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Original Article

Engineered Nanoparticles Cytotoxicity Prediction Using an Enhanced Convolutional Neural Network

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Abstract - *Engineered nanoparticles (ENPs) possess distinctive physicochemical properties that drive innovation across various fields. However, their potential cytotoxic effects, combined with the inherent complexity of their biological interactions, pose significant challenges for accurate toxicity assessment. Traditional machine learning methods often fall short in modeling the nonlinear and high-dimensional nature of ENP data. To address this limitation, this study introduces a novel feature aggregation technique called Horizontal Sequence Pooling (HSP) integrated within a Convolutional Neural Network framework to improve cytotoxicity prediction. The dataset employed was compiled from multiple peer-reviewed sources published between 2010 and 2022, comprising 4,863 samples characterized by 28 descriptors. Data preprocessing involved median-based univariate imputation for handling missing values and one-hot encoding of categorical variables to ensure compatibility with the CNN architecture. The CNN-HSP model was evaluated against CNN variants utilizing conventional max and average pooling strategies. Experimental results demonstrate that the CNN-HSP model consistently achieved superior performance, reflected in significantly reduced error metrics (MSE, MAE, and RMSE) and a high coefficient of determination R-squared value of 0.9975, indicating strong alignment between predicted and observed values. The enhanced pooling method effectively preserved critical spatial data relationships, allowing the model to learn complex toxicity-related patterns more accurately. Overall, the CNN-HSP model provides a robust and interpretable framework for ENP cytotoxicity prediction, offering a valuable tool for risk assessment and safer nanomaterial development.*

Keywords - *Engineered Nanoparticles, Cytotoxicity, Convolutional Neural Networks, Pooling algorithms, Prediction.*

1. Introduction

Engineered nanoparticles (ENPs) have become indispensable in diverse industries such as medicine, electronics, and environmental remediation due to their customizable physicochemical properties and nanoscale behavior, enabling unprecedented functionality and efficiency [1]. However, this technological advancement introduces significant safety concerns, as nanoparticle structure and composition modification can inadvertently alter their biological interactions, potentially leading to unforeseen toxicological effects [2, 3]. Therefore, accurately predicting ENP cytotoxicity is a critical research priority for ensuring their safe and responsible deployment. Despite efforts to model ENP toxicity using traditional machine learning methods [4], these models often struggle with the complex, nonlinear interactions inherent in nanoparticle-biological systems. Their limited capacity to generalize across diverse ENP types and the oversimplification of feature relationships restrict their reliability and interpretability in practical applications. Deep learning has recently advanced, notably in Convolutional Neural Networks (CNNs), offering promising alternatives due to their ability to extract hierarchical features from complex datasets automatically. CNNs have shown potential in toxicity prediction, but a key challenge remains in how spatial features are condensed through pooling operations. Conventional pooling methods, such as max pooling and average pooling, may discard or dilute essential information by uniformly applying reductions across feature maps. This becomes a critical drawback when modeling ENPs, where position-dependent and subtle descriptor patterns can be vital to understanding toxicological outcomes. This study addresses this specific gap by introducing a novel pooling mechanism called Horizontal Sequence Pooling (HSP), which is designed to more effectively preserve key spatial dependencies and feature relationships. Unlike traditional pooling strategies that treat spatial data uniformly, HSP applies a sequence of positional feature-specific pooling operations to selectively retain prominent and contextually relevant features. Doing so minimizes information loss and improves the network's capacity to model the complex and varied toxicity behaviors of ENPs. To establish the value of this approach, the performance of the HSP-enhanced CNN

model is rigorously compared with standard CNN architectures using standalone max pooling and average pooling. The evaluation relies on robust statistical metrics like Mean Square Error (MSE), Mean Absolute Error (MAE), Root Mean Square Error (RMSE), and R-squared (R^2) to validate predictive accuracy and model robustness.

This research introduces a novel domain-specific pooling strategy within the CNN framework directly tailored to the complexity of ENP cytotoxicity data. This contribution advances CNN architecture design and provides a more accurate and interpretable tool for nanotoxicology, with implications for safer material design and regulatory decision-making.

2. Literature Review

2.1. Engineered Nanoparticles and their Cytotoxicity

Engineered nanoparticles (ENPs) are intentionally designed materials with at least one dimension in the nanoscale range (1 to 100 nanometres), known for their high surface area-to-volume ratio and tunable physical and chemical characteristics [5]. Their widespread use in medical, environmental remediation, electronics, and consumer products arises from their adjustable morphology, surface charge, reactivity, and coating profiles [6].

However, these same properties that drive innovation can also introduce unanticipated toxicological effects, especially when ENPs interact with biological systems in complex environments [2]. After inhalation, ingestion, or dermal contact exposure, ENPs can induce oxidative stress, inflammation, genotoxicity, or cell apoptosis [7, 8].

Moreover, the environmental accumulation of ENP through industrial effluents, wastewater discharges, or soil infiltration presents growing risks to aquatic life and microbial ecosystems [9]. The wide range of ENPs and the complexity of their dose response make experimental toxicological evaluation difficult. The time and resources required for laboratory-based cytotoxicity testing make it impractical to assess the vast array of emerging ENPs [10]. Additionally, the inconsistency between in vitro and in vivo outcomes complicates safety standardization [11].

To address this, computational toxicology has gained prominence. Traditional models, such as Quantitative Structure-Activity Relationship (QSAR) models and basic machine learning algorithms, have been explored in predicting chemical toxicity based on molecular descriptors [4, 12]. However, these methods often fall short when modeling the highly nonlinear and interdependent physicochemical attributes of ENPs. Their limited generalization across diverse nanoparticle configurations highlights the need for more advanced data-driven approaches capable of learning deeper feature interactions from structured, high-dimensional datasets.

2.2. Convolutional Neural Network

Convolutional Neural Networks have become a cornerstone of deep learning due to their hierarchical learning ability and success across domains, including image analysis, speech recognition, and molecular property prediction [13]. By leveraging convolutional layers, activation functions, and pooling operations, CNNs can automatically learn spatial and positional feature relationships from complex datasets.

Over the years, CNN architectures have evolved substantially, starting from early models like LeNet-5 [14] and AlexNet [15] to more complex designs such as ResNet [16] and EfficientNet [17]. While initially applied in computer vision, CNNs are now increasingly used in cheminformatics and bioinformatics for drug toxicity screening, compound classification, and molecular interaction analysis [18, 19].

In the context of ENP, recent studies have begun to explore CNN-based models for predicting toxicity by transforming ENP descriptors into input formats suitable for deep learning. These formats include molecular fingerprints, 2D/3D structural grids, and graph-structured data processed using graph convolutional networks [20]. These models have demonstrated the capacity to capture intricate substructure patterns and predict toxicity more accurately than traditional models.

However, the performance of CNNs in this domain is highly sensitive to architectural design choices, including how pooling layers aggregate feature information. Since ENP toxicity is often linked to subtle, position-dependent features (e.g., specific surface coatings or charge distributions), retaining and interpreting fine-grained information is crucial. Thus, optimizing pooling strategies remains a key challenge for deep-learning models in nanotoxicology.

2.3. Pooling Methods and their Role in Predictive Modeling

Pooling layers in CNNs are designed to reduce feature map dimensionality, enhance generalization, and manage computational complexity. The two most common strategies, max pooling and average pooling, summarize spatial regions by extracting either the most prominent or the average signal within a defined window [21, 22]. While these methods are efficient, they can lose important spatial dependencies or dilute key signals, especially in tasks that require more detailed pattern retention.

The deep learning community has developed various advanced pooling techniques to overcome these limitations. Mixed pooling combines max and average pooling for better generalization [23], while rank-based average pooling (RAP) introduces statistical ordering to pooling [24]. S3Pooling uses stochastic spatial sampling to prevent overfitting and improve generalization [25], and LEAP (Learning Pooling) employs trainable pooling operations to adaptively learn pooling behavior during training [26].

Traditionally, max pooling and average pooling are the most common methods [21, 14]. Max pooling extracts the maximum value within a window, effectively preserving the most significant features. Average pooling calculates the average value, offering a smoothed representation of features within each window. Global pooling is another variant that aggregates all values across the entire feature map, reducing dimensionality [27]. Other innovations, such as Generalized Max Pooling [28], Chebyshev Pooling [29], and EDS Pooling [30], aim to balance feature prominence with context preservation. Horizontal Max Pooling [31] specifically addresses spatial sensitivity, a critical factor for position-dependent tasks such as image segmentation and structural feature recognition.

Despite the growing pool of advanced techniques, limited research has focused on tailoring pooling operations to the unique challenges of ENP cytotoxicity modeling. Conventional pooling layers may not adequately capture the complex and spatially structured interactions embedded in ENP feature representations. Therefore, exploring novel pooling methods, such as the proposed HSP, offers an opportunity to preserve critical toxicological features, reduce signal loss, and improve model interpretability and predictive accuracy.

3. Materials and Methods

3.1. Data Collection and Preprocessing

This study relied on a dataset from journal publications released between 2010 and 2022, curated by [4]. A total of 4,863 samples with 28 descriptors containing various parameters that describe the properties of the ENPs, including their synthesis, physical characteristics, and cytotoxicity (cell viability) effects on different cell lines under various conditions. The dataset is stored in a Comma Separated Value (CSV) format and divided into an 80% training set for model training and fine-tuning and a 20% test set to assess model performance. Missing values were pre-processed and managed using the median univariate imputation method, which replaced missing values with the median of the corresponding column (descriptors). To ensure compatibility with the model, categorical descriptors were converted into numerical values using one-hot encoding.

3.2. Enhanced CNN Prediction Model with Modified Pooling Algorithm

In this study, an enhanced feature pooling CNN model was employed to predict the cytotoxicity of ENPs. The model comprises two one-dimensional convolution layers featuring 64 filters (kernel size 3) and 128 (kernel size 3) filters. The Rectified Linear Unit (ReLU) activation function was used. Batch normalization was applied to enhance training efficiency. In the pooling layer, the Horizontal Sequence Pooling algorithm was applied, using modified pool and stride sizes of 2. The network architecture further included a flattened layer, succeeded by two dense layers containing 128 and 64 neurons, respectively. The Dropout [32] technique was incorporated to mitigate overfitting. Figure 1 shows the CNN model with enhanced feature pooling using the HSP algorithm.

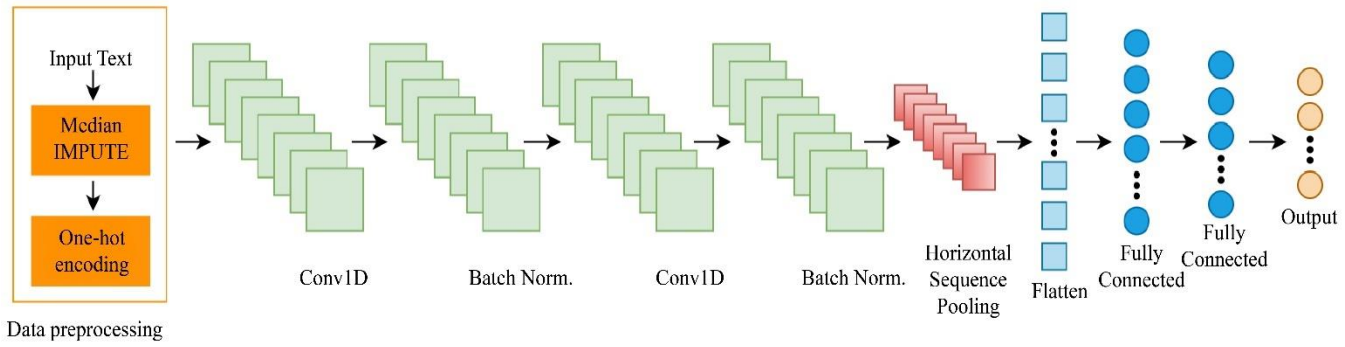

Fig. 1 CNN model with horizontal sequence pooling

3.3. Horizontal Sequence Pooling Algorithm

The Horizontal Sequence Pooling algorithm is utilized as a feature pooling technique in CNNs by capturing complex cytotoxicity interactions between input features. Given an input tensor X with dimensions corresponding to batch size and feature channels, HSP operates over the tensor using a specified pooling window size p and a *stride*.

For each window position I, starting from 0 and moving in increments of *stride*, a local W_i is extracted from X, spanning p steps across feature channels. HSP computes two sets of maximum values within each window to capture the positional maxima. Specifically, the *feature* is derived by taking the maximum values across the first and third indices along the feature dimension. In contrast, $feature_b$ is obtained by computing the maximum values across the second and fourth indices similarly. These positional maxima are then averaged to form the pooled feature for the window, ensuring that significant features are preserved. Mathematically, this pooled feature for window W_i is represented in Equation 1:

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2} \quad (1)$$

By iteratively tuning parameters such as pool size, stride size, and feature pooling indices, the configuration is optimized to align with the dataset's characteristics. Algorithm 1 presents the pseudocode for the Horizontal Sequence Pooling algorithm.

Algorithm 1. Horizontal Sequence Pooling
Input:
X – Input tensor (shape: 4 x *m*)
p – Pool size
stride – Stride size
Output:
HSP – Final pooled tensor containing aggregated features

1. Initialize an empty list of *HSP*.
2. Define the total number of windows:
   $num_{windows} = floor(m - p) / stride + 1$
3. For each window index i from 0 to $num_{windows} - 1$:
4. Define the start and end indices of the current window:
   $start_x = i \times stride$
   $end_x = start_x + p$
5. Extract the window matrix W_i: $W_i = X[:, start_x : end_x]$
6. Calculate max_a: $max(W_i[:,:,[0,2]], axis = 1)$
7. Calculate max_b: $max(W_i[:,:,[1,3]], axis = 1)$
8. Compute the pooled feature for the window:
   $pooled_{feature} = \text{ave}(max_a + max_b)$
9. Append the $pooled_{feature}$ to *HSP*.
10. Stack all pooled features: $HSP = stack(HSP, axis = 1)$
11. Return *HSP*.

3.4. Performance Metrics

The model's performance was assessed using four key metrics: MSE, MAE, RMSE, and R^2. MSE measures the average squared errors between actual cytotoxicity and the model's predicted values. MAE calculates the average absolute errors between the actual and predicted cytotoxicity. RMSE provides the average magnitude of the prediction errors. Additionally, R^2 evaluates how well the model's predictions explain the variability in the actual cytotoxicity.

$$MSE = \frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2 \quad (2)$$

$$MAE = \frac{1}{n}\sum_{i=1}^{n}|y_i - \hat{y}_i| \quad (3)$$

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2} \quad (4)$$

$$R^2 = 1\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2} \quad (5)$$

In the equation, n denotes the number of samples or observations, i is the number of iterations, y_i is the actual cytotoxicity, $\hat{y}_i$ is the predicted cytotoxicity, $\bar{y}$ and represents the mean of the actual cytotoxicity. The optimal model for predicting cytotoxicity was selected based on the lowest MSE, MAE, and RMSE values combined with the highest R^2 value.

4. Results and Discussion

4.1. Experimental Setup and Data

The prediction model was developed using Python 3.9.12 within the Jupyter Notebook environment, leveraging key packages such as numerical computing (Numpy), data manipulation (Pandas), deep learning (Tensorflow), machine learning (Scikit-learn), and data visualization (Matplotlib). The model was trained and evaluated on a system configured with an Intel(R) Core i7 10870H (2.20GHz) processor, 32GB of RAM, and a 6GB NVIDIA GeForce RTX 3060 GPU. The CNN models were compiled using the Adam [33] optimizer with a learning rate 0.0001, minimizing the MSE loss function. To evaluate the enhanced CNN model, its performance was directly compared against standard CNN architectures employing max pooling and average pooling layers, respectively. Training for all models involved 120 epochs with a batch size of 32.

4.2. Model Training and Convergence Behaviour

The learning dynamics of the three CNN models (CNN-HSP, CNN-Max Pooling, and CNN-Average Pooling) are shown in Figures 2 to 4 using MSE, MAE, and RMSE metrics across 120 training epochs. Initially, all models exhibit a sharp drop in error values during the first 20 epochs, reflecting the fast acquisition of basic feature representations from the ENP dataset. Beyond this point, a clear divergence in performances emerges. The CNN-HSP model continues to decline steadily across all error metrics, achieving the lowest and most stable values throughout training. In contrast, CNN-Max Pooling shows inconsistent error behavior with significant fluctuation and early plateauing, indicative of optimization instability. CNN-Average Pooling performs moderately better but stabilizes at a higher error level than CNN-HSP.

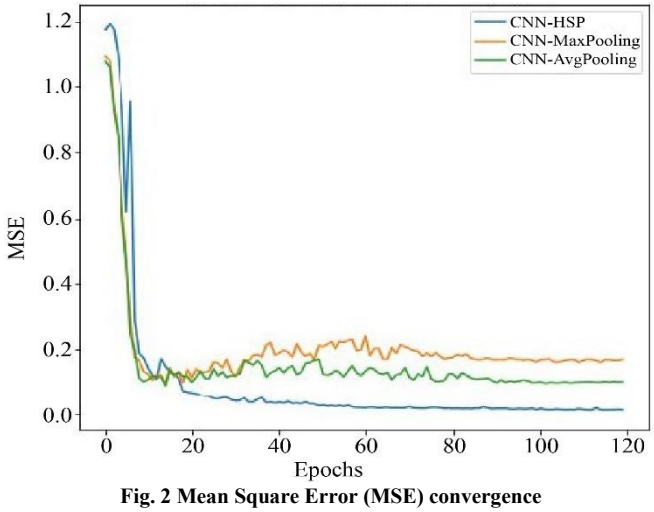

Fig. 2 Mean Square Error (MSE) convergence

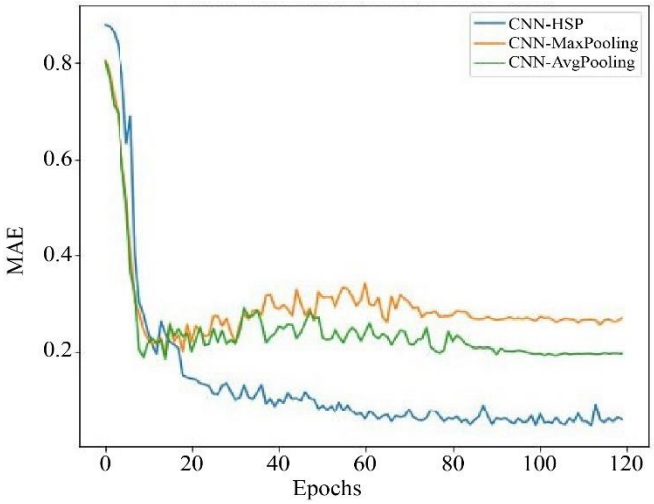

Fig. 3 Mean Absolute Error (MAE) convergence

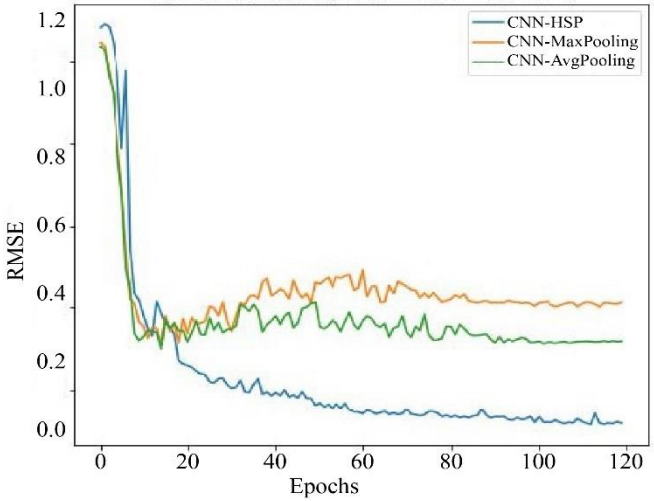

Fig. 4 Root Mean Square Error (RMSE) convergence

This consistent improvement in the CNN--HSP model is due to its enhanced pooling mechanism that preserves spatial and contextual patterns, facilitating more precise learning of complex toxicological features.

4.3. Comparative Prediction Performance on the Test Set

Table 1 presents the final performance metrics of the three models on the test dataset. The CNN-HSP model outperformed both traditional pooling strategies in all metrics. The CNN-HSP demonstrated 97.1% lower MSE than CNN-Max Pooling and 95.2% lower than CNN-Average Pooling. The model achieved an over 80% reduction in MAE relative to Max Pooling and demonstrated exceptional predictive accuracy with an R^2 of 0.9957. These results validate the hypothesis that the Horizontal Sequence Pooling method enhances the model's ability to extract fine-grained, position-sensitive features crucial to accurate ENP cytotoxicity prediction.

Table 1. Performance comparison of the CNN model with different pooling algorithms

MODEL	METRIC			
	MSE	MAE	RMSE	R^2
CNN-Max Pooling	0.1485	0.2540	0.3853	0.8540
CNN-Average Pooling	0.0896	0.1817	0.2993	0.9120
CNN-Horizontal Sequence Pooling	0.0043	0.0501	0.0658	0.9957

4.4. Actual vs. Predicted Value Analysis

Figures 5 to 7 compare actual and predicted cytotoxicity values for all three models across 20% of test samples. Figure 5 (CNN-HSP) shows an almost perfect alignment of predicted values (red) with actual values (blue). The model tracks dynamic changes in cell viability with minimal deviation, demonstrating strong sensitivity to local and global patterns in the data. Figure 6 (CNN-Max Pooling) exhibits clear misalignment and volatility in predictions.

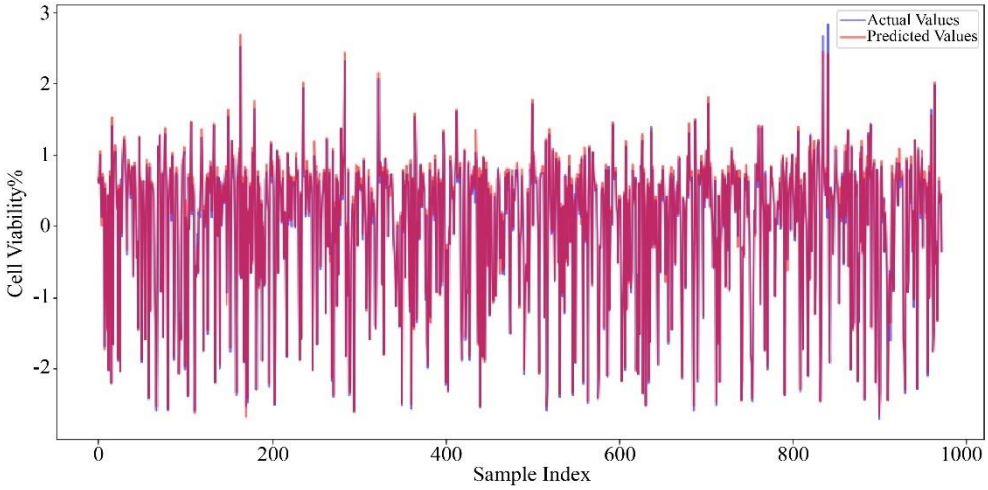

Fig. 5 Actual vs Predicted values of the CNN model with horizontal sequence pooling algorithm

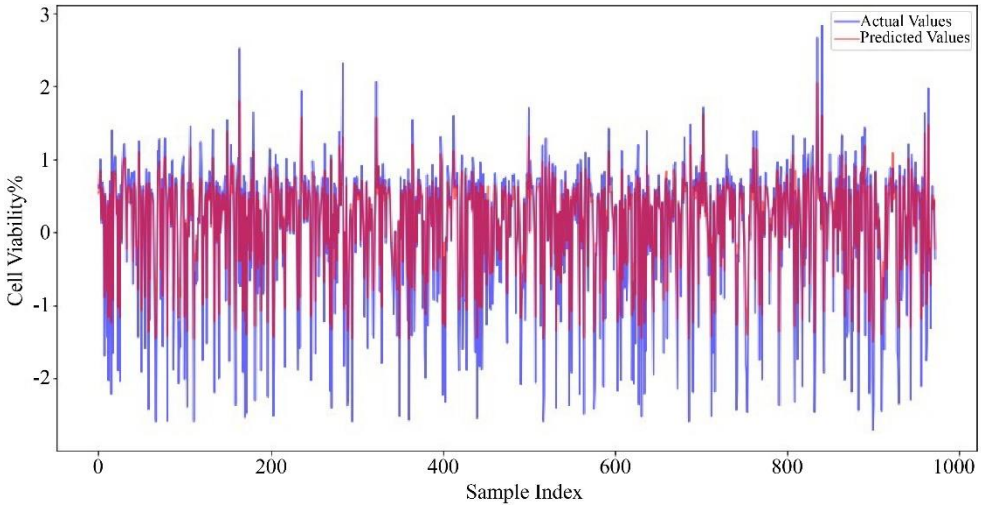

Fig. 6 Actual vs Predicted values of the CNN model with the max pooling algorithm

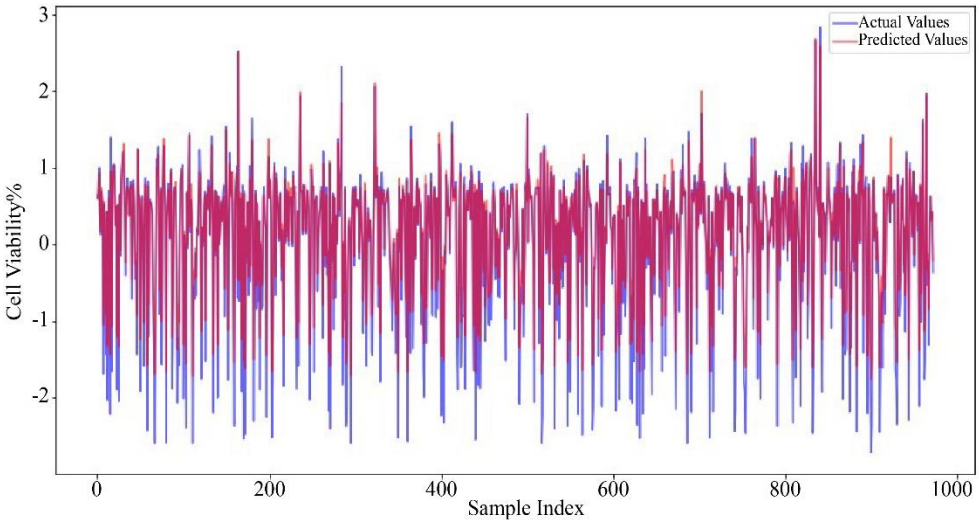

Fig. 7 Actual vs Predicted values of the CNN model with average pooling algorithm

The model often overshoots or undershoots actual values, reflecting its tendency to overemphasize dominant features while discarding essential details. While Figure 7 (CNN-Average Pooling) shows smoother results, it still underestimates sharp changes and flattens peaks and troughs due to its averaging nature.

This results in muted predictions that fail to capture high-intensity signals critical to toxicological inference. The superior predictive performance of CNN-HSP demonstrates its ability to retain contextual cues during pooling, enabling more nuanced and accurate predictions.

4.5. Residual Error Analysis

Residual plots (Figures 8 to 10) further validate model performance by analyzing the distribution of prediction errors. CNN-HSP residuals (Figure 8) show a tight, random scatter around the zero line, indicating minimal bias and a well-generalized model. No significant pattern or heteroscedasticity confirms consistent performance across the prediction range. CNN-Max Pooling residuals (Figure 9) show a curved pattern with pronounced error at both ends of the prediction scale. This reflects poor generalization and bias introduced by retaining only extreme feature activations. While CNN-Average Pooling residuals (Figure 10) show better than Max Pooling, the residuals still deviate from the baseline, especially at high predicted values, suggesting underestimation due to feature smoothing.

The CNN-HSP model's residual characteristics strongly support its robustness and high fidelity, making it capable of accurately capturing common and rare cytotoxicity patterns.

4.6. Contribution Beyond State-of-the-Art

Compared to prior work, such as [4], which employed regularized regression models for ENP cytotoxicity with moderate accuracy, our model represents a significant advancement. While conventional CNN approaches in related

studies have shown improvements, they rarely address the pooling layer as a bottleneck. The Horizontal Sequence Pooling method fills this gap by introducing a position-aware pooling strategy that retains biological relevance during down-sampling, a novel contribution to CNN-based toxicity prediction.

This study not only achieves state-of-the-art accuracy but also demonstrates the critical role of customized architectural components in advancing AI-driven nanotoxicology. The superior performance, validated through multiple quantitative and visual evaluations, establishes CNN-HSP as a reliable tool for rapid and scalable ENP risk assessment.

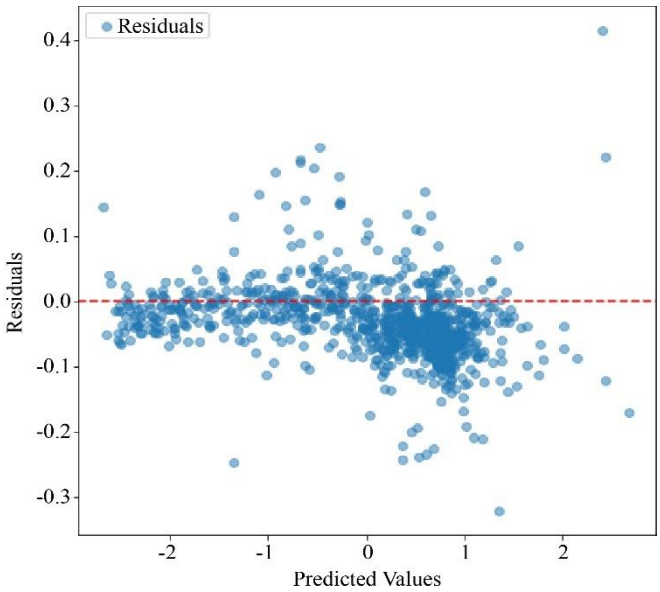

Fig. 8 Residual plot of the CNN model with horizontal sequence pooling algorithm

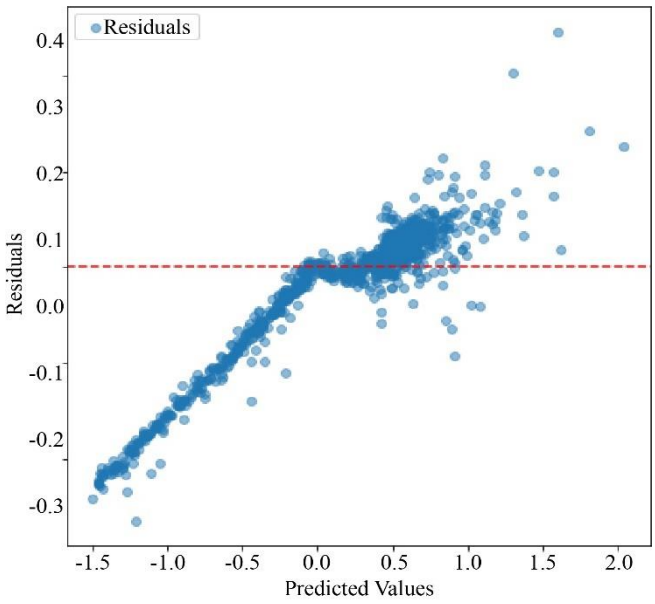

Fig. 9 Residual plot of the CNN model with max pooling algorithm

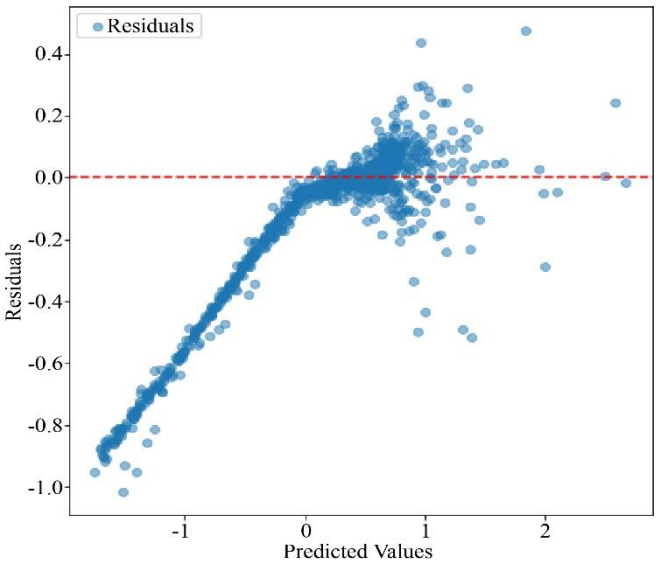

Fig. 10 Residual plot of the CNN model with average pooling algorithm

5. Conclusion

This research highlights the significant potential of the Horizontal Sequence Pooling strategy in improving Convolutional Neural Networks' performance for predicting engineered nanoparticles' cytotoxic effects. Unlike conventional pooling methods, HSP is designed to retain essential spatial and positional information, enabling the model to capture the intricate patterns underlying ENP-induced biological responses more accurately. Empirical results show that the CNN-HSP model consistently outperformed models using standard max pooling and average pooling across all evaluation metrics. It achieved remarkably low prediction errors (MSE: 0.0043, MAE: 0.0501, RMSE: 0.0658) and a near-perfect R2 score of 0.9957, demonstrating strong alignment between predicted and actual cytotoxicity outcomes. These outcomes confirm the importance of context-aware feature aggregation in enhancing model sensitivity and generalizability for toxicological prediction tasks. The findings offer a valuable step forward in the field of computational nanotoxicology by introducing a model that balances predictive power with interpretability. This approach supports the design of safer nanomaterials and contributes to advancing AI-assisted toxicology frameworks that can better inform public health and regulatory decisions. Future research may explore integrating HSP with hybrid architectures such as attention-based networks or transformer models to enhance pattern recognition and prediction accuracy, particularly for highly heterogeneous and multi-modal ENP datasets.

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