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Advancing risk assessment of engineered nanomaterials using deep learning approach

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Abstract

Nanotechnology is a novel technology that develops material at a size of 100 nm or less which has become beneficial in various human endeavors because of its unique characteristic features. Nano-materials are utilized in medicine, Engineering, and agricultural industries. The unique properties of these materials are applied for beneficial purposes and at the same time may also have negative toxicological and environmental impacts. Considering the impacts on the environment and human health, nanomaterials could be harmful because they are easily distributed through the environment, aquatic, and human systems. Particularly in human body system, the unique properties have made its transportation and distribution through the skin, lungs, gastrointestinal tract very easy. However, several toxicological studies have shown considerable inherent toxicity of some nano-particles to living organisms, and their negative and harmful effects on the environment and aquatic systems for which both quantitative structure activity relationship and relatively tedious animal testing procedures are available in various literatures for their characterization. Because of the large number of nanoparticles manufactured with the different intrinsic properties especially sizes and coatings, there is therefore need to explore an alternative approach that will not necessitate conducting test on every nano-particle produced. It is the apprehensions of these potentially harmful effects of nanomaterials that constitute serious setback to nanotechnology commercialization. The objective of the study is to develop intelligent models to assess, evaluate, and manage the inherent risks. In view of these side effects, there is therefore the need to design and develop classification and nanomaterials toxicity predictive models using deep learning intelligent systems. This paper, therefore, focuses on the capability of deep learning techniques to model physicochemical properties and toxic effects of nanomaterials. Hence, the main motivation of this research work is to assist the users of nanomaterials in classifying, assessing and determining the risk of nanomaterials toxicity.

Keywords: Deep learning; Artificial Neural Network; Long Short-term Memory; Gated Recurrent Unit; Nanotechnology; Toxicity

1. Introduction

Nanotechnology is a novel technology that develops material at a size of 100 nm or less which are utilized in various human endeavors because of their unique characteristic features [1]. Nanomaterials are applied in medicine, Engineering, and agricultural industries. The unique properties of these materials are used for beneficial purposes and at the same time may also have negative toxicological and environmental impacts. Considering the impacts on the environment and human health, nanomaterials could be harmful because they are easily distributed through the environment, aquatic and human systems [2, 3, 4].

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Because of the large number of nanoparticles manufactured with the different intrinsic properties especially sizes and coatings, there is therefore the need to explore an alternative approach that will not necessitate conducting test on every nano-particle produced.

In recent years, it has been reported from various studies, that ENMs have hazardous potentials and harmful to human health. In the research work of Sharma et al., [5], carbon nanotubes (CNTs) were reported to have the potential of inducing reactive oxygen species (ROS) and pulmonary effects. Further studies of Saquib, et al [6] have also reported that titanium dioxide (TiO_2) nano-particles have the tendency to induce cytotoxic, genotoxic [7], and inflammatory effects [8]. Similarly, it was also reported by Asare et al. [7] that silver nanoparticle is capable of causing harmful effects arising from exposure to nano-silver. More detailed information about the negative side- effects of various ENMs has been reported by several researchers [4,8,9].

It is the apprehensions of these potential harmful effects of nanomaterials that constitute serious hindrance to nanotechnology commercialization. The objective of the study is to develop intelligent models to assess, evaluate, and manage the inherent toxic risks nanomaterials. In view of these side effects, there is therefore the need to design and develop classification and nanomaterials toxicity predictive models for using deep learning intelligent systems. This paper, therefore, focuses on the capability of deep learning techniques to model physicochemical properties and toxic effect of nanomaterials. Hence, the main motivation of this research work is to assist the users of nanomaterials in classifying, assessing, and determining the risk of nanomaterials toxicity**.**

Here, deep learning Systems such as Restricted Boltmann Machines, Deep Belief Network Deep Neural Network, Recurrent Neural Network (RNN), Long Short-Term Memory (LSTM), and Gated Recurrent Unit (GRU) systems have been explored as an alternative to establish the relationship between physicochemical properties and biological activity. For the modeling purposes, the important descriptors such as size, shape, and surface charge, can be measured by means of various experimental techniques. Considering the established consensus on measurement and modeling descriptors of traditional (Q) SAR analysis, these descriptors are to be applied for nano-Intelligent system [10,11,12,13].

The identification of toxicity-related properties that can be used as descriptors of harmful effects of ENMs is the first step in the modelling process. The recommended list of characteristics and properties by almost all nanotoxicologists as important determinants of toxicity include: size distribution, agglomeration state, shape, crystal structure, chemical composition, surface area, surface chemistry, surface charge, exposure time, and concentration. This paper, will therefore explore the capability of deep learning systems to model physicochemical properties and toxic effect of nanomaterials for the prediction of nanomaterials toxicity.

Section 1 gives a brief introduction. Section 2 highlights the physico-chemical characteristics dependent toxicity. Section 3 discusses materials and method. Section 4 discusses the prediction of Toxicity. Section 5 discusses the results and discussion. Finally, Section 6 discusses the conclusion of the study.

2. Physico-Chemical Characteristics Dependent Toxicity

Several mathematical correlations between various physico-chemical characteristics of nano-based products and the potential harmful effects have been reported by many researchers. In the following section, the descriptors which are considered to be critical toxicity determinant will be discussed.

2.1. Nanomaterial Size

Several toxicological studies have shown that nanomaterial size has been one of the most critical properties influencing the toxic effects of ENMs because as the particle size decreases, surface area which also affect the surface energy and the overall reactive ability increases. Also, the size of nano-based products influences the ability of these materials to transport, retain and interact with living systems as well as the release of ENMs within the environment and human body [14,15,16].

Monteiro-Riviere et al [17] also reported that the harmful side effects exhibited by nano-particles increases as particle size decreases. Fubini [18] further reported that respiratory organs of living organism can be affected adversely by nanoparticles (<100 nm) , when compared with larger particles produced from the same material. For instance, Jiang [2,3] illustrated this through an uptake of titanium oxide particles of two different sizes, 20 nm and 250 nm diameter by rat, and it was shown that smaller particles produced a more pronounced lung inflammatory reaction.

2.2. Aspect ratio

Some researchers have reported that the aspect ratio nanoparticle affects the toxic effects of nano- particle in such a way as it increases so also is the toxicity of nano-based materials [2,3]. The effects of aspect ratio on toxicity can also explained for CNTs. It was reported by Poland et al. [15] that short MWCNTs are less toxic than long multi-walled CNTs (MWCNTs). (Powers et al. [13,14] also reported that the antibacterial activity of silver NPs is influenced by shape. Gratton et al. [16] has also confirmed in his research work that rod-like shape indicating high aspect ratio nanoparticles are transported and deposited easily into cells than cylindrical nano-particles.

2.3. Concentration

Research works have shown that particle aggregation is influenced by a high concentration of ENMs [2,3] and therefore the potential toxic effects is less pronounced compared to lower concentrations. Most aggregates observed at a threshold value of 100 nm, may have serious adverse health effects.

2.4. Crystal Structure (Crystallinity)

Reports from research work of Jiang et al. [2,3] have shown that ENMs having different atomic and crystal structure may have different toxicological effects despite the fact that they are made of the same chemical composition. Particularly, the effect of crystallinity on nano-particle activity was investigated by comparing the ROS generating capacity of TiO_2 NPs with similar size but different crystal phases (amorphous, anatase, rutile, and anatase/rutile mixtures). It was reported that the highest level of ROS activity was manifested in amorphous samples followed by pure anatase and anatase/rutile mixtures, while the lowest level of ROS was exhibited by pure rutile.

2.5. Surface characteristics

Surface characteristics is also considered to be important in the reactivity and aggregation behavior of nano-particle in liquid media. For instance, research works have reported that the surface coating has serious influence on the toxicity of Ag-nano-particles [19,20,21,22,23,24,25]. The results from Nguyen et al. [20] also confirmed that coated Ag-nano-particles are less toxic than uncoated Ag-nanoparticles.

2.5.1. Surface area

Nanoparticles with large surface area have been reported to impact a greater toxicity than their smaller surface area with identical chemical and crystalline structure. From research studies, it can be concluded that the inflammatory effect may depend on the surface area of Nanoparticles. Actually, the higher the surface area and particle number per unit mass, the more pronounced is the reactivity [2,3] and source of ROS, as reported *from vitro* experiments [9].

2.5.2. Surface charge

The biological interactions and hence, toxicity of ENMs are also largely affected by surface charge. Jiang [2,3] analyzed the effect of surface charge on toxicity using negatively and weakly negatively charged silica-NPs. They observed that negatively charged silica-NPs exhibited higher cytotoxicity than weakly negatively charged silica-NPs. In another experiment, the core of silicon-NPs was coated with different organic monolayers in order to induce different surface charges (positive, negative, and neutral) [25]. It was discovered that positively charged silicon-NPs showed a greater toxic effect than neutral silicon-NPs, while negatively charged silicon-NPs exhibited virtually zero cytotoxicity. Zeta potential measurement is usually used to quantify the surface charge because of the difficulty in measuring directly the charge at the surface of particles.

3. Material and Method

Deep Learning is a collection of intelligent computational methodologies such as Restricted Boltmann Machines, Deep Belief Network Deep Neural Network, Recurrent Neural Network (RNN), Long Short-Term Memory (LSTM), and Gated Recurrent Unit (GRU) systems that attempts to solve problems not easily solvable by conventional mathematical tools. In this study the deep learning systems are therefore applied to relate the biological endpoints of a series of nanomaterials to their physicochemical properties in a quantitative way (Monteiro-Riviere et al [17]: Puzyn [11,12].

3.1. Basic Neural Network Components

An artificial neural network (ANN), consists of many simple units known as neurons which are interconnected together and designed mimic human nervous system. ANNs transform the inputs to outputs by adjusting the weights during a training of the network through a process known as back propagation. In a basic multi-layer ANN structure, as shown

in Fig. 1, the input layer of the artificial neural network gets information from the environment and the output layer sends the response back to the environment. The layers between the input layer and the output layer of an ANN are called the hidden layers which has no direct communication with the environment. The number of hidden layers varies and may be one or more depending to the problem being solved. The output of an ANN depends on the weights of the connections between neurons in different layers which indicates relative importance of a particular connection. [26]

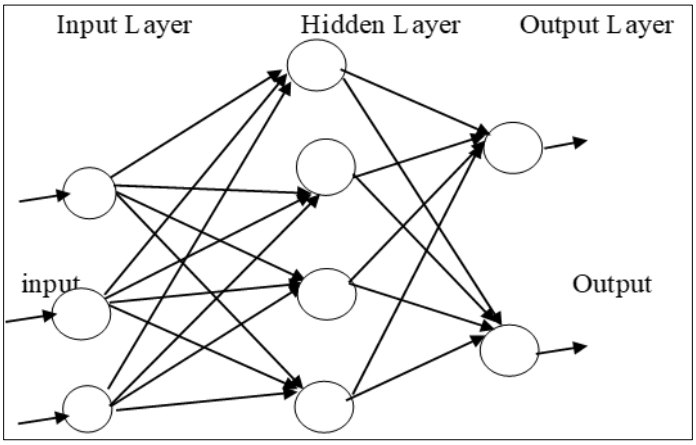


Figure 1 Multi-Layer Perceptron

3.2. Restricted Boltzmann Machines

A restricted Boltzmann machine (RBM) , as shown in Fig. 2, is a type of generative neural network which is made up of a visible layer, hidden layer, and connections between the two layers [27,28]. The mode of operation of the machine involves the propagation of the input upwards from the visible layer to the hidden layer, after which the hidden layer will propagate the data back down into the visible layer to produce a new set of inputs. The training of RBMs is accomplished by adjusting the weights between the visible and hidden layer. A sigmoidal activation function was applied since most implementations of restricted Boltzmann machines have functioned well with this particular function. Several steps are involved in updating the weights of an RBM.

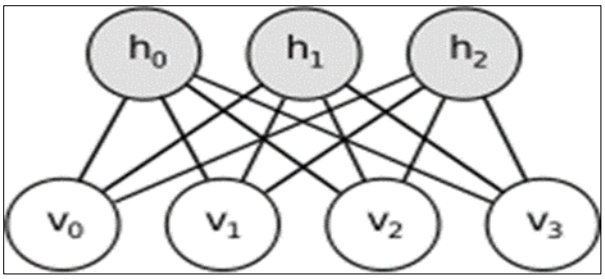


Figure 2 A Restricted Boltzmann Machine

First, compute the probability of a given hidden unit by summing all the activations over every visible unit. This is used to determine whether each hidden unit is activated or not. Apply the same process in reverse to propagate downwards to the visible units. The weights are then updated, and this process is repeated over all training examples, until either a certain minimum error is reached or a maximum number of training steps is exceeded.

3.3. Deep Belief Networks

The Deep Belief Network is designed by a combination of more than one RBMs as shown in Fig.3. It was shown that RBMs can be combined and trained in a greedy manner to form so-called Deep Belief Networks (DBN) [29,30].

The principle of greedy layer-wise unsupervised training can be applied to DBNs with RBMs as the building blocks for each layer.

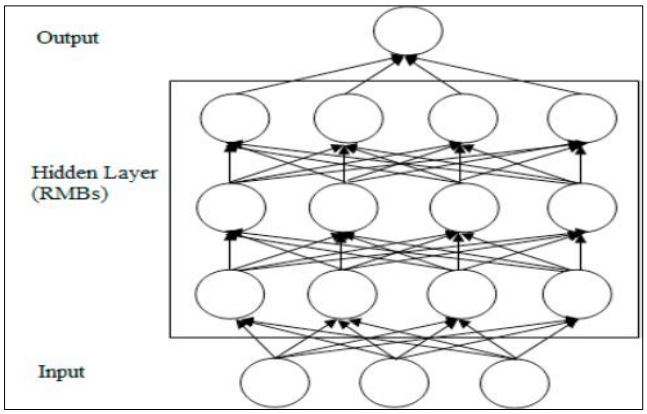


Figure 3 Deep Belief Network

The process is as follows:

- Train the first layer as an RBM that picks up the raw input as its visible layer.
- Use the data in the first hidden layer to obtain a representation of the input that will be used as data for the second layer.
- Train the second layer as an RBM, taking the transformed data (mean activations) as training examples for the visible layer of that RBM)
- Iterate (2 and 3) for the desired number of layers, each time propagating upward either samples or mean values.

3.4. Fully-Connected Networks

The basic neural network architecture called the multilayer perceptron (MLP) has one hidden layer, which is the simplest form of a fully connected network as shown in Fig.1. However, a layout in which we have more than one hidden layer model as provided in Fig. 4, is known as fully connected network or deep neural network. MLPs are feed-forward, meaning that information flow is always directed towards the output layer. It has been shown that they can used to approximate function [27,28,29]. MLPs have an input layer whose values are obtained by the input samples, more than one hidden layer whose values are derived from previous layers, and an output layer whose values are derived from the last hidden layer. Each neuron in the input and hidden layers has a forward-directed connection to each neuron in the next layer. A non-linear activation function at each neuron introduces non-linearity to the neural network [27,28,29]. Each neuron in the network receives data from every neuron in the previous layer and each of these inputs is multiplied by an independent weight. The weighted inputs are summed and are then sent through an activation function to produce the output values.

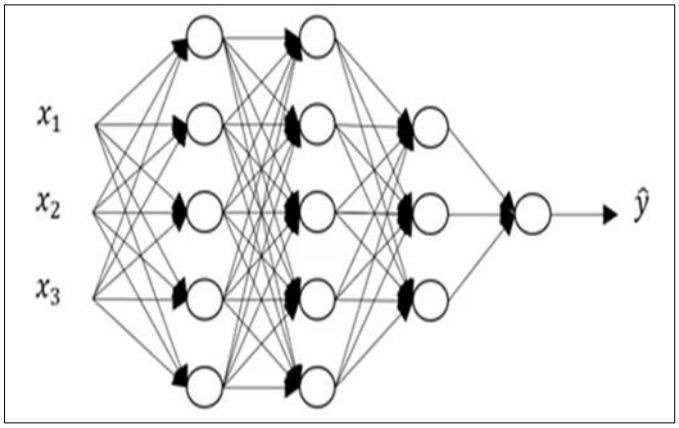


Figure 4 Deep Neural Network

The outputs from each neuron can then be fed into the next layer of the neural network in the same manner. However, simple DNN was trained by Back-propagation algorithm.

3.5. Long Short-Term Memory (LSTM)

Short-term memory (LSTM) is a deep learning system that avoids the vanishing gradient problem associated with recurrent neural network. It consists of recurrent gates called "forget" gates. LSTM prevents back-propagated errors from vanishing or exploding thus making it possible to flow backwards through unlimited numbers of layers unfolded in space.

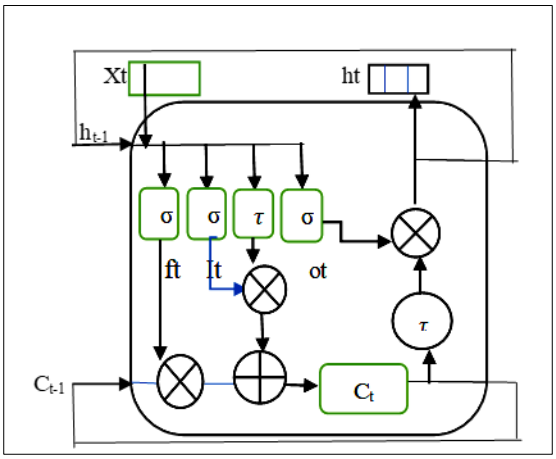
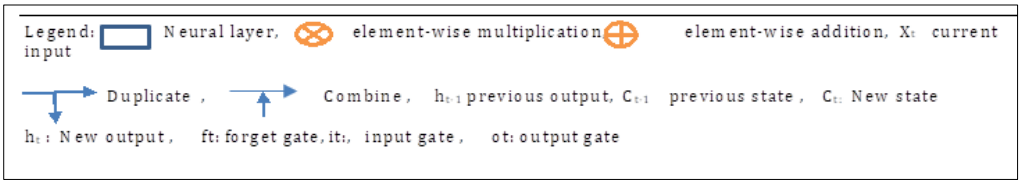


Figure 5 Long short-term memory unit



The LSTM operates on a memory cell Ct that can maintain its state information over time, which allows gradients to flow over long sequences. The flow of information into and out of the memory cell Ct is controlled by three gates: an input gate, (it), a forget gate, (ft) and an output gate, (ot). During a forward pass, the cell states (st) and outputs (ht) of the LSTM layer at each time-step t, are calculated using (4) - (9) [31,32,33,34,35,36,37,38]. In the first step, the LSTM layer determines which information should be removed from its previous cell states s_{t-1}. Therefore, compute the activation values of the forget gates at time step t based on the current input xt, the outputs h_{t-1} of the memory cells at the previous time step (t-1), and the bias terms, bf of the forget gates. The sigmoid function is usually applied to reduce all activation values into an interval between 0 (completely forget) and 1 (completely remember):

$$ft = \sigma\ (W_{ft}\ * x_t + W_{fh} * h_{t-1} + b_f \quad (4)$$

In the second step of LSTM layer, information which should be added to the network's cell states (st) is determined and this process is done by two operations: First, the potential candidate values $\hat{S}_T$, which could be added to the cell states, are determined. Secondly, the activation values of the input gates (it) are computed:

$$\hat{S}_T = tanh\ (W_{sx}\ * x_t + W_{sh} * h_{t-1} + b_s \quad (5)$$

$$it = sigmoid\ (W_{ix}\ * x_t + W_{ih} * h_{t-1} + b_i \quad (6)$$

The third step calculates the new cell states (st) based on the results of the previous two steps with ° denoting the Hadamard product:

$$st = ft \circ s_{t-1} + it \circ \hat{S}_T \quad (7)$$

Finally, the output (ht) of the memory cells is computed using the following two equations:

$$ot = \sigma (W_{ox} * x_t + W_{oh} * h_{t-1} + b_0 \quad (8)$$

$$ht = ot \; o \; \tanh (st) \quad (9)$$

3.6. Gated Recurrent Unit

Gated Recurrent Unit is a type of recurrent neural network designed to address the inherent long-term dependencies which is capable of leading to either exploding or vanishing gradient. This is accomplished by storing memory from the previous time for the purpose of future predictions [32,33,34,35,36,37,38,39]. The governing equations for GRU are:

$$Z = \sigma (W_z * x_t + U_z * h_{t-1} + b_z \quad (10)$$

$$r = \sigma (W_r * x_t + U_r * h_{t-1} + b_r \quad (11)$$

$$\check{h} = tanh (W_h * x_t + r * U_h * h_{t-1} + b_z \quad (12)$$

$$h = Z * h_{t-1} + (1 - Z) * \check{h} \quad (13)$$

Update Gate, Z: The activation value of update gate is computed by taking in the input and the hidden state from the previous timestamp t-1 and are multiplied by Wz and Uz respectively to which update bias b_z is added as shown in equation (10) . The sigmoid function is usually applied to reduce all activation values into an interval between [0, 1]. .

Reset Gate, r: The purpose of reset gate is to allow the network to ignore past information that may be irrelevant in the future time steps. The value of rt is computed using equation (11) will be in the interval [0, 1] because of the sigmoid function. Here Ur and Wr are weight matrices for the reset gate.

The resultant value is the candidate's hidden state is computed as shown in equation (12). The most important aspect of (12) is how the value of the reset gate can be used to control the the influence of previous hidden state on the candidate state. The final output is computed using equation (13) which also shows the influence of Z. Surpose the value of Z is around 0 then the first term in the (13) will vanish which indicates that the new hidden state will not have much information from the previous hidden state. On the other hand, the second part becomes almost one which indicates that the hidden state at the current timestep will essentially have the information from the candidate state only.

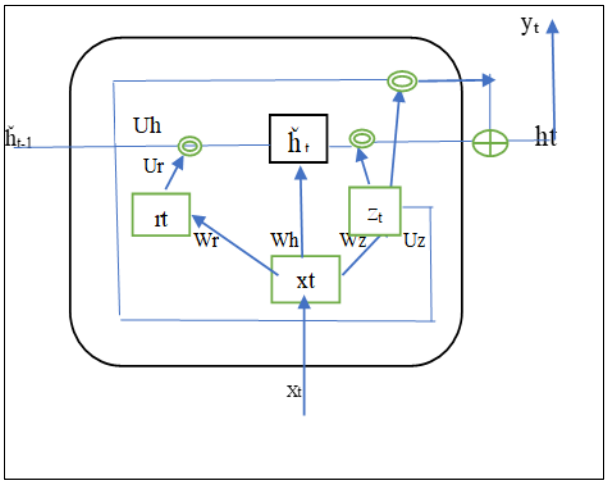
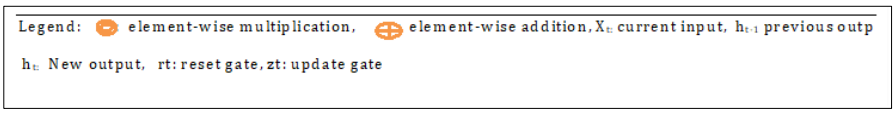


Figure 6 Gated Recurrent Unit (GRU) Cell Architecture



4. Prediction of Toxicity

The data used for the prediction of toxicity of nanomaterials were obtained from Arts et al. [40] and Dossiers of the OECD Working Party on Manufactured NMs. Sponsorship Program on the testing of NMs (OECD, 2015a,b,c,d [41,42,43,44];

The DF4nanoGrouping process allows nanomaterials to be assigned to any of the four main groups, to sub-group, active NMs and passive NMs. This will facilitate the determination and evaluation of the required information for hazard and risk [40]

- MG1: This group have soluble and non-bio-persistent nanomaterials which depend on chemical structure for hazard assessment.
- MG2: This group has bio-persistent, High Aspect Ratio (HAR) nanomaterials which have shown certain level of rigidity and meets WHO conditions for respirable fibres.
- MG3: These are passive, bio-persistent, non-fibrous which are neither MG1 nor MG2 nanomaterials. They do not (i) show high surface reactivity; (ii) do not exhibit toxic effects (chemical composition do not possess active ingredients; no known cellular effects); and (iii) are immobile (agglomerates in biological fluids) . From the In-vivo test, the passive nature of NMs is confirmed due to lack of elicit apical toxic effects.
- MG4: These are active bio-persistent, non-fibrous nanomaterials with harmful potential. Arts et al. [40] proposed assigning NMs to MG4 by considering chemical composition, dissolution in biological media, surface reactivity, dispersibility, or cellular effects. In vivo, active NMs can exhibit apical toxic effects at a lower concentration.

According to vivo screening, research shows that the STIS NOAEC (Short-term inhalation study: STIS, No Observed Adverse Effect Concentration: NOAEC), the toxic potency is as shown below:

Table 1 Nanomaterials Toxic Potency

Listed species of a nanomaterial	Water solubility mg/L	Solubility in Biological media mg/L	Surface Reactivity µUFRAS/ m^2.h	Surface Charge	Nanomaterial Size (nm)	Specific Surface area	Exposure Time (day)	Aspect Ratio	Cytotoxicity (EC_{50}) mg/m^3	Class Label
CeO_2 A	9.0	9.0	0.0073	16.0	9.7	66.0	44.0	0.97	8.0	1
CeO_2 B	19.0	8.0	0.0324	42.0	40.0	27.0	44.0	4.0	7.9	1
CeO_2 C	18.0	7.255	0.0434	15.0	15.0	48.0	50.0	1.5	7.5	1
CeO_2 D	18.0	7.25	0.0424	16.0	10.0	61.0	44.0	1.0	7.6	1
CeO_2	19.5	8.018	0.0324	17.0	70.2	33.0	46.0	7.0	7.7	1
TiO_2 1	0.08	0.063	0.0244	-17.0	21.0	51.0	44.0	2.0	9.0	1
TiO_2 2	0.08	0.073	0.0245	-17.0	27.0	40.0	42.0	2.7	9.5	1
TiO_2 3	0.07	0.015	0.0243	-20.0	25.0	45.0	41.0	2.5	8.5	1
$BaSO_4$ NM220	6.0	0.675	0.0503	-39.0	32.0	41.4	30.0	3.2	10.6	-1
ZnO NM-110	0.0	98.0	0.078	20.0	70.0	12.0	35.0	7.0	15.0	-1
ZnO NM-111	0.0	99.0	0.0389	21.0	82.0	15.0	14.0	8.0	16.5	-1
CuO NM	18.0	120.0	2.205	28.0	10.0	47.0	20.0	4.0	17.0	-1
Fe2O3 Hematite	0.8	0.5	0.0372	-27.0	15	85.0	38.0	1.5	?	?

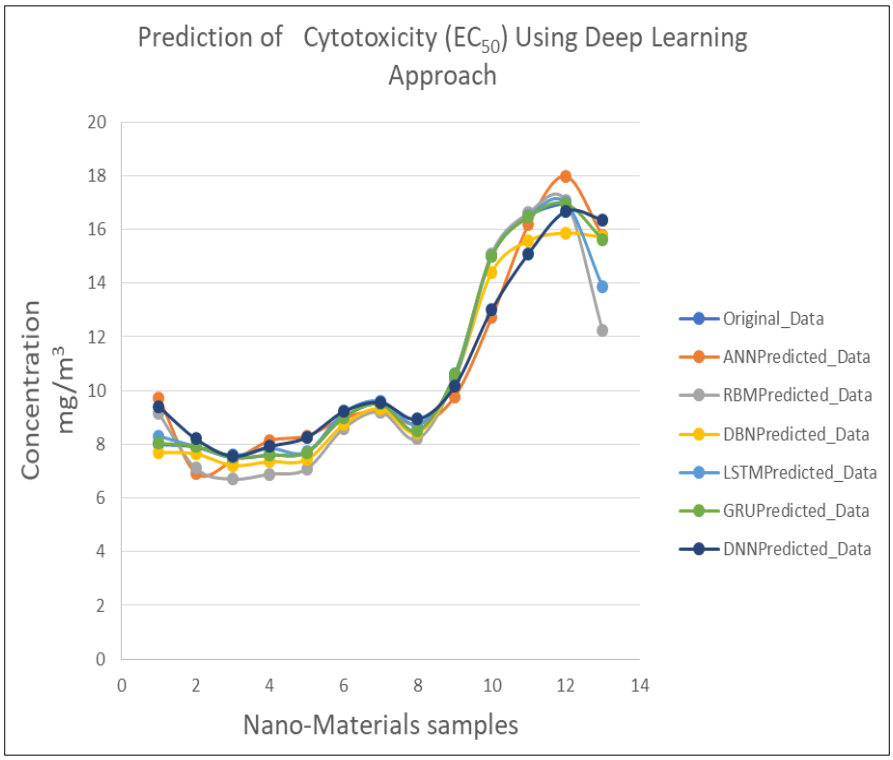


Figure 7 Prediction of Cytotoxicity (EC50)

Table 2 Performance of Deep Learning Models

	RMSE	**R^2**	**Predicted Cytotoxicity (EC_{50}) mg/m³**
Standard Artificial Neural Network (ANN)	0.9858	0.9588	15.77
Restricted Boltmann Machine (RBM)	0.567	0.9913	12.25
Deep Belief Network (DBN)	0.499	0.9991	15.72
Long Short-Term Memory (LSTM)	0.1551	0.9995	13.87
Gated Recurrent Unit (GRU)	0.0192	0.9999	15.64
Deep Neural Network (DNN)	0.8651	0.9817	16.34

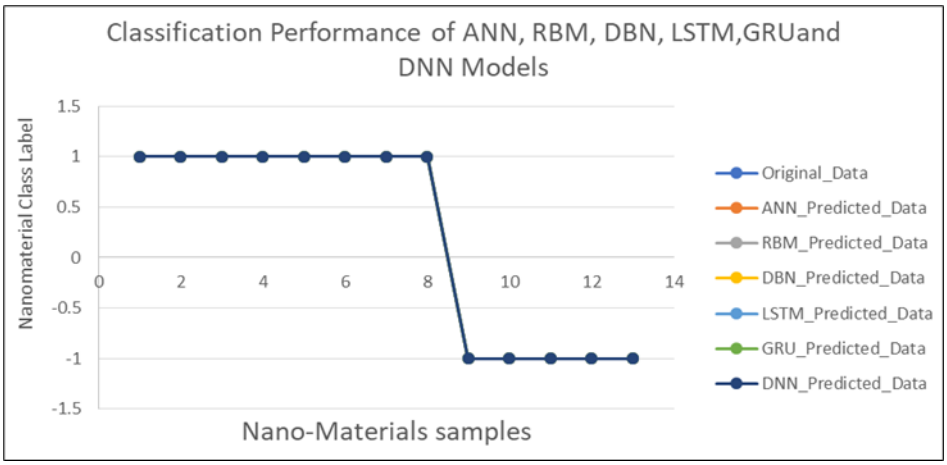


Figure 8 Classification of Nanomaterial

Table 3 Classification Performance of Deep Learning Models

	R^2	Non Toxic Materials	Toxic Materials	True Positive	False Negative	True negative	False Positive	Specificity (%)	Sensitivity (%)	Predicted Cytotoxicity (EC_{20})
Restricted Boltmann Machine (RBM)	1.00	5	8	8	0	5	0	100	100	-1
Deep Belief Network (DBN)	1.00	5	8	8	0	5	0	100	100	-1
Long Short Term Memory (LSTM)	1.00	5	8	8	0	5	0	100	100	-1
Gated Recurrent Unit (GRU)	1.00	5	8	8	0	5	0	100	100	-1
Deep Neural Network (DNN)	1.00	5	8	8	0	5	0	100	100	-1

5. Results and discussion

In this case study, nanoparticle of metal oxides and sulphates were examined. We have five materials (10nm CuO, ZnONM-110 and NM-111, $BaSO_4$ NM-220, 15nmFe_2O_3) which are passive NMs while eight materials (CeO_2 NM-A, NM-B, C,D TiO_2 NM-1-3 are active (Toxic NMs) .The predicted toxicity classification label of 15nm Fe_2O_3 is -1 indicating that it is passive (non-toxic) . The training and testing dataset used for the model implementation are as presented in Table1. The two classification errors are Type I and Type II errors. The Type I refers to when toxic material was erroneously classified as non- toxic material while Type II refers to erroneous classification of non- toxic material as toxic material. The predicted result is as listed in Fig. 8 and Table 3. We observed form these results that ANN, RBM, DBN LSTM and GRU models exhibited satisfactory performance for predictive correlations. The models showed high classification performance, and with no absolute percent relative error type and type II errors, no root mean square error, and the 100% correlation coefficient among other correlations for the two distinct data sets.

The predicted toxicity (Cytotoxicity (EC_{50}) of 15nm Fe_2O_3 are as shown in Table 2. The toxic potency (STI NOAEC) according to tier 3 in [40]. is ≥10mg/m^3. The performance of the five models, ANN, RBM, DBN LSTM and GRU, are very competitive with values >10mg/m^3. However, GRU has the lowest RMSE of 0.01923 against other models as shown in the Table 2 and also has R^2 99.9% with predicted toxicity (Cytotoxicity (EC_{50}) of 15.64 mg/m^3. In essence, the results of all the models are highly competitive for the prediction of cytotoxicity value. The predicted curves of the five models show little deviation from the experimental curves. Fig 7 shows the value of predicted cytotoxicity curve by ANN, RBM, DBN LSTM and GRU models which are >10mg/m^3. Therefore, predicted toxicity (Cytotoxicity (EC_{50}) of 15nm Fe_2O_3 is 15.64 mg/m^3 being the value of GRU model having the lowest RMSE and highest R^2. This also confirms the classification of 15nmFe_2O_3 as passive (non-toxic) nanomaterial.

6. Conclusion

This study developed and compared the performance of ANN, RBM, DBN LSTM and GRU models to predict toxicity. The study and understanding of the ANN, RBM, DBN LSTM and GRU models and their roles in regression and classification capabilities were achieved. These techniques were implemented using the Microsoft C# programming language to perform regression and classification task for the nanomaterial toxicity. The deep learning approach therefore provided

means of predicting the toxicity of nanomaterials. In view of the uncertainty surrounding the classification of nanomaterials and prediction of toxicity of nanomaterials, Fuzzy Logic (FL) concept will be considered as part of the future work.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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