studies. Various related publications were investigated and the summary is explained with the use of distinct fields such as no. of NPs, descriptors used, learning process and origin of datasets are some of the fields which are presented in the paper.

Oksel et al in [33][52] provides the details about core requirements for QSAR model. They have reviewed the characterization of nanomaterials, in-silico tools for QSAR model and summary of previous studies in this area. This paper can prove helpful while working on nanotoxicity computational modelling.

6. Conclusion
Nano QSAR needs a lot of efforts at every step, from pre-processing to model development. A biggest challenge is the lack of proper and sufficient experimental data. The major reason behind this inadequacy of data, is the complication in standardizing the toxicity testing methods and characterization of properties. The characterization of nanoparticles plays important role not only in identification of relationship between nanostructure and biological activities, but also in hastening the computation of engineered NM. There is a need for standard computation models, which collect experimental data and convert it to standard formats, to process it further for prediction model. The paper tries to be outright in its scope by reviewing considerable work in the field of NanoQSAR. We have analysed the previous work to bridge the gap between two research areas that are nanotoxicity and computational modelling, by providing the base as well as fusion of these two areas. Various techniques applied in past for experimental data collection, conversion to standard formats, QSAR and NanoQSAR are discussed in detail. To carry out comprehensive utilization of research data from bioscience groups, interoperable and efficient techniques are required which also help in building up an open data comming culture. We encourage the use of data mining techniques in the field of nanotoxicity, to programmatically execute the experimental data and predict the toxicity of nanomaterials before their manufacture and use.

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