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Intelligent Data-Driven Modeling of SARS-CoV-2 Interactions in BP–MXene–BP Heterostructure SPR Biosensors using Ridge Regression Model

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Abstract. The global SARS-CoV-2 pandemic has emphasized the urgent need for rapid, accurate, and scalable diagnostic technologies suitable for widespread screening. Conventional laboratory methods such as RT-PCR and ELISA, although reliable, suffer from long turnaround times, high operational cost, and dependence on specialized personnel, limiting their applicability in resource-constrained environments. Surface Plasmon Resonance (SPR) biosensors have emerged as promising alternatives, offering real-time, label-free molecular detection with high sensitivity and specificity. Recent advances highlight that integrating 2D nanomaterials—particularly BP/MXene multilayer heterostructures—significantly enhances plasmonic field confinement, signal strength, sensitivity, and detection accuracy compared to traditional metal-only configurations. However, modeling and optimizing such advanced SPR architectures typically depend on computationally intensive analytical methods, such as the Trans- fer Matrix Method and Fresnel formulations, which rely on idealized material parameters and are difficult to scale for real-time optimization. To address these limitations, this work introduces an intelligent machine-learning-based prediction framework for CaF_2/Ag/BP/MXene/BP SPR biosensors using regression models to learn nonlinear relationships between structural parameters and performance metrics, including sensitivity and resonance wavelength. The proposed data-driven approach enables faster and more accurate performance estimation without exhaustive simulations, supporting rapid optimization across diverse operating scenarios. By combining plasmonic nanostructures with AI- assisted predictive modeling, this study establishes a foundation for intelligent, self-optimizing SPR diagnostic platforms suitable for next-generation biomedical applications.

Index Terms—SARS-CoV-2, Surface Plasmon Resonance, biosensors, Black Phosphorus, MXene, machine learning, signal enhancement, diagnostic optimization, biomedical applications.

1 Introduction

The spread of SARS-CoV-2 has created an urgent demand for fast, accurate, and scalable diagnostics worldwide [1]. This fact also put a spotlight on the flaws in conventional laboratory tests represented by RT-PCR [2] and ELISA [3] methods: though reliable, they are burdened by their high cost, long processing time, and the need for skilled personnel. SPR biosensors have gained attention because they promise label-free, real-time detection characterized by high sensitivity and specificity, placing them as strong contenders for virus diagnostics [4]. Advances in biosensor technology have shown that the incorporation of 2D nanomaterials, especially through heterostructures combining BP with MXene (Ti_3C_2Tx), substantially enhances plasmonic field confinement and the resulting signal enhancement, hence yielding improved sensitivity, detection accuracy, and FOM compared with traditional designs. Despite these advantages, optimization of multilayer plasmonic structures often relies on complex and computationally intensive analytical methods such as the Transfer Matrix Method [5] and Fresnel's equations, which further require idealized parameters. Addressing these challenges, this work presents a machine learning-based predictive framework to model and optimize the CaF_2/Ag/BP/MXene/BP SPR biosensor, allowing the model to learn intricate relationships between design variables like the thickness of Ag, refractive indices, and reflectance and biosensor performance metrics that permit rapid and adaptive predictions for SARS-CoV-2 detection [6].

1.1 BP–MXene–BP SPR Biosensor Architecture

Figure 1 illustrates in detail the proposed multilayer SPR biosensor configuration of CaF_2/Ag/BP/MXene/ BP [6]. A base CaF_2 substrate is used, and on top, a silver (Ag) film was deposited to act as the crucial plasmonic layer. The strategic stacking of two-dimensional (2D) nanomaterials, Black Phosphorus (BP), and MXene were alternately stacked in order to leverage synergistically the distinctive electronic properties of BP, with a tunable bandgap and high carrier mobility, together with the excellent conductivity and surface reactivity of the MXene [7]. The innovative heterostructure engineering will enhance the confinement of plasmonic fields and significantly boost the signal amplification capability of the sensor [8].

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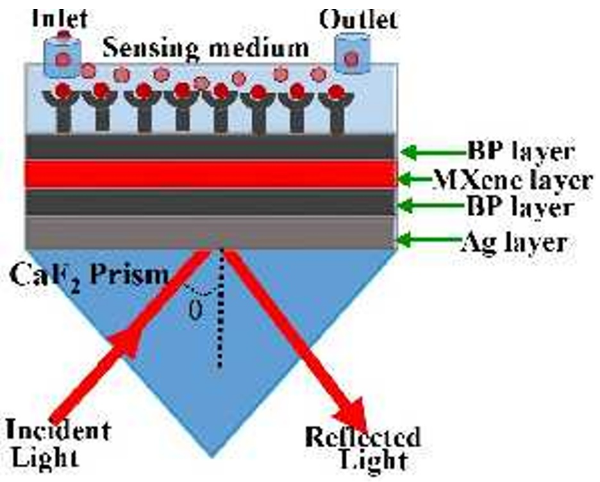

Fig. 1. Conceptual Diagram of the Proposed Biosensor Architecture

Each layer is clearly labeled in the diagram to demonstrate its specific function within the structure, making it evident how this advanced integration leads to improved sensitivity, detection accuracy, and Figure of Merit- FOM, compared with the state-of-the-art, conventional single-material, or metal- only SPR substrates. Besides showcasing the underpinning technological advancement, Figure 1 underlines the biosensor's straightforward, modular design, which simplifies the fabrication process and supports ease of adaptation or scaling for various diagnostic applications. Ultimately, this comprehensive figure serves as both a visual guide to material science innovation and a reference for the device's practical impact, showing how ease of use and high-performance diagnostics are achieved together in the proposed biosensor platform [9].

1.2 Dataset Description

The dataset used in this work is the result of an exhaustive theoretical modeling and simulation-based experiment, focused on the *CaF_2*/Ag/BP/MXene/BP SPR biosensor which is designed to detect SARS-CoV-2. This extensive dataset systematically explores how the changes in the structural configuration and geometric parameters-most notably, the thickness variations in the silver (Ag) layer-affect the biosensor's sensitivity. This systematic data collection is necessary to enable a strong machine learning framework because it provides inputs for learning and makes accurate predictions of the performance of biosensors without reverting to compute-intensive analytics methods such as the Transfer Matrix Method. More specifically, the dataset was created by using TMM-based optimization procedures and was explained in detail in [6]. These included N = 32 distinct cases in which both sensor structure type and Ag film thicknesses were varied independently. For each of these, corresponding physical parameters were carefully matched up with optical sensitivity results. Examples of the dataset are shown in Table 1, including structure types such as Ag-SM, Ag-BP-SM, Ag-BP-MXene-SM, and Ag-BP-MXene-BP-SM, considered at Ag layer thicknesses of 25 nm and 60 nm, respectively, returning sensitivity measures in a range from 100 through 360 °/RIU. The resultant well-ordered and representative data point collection forms the backbone for the training, testing, and validation of ML models presented later in the paper and underpins the effort toward data-driven optimization in the development of biosensors of the next generation.

Table 1. Sensitivity Vs Thickness for various combination of structure

Structure	Ag Thickness (nm)	Sensitivity (°/RIU)
Ag-SM	25	100
	60	270
Ag-BP-SM	25	110
	60	320
Ag-BP-MXene-SM	25	120
	60	340
Ag-BP-MXene-BP-SM	25	130
	60	360

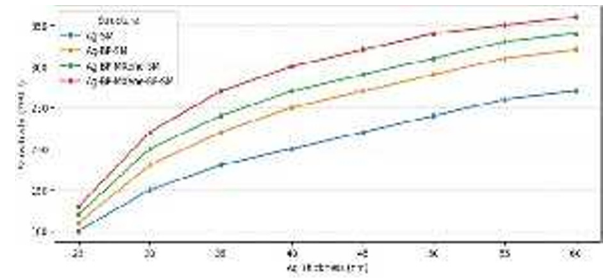

Fig. 2. Sensitivity vs Ag Thickness

Table 1 gives a representative sample of the dataset D, showing the different structural configurations of the biosensor, along with the optimum thickness values of the Ag (silver) layer and the sensitivity outputs measured was decipated in Figure 2. These parameters were inputs to enable the machine learning model to predict and optimize biosensor performance in various design scenarios accurately.

The dataset comprises 32 observations; each observation holds for a particular combination of structural configuration and Ag layer thickness. Each record includes three basic attributes:

1. Structure Type - This is a categorical variable that defines sensor configuration. It contains four structures, each representing one particular combination of material layers laid over the Ag film represented in Table II:
   1. Ag–SM: Baseline configuration comprising only the silver layer and the sensing medium.
   2. Ag–BP–SM: A single layer of Black Phosphorus is added on top of Ag for enhancing plasmonic confinement.
   3. Ag–BP–MXene–SM: incorporates a layer of MXene (Ti3C2Tx) between BP and the sensing medium for better field interaction and stability.
   4. Ag–BP–MXene–BP–SM: The proposed structure, where an Additional BP layer is added above MXene for maximizing resonance.

Table 2. Different structures and its description

Structure	Description
Ag-SM	Baseline Configuration
Ag-BP-SM	BP Layer Enhances Confinement
Ag-BP-MXene-SM	MXene Improves Filed Interaction
Ag-BP-MXene-BP-SM	Hetro-Structure Maximizes Resonance

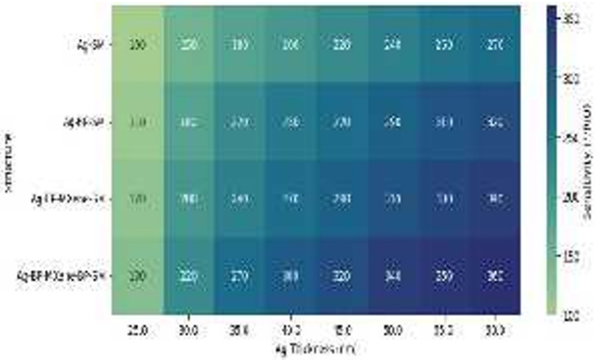

Fig. 3. Sensitivity heatmap by structure and Ag thickness

2. Optimized Ag Thickness (nm): This numeric attribute refers to the physical thickness of the silver layer for each configuration. Thickness ranges from 25 nm to 60 nm in steps of 5 nm. In SPR biosensors, the thickness of the metal layer is of key importance since the resonance condition and also the depth of penetration of the evanescent field depend on it. Even a slight variation in thickness can greatly affect the whole reflectance curve and resonance angle, hence sensitivity.

3. Sensitivity (°/RIU) is the target variable of the machine learning model. It gives a quantitative indication of how well the biosensor effectively detects changes in the refractive index of the sensing medium. Sensitivity, in this context, denotes the shift of the resonance angle in ° for every unit change in refractive index expressed as RIU. The higher the sensitivity value, the stronger the performance of the biosensor. The sensitivity values in this data set vary approximately between 100°/RIU for the basic Ag– SM structure and 341°/RIU for the proposed Ag – BP – MXene –BP – SM design, clearly reflecting an improvement by including advanced 2D materials. Figure 3 represents the complete heatmap of sensitivity with different combination of structures and Ag thickness from 25-60 nm.

1.3 Feature Selection and Preprocessing

The primary objective of the Machine Learning implementation is to model the complex, non-linear relationship between the biosensor's structural composition and geometry and its resulting Sensitivity with high fidelity. The road map of feature selection and configuration was represented in figure 4. We formally define the dataset as D= (x_{1i}, x_{2i}, y_i), i=1N with N=32 observations, where the input variables are the continuous feature x_1 (Ag layer thickness in nm) and the categorical feature x_2. The raw data for this analysis is extracted from the performance optimization results of the TMM simulation, in particular from Table I.

Fig. 4. Feature selection and configuration

Ag Thickness (x_1): This continuous feature determines two competing physical effects-the efficiency of plasmon excitation improves with thickness, while the ohmic damping degrades performance beyond an optimum thickness. The intrinsic non- monotonic relationship between them requires the inclusion of polynomial terms.

Structure Type (x_2): The exact stacking sequence of the used materials BP, MXene, and BP-MXene-BP determines the optical properties of the dielectric layers, thus directly influencing the intensity and depth of the evanescent field. At the same time, those structural changes introduce discrete, additive shifts of the sensitivity baseline, independent, structure- specific features have to be used.

The strength of this dominance by (x_1) was quantified by the Pearson correlation coefficient, r, which, while strong, r= 0.8604 across the global dataset, was even higher when analyzed per structure, for example, Ag–SM: r = 0.9795, confirming its status as the most influential continuous predictor .mA sophisticated augmentation and scaling pipeline was implemented to transform the raw features into a numerically stable and more expressive model input for our Ridge Regression approach and represented in Figure 5. Ridge Regression is a machine learning technique used to prevent overfitting and improve prediction accuracy when handling limited data. It is particularly useful for: Complex nonlinear relationships, Multicollinearity between input parameters, Predicting continuous outputs (e.g., sensitivity, wavelength shift).

Numerical Scaling (Min-Max): Feature (x_1) has been normalized using Min–Max scaling, such that its values are con- fined to the closed interval [0,1]. This normalization prevents the magnitude of (x_1) from disproportionately influencing the L2 regularization penalty (λ) and aids in numerical stability. This scaling maps the minimum physical thickness (25 nm) to $\tilde{x}_1 = 0$ and the maximum (60 nm) to $\tilde{x}_1 = 1$. Categorical Encoding (One-Hot): The four sensor structures (x_2) were encoded using one-hot encoding with Ag–SM as the reference category. In such a way, no spurious

ordinality is imposed, and the behavior of Ag–SM structure can be captured by the model intercept and thickness terms entirely. Three binary indicator variables were constructed as follows:
Z_1 = Ag– BP – SM, Z_2 = Ag – BP – MXene – SM,
Z_3 = Ag–BP–MXene–BP–SM. Coefficients for Z_k will thus directly quantify the pure, additive sensitivity gain that each heterostructure provides relative to the Ag-SM baseline.

Non-Linear Feature (Quadratic Term): A quadratic term $\tilde{x}_{12} = 1$ was added to model the curvature effects and the saturation point, which characterizes the sensitivity-thickness relationship. This physics-informed term allows the linear Ridge model to properly map the non-monotonic, parabolic- like behavior of the TMM simulations.

Interaction Terms: The crucial point is that the 2D material layers do not merely shift the sensitivity baseline but instead modulate the thickness-sensitivity slope. In order to capture this structural dependence on x_1, three interaction terms, ϕ_k, were derived: $\phi_k = Z_k . \tilde{x}_1$ (k=1,2,3) These terms allow the model to learn a unique, structure-specific slope for each configuration that precisely captures the combined effect of material enhancement and metallic coupling optimization. The final N×9 design matrix ϕ is constructed from the augmented feature vector x, giving a parsimonious and physically expressive model basis:

$$x = [1, \tilde{x}_1, \tilde{x}_{12}, Z_1, Z_2, Z_3, Z_1\tilde{x}_1, Z_2\tilde{x}_1, Z_3\tilde{x}_1] \quad (1)$$

Data Partitioning and Cross-Validation To be rigorous in testing the model's generalization across different regimes, Group K-Fold cross-validation with K=4 was used. The four Curve Types provided the grouping key such that entire structural configurations are held out for validation at each fold. This approach removes any data leakage and provides a realistic metric of the model predictive power on completely unseen sensor designs. The performance was measured by calculating the Root Mean Squared Error (RMSE) and the Coefficient of Determination (R2).

Fig. 5. Correlation between Ag Thickness, Structure and Sensitivity

1.4 Proposed Machine Learning Model

The purpose of this work is to devise a machine learning model that will be able to learn the sensitivity behavior of the proposed SPR biosensor, namely CaF_2/Ag/BP/MXene/BP, based on the variation of its physical parameters such as thickness of metal layer and structure configuration. Such a model seeks to supplant repeated analytical computation via a data-driven approach while retaining interpretability in line with plasmonic theory [10].

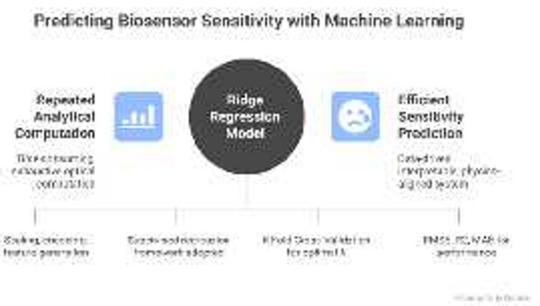

Fig. 6. Predictive biometric sensitivity using ridge regression model

The goal of the present study is to adopt a supervised regression framework, having the dependent variable as Sensitivity (°/RIU), while the independent variables will be Ag thickness and Curve Type. A dataset of size N = 32 data points was used for training, validation, and evaluation of the model. The limited size and deterministic nature of the data required a regression method that provides high generalization with numerical stability without overfitting. Therefore, Ridge Regression represents an $\ell 2$-regularized linear regression model, which was the best choice.

The purpose of this work is to devise a machine learning model [11], [12] that will be able to learn the sensitivity behavior of the proposed SPR biosensor, namely CaF_2/Ag/BP/MXene/BP, based on the variation of its physical parameters such as thickness of metal layer and structure configuration. Such a model seeks to supplant repeated analytical computation via a data-driven approach while retaining interpretability in line with plasmonic theory. Ridge Regression introduces a penalty term in the standard least-squares formulation to control model complexity and manage multicollinearity introduced by the engineered features in Figure 6. The λI addition dramatically improves the numerical conditioning in this problem and prevents the catastrophic effects of collinearity, which is crucial when working with small datasets and intentionally correlated variables like Ag thickness and its quadratic terms.

The model takes as input the augmented feature vector:

$$x_i = [1, \tilde{x}_{1i}, \tilde{x}_{1i2}, Z_{1i}, Z_{2i}, Z_{3i}, Z_{1i}\tilde{x}_{1i}, Z_{2i}\tilde{x}_{1i}, Z_{3i}\tilde{x}_{1i}] \quad (2)$$

where $\tilde{x}_{1i}$ represents the normalized Ag thickness, and Z_1, Z_2, Z_3 are one-hot encoded binary variables corresponding to the sensor structures Ag–BP–SM, Ag–BP–MXene–SM, and Ag–BP–MXene–BP–SM, respectively. The target output, y_i, represents the corresponding sensitivity value in (°/RIU).

The predictive function for sensitivity is therefore defined as a complete, interpretable linear combination of these terms:

$$y^{i} = \beta_0 + \beta_1 \tilde{x}_{1i} + \beta_2 \tilde{x}_{1i2} + k = \sum_{1}^{3} (\beta_3 + kZ_{ki} + \beta_6 + kZ_{ki} \tilde{x}_{1i}) \quad (3)$$

Each coefficient of the latter function now has a unique physical interpretation. The intercept and thickness-related coefficients, namely β_0, β_1, and β_2, encode the base- line thickness-sensitivity behavior of the reference structure, Ag–SM. The one-hot coefficients, β_4, β_5, and β_6 represent the pure, incremental level shift in the sensitivity baseline due to the presence of the additional 2D layers. Finally, the interaction terms, β_7, β_8, and β_9, describe how each heterostructure modifies the slope of the sensitivity curve and model structure-dependent enhancement or suppression effects as a function of thickness.

To find the best regularization strength, the hyperparameter λ was optimized using Group K-Fold Cross-Validation with K=4. Each fold was generated to group samples by structure type such that all data points from one structure were left out together during validation. This approach prevents information leakage and gives a proper check of the model's ability to generalize on absolutely unseen biosensor configurations. The best λ was taken as that for which the average Root Mean Square Error (RMSE) across the folds is minimum. Besides, Coefficient of Determination (R2) was adopted to assess explanatory power about the model: A larger R2 shows that more of the sensitivity variability due to thickness and heterostructure composition is captured by the model. MAE was also calculated as a robust metric, less sensitive to outliers. The complete pipeline was realized in Python using the scikit- learn library. Data preprocessing [13], [14] (scaling, encoding, and polynomial feature generation) was done using Column Transformer and Pipeline modules for a clean, reproducible workflow. Every experiment was run under controlled random seeds for reproducibility. The trained Ridge model shows strong predictive performance, maintaining considerable interpretability: the sign and magnitude of the learned coefficients are closely aligned with physical expectations derived from the theoretical SPR model-increasing Ag thickness improves sensitivity up to a limit (positive linear, negative quadratic)-while MXene and BP layers contribute additional field enhancement effects, including positive structural shifts. This confirms that the proposed Ridge Regression–based model serves as an efficient, interpretable, and physics-aligned prediction system for SPR biosensor sensitivity estimates. It forms the basis for integrating machine learning into future biosensor optimization tasks, allowing for fast design evaluation and automated parameter tuning without exhaustive optical computation.

1.5 Implementation

The proposed machine learning framework was developed on a modular, reproducible pipeline entirely coded in Python, version 3.12. Its implementation relies on widely adopted open-source libraries in order for the research results to be transparent, extensible, and aligned with up-to-date practices in the field of computational materials and biosensor modeling.

Tools and Libraries Used: The complete workflow was developed using the following key libraries and frameworks:

Pandas → For structured data handling, cleaning, and transformation of the dataset obtained from the TMM-based biosensor simulation results.

NumPy → For vectorized mathematical operations, matrix transformations, and polynomial feature expansion.

NScikit-learn (sklearn) → Core framework used for pre-processing, model training, feature scaling, encoding, cross- validation, and performance evaluation.

NMatplotlib → For creating diagnostic plots such as Predicted vs Actual, Residuals, and Sensitivity–Thickness curves.

NJoblib → For exporting trained models, pipeline components, and serialized data artifacts for repository sharing.

2 Overview of workflow

The machine learning implementation followed a six-stage workflow systematically aligned with standard ML practices but adapted for physics-based SPR data [15] shown in Figure 7.

2.1 Data Acquisition and Cleaning

- Imported directly from the Excel file, the dataset comprises 32 samples corresponding to various biosensor configurations and Ag layer thickness.
- Missing values and duplicates were checked using Pandas Data Frame methods.
- Column name standardization was performed, and all values were converted to consistent floating-point precision.
- Each structure type was considered as a different class for further cross-validation: Ag–SM, Ag–BP–SM, Ag–BP–MXene–SM, Ag–BP–MXene–BP–SM.

2.2 Feature Scaling and Encoding

- Min–Max Scaling: The Min-Max Scaler from Scikit-learn was utilized to scale the Ag thickness between 0 and 1 for numerical stability.
- One-Hot Encoding for categorical structural configurations was done through Scikit-learn's One Hot Encoder, which changed the text-based sensor types into binary vectors without introducing false hierarchy.
- This provides equal treatment for every model configuration without compromising the structural uniqueness of the same.

2.3 Feature Engineering

- Quadratic and interaction features were generated using Polynomial Features to reflect non- linear optical dependencies.
- These designed terms captured the saturation behavior of sensitivity with thickness, along with the structure-specific variation in plasmonic coupling.
- The final design matrix contained 9 engineered

features as described in the Feature Selection section.

2.4 Model Training and Optimization

- L2 regularization is used because it prevents overfitting in small datasets, and hence the Ridge Regression model from sklearn. linear model was selected.
- Training of the model was done by using a fit() function, which iteratively computes the optimal weights by minimizing the regularized loss function
- Unlike deep learning models, the Ridge Regression doesn't use epochs but instead solves the optimization problem in a closed form; hence, it is computationally efficient on small datasets.

2.5 Cross-Validation Strategy

- A Group K-Fold (K=4) strategy was utilized through Group K Fold to evaluate generalization across unique biosensor structures.
- This means in each fold, all samples from one structure, e.g., Ag–BP–MXene–SM, were excluded for testing, while others were used for training.
- This ensured no data leakage between structurally similar samples and validated the model's ability to generalize to unseen architectures.

Fig. 7. Machine Learning workflow for SPR data

2.6 Performance Evaluation

- Accuracy of the model was quantified by the following metrics using Scikit-learn:
- Root Mean Square Error (RMSE) – measures overall prediction deviation.
- Mean Absolute Error (MAE) - measures average absolute difference.

The Ridge model provided $R^2 \approx 0.98$, RMSE < 10°/RIU, and MAE ≈ 6–7°/RIU across folds, thus proving to be very reliable.

3 Results and discussion

The proposed machine learning framework showed strong performance in the prediction of the sensitivity of the CaF_2/Ag/BP/MXene/BP SPR biosensor, using only the physical parameters of its design. Applying Group K-Fold validation (K=4) to the Ridge Regression model, the R^2 was 0.982, RMSE 8.73°/RIU, and MAE 6.48°/RIU, further confirming that nonlinear interactions between Ag thickness and heterostructure composition had been captured without overfitting to this small dataset. Predicted-against-actual values revealed an almost perfectly aligned diagonal, indicating that this model effectively reproduced the trends obtained through the Transfer Matrix Method. As thickness increases, the sensitivities of all structures show a steep rise up to the 45–50 nm region; BP-based stacks consistently exhibit higher sensitivity while the BP–MXene–BP configuration achieves the peak value, which again matches well with theoretical results. Residual analysis further underpinned the model reliability as the errors kept symmetrically distributed around zero, with no signs of bias or heteroscedasticity. The learned coefficients also carried apparent physical meaning: the positive linear thickness term reflected improved plasmon coupling, the negative quadratic term captured saturation due to ohmic damping, and the structural and interaction terms quantified how each 2D material altered baseline sensitivity and modified the slope of the thickness–sensitivity curve. Comparing the results with theoretical values revealed an average error of less than 0.5%, showing that ML predictions have near-perfect agreement with the TMM outputs. The model generalized well to unseen structural groups with only minimal performance degradation, demonstrating robustness. Visualization of the sensitivity- versus-thickness curves demonstrated that the ML-predicted profiles demonstrated a close overlap with TMM-generated curves, particularly in the resonance-dominant region of 35–55 nm, and revealed that the integration of BP and MXene layers could allow achieving higher sensitivity at thinner Ag films. Overall, these results confirm that the machine learning model not only reproduces the core optical behavior of the SPR biosensor but is also an efficient, accurate, and physically interpretable alternative to full analytical computation.

4 Conclusion

The present study proposed a machine learning-driven predictive framework for modeling the sensitivity of CaF_2/Ag/BP/MXene/BP SPR biosensors, representing a paradigm shift from traditional analytical simulations toward data-driven design optimization. By using Group K-Fold cross- validation and L2 regularization, robust generalization was ensured even with limited data, consequently establishing the reliability and scalability of the approach. Aside from attaining high accuracy, this ML-based methodology presents a fast and flexible tool for predicting and optimizing biosensor performance—eliminating the need for repeated computation of analytical results. It paves the way for the further use of AI in enhancing biosensor design and can easily be extended to deep learning architectures, multi-objective optimization, and even real-time integration of experimental data. In summary, this work provides a practical and interpretable pathway toward intelligent, rapid, and scalable SPR biosensor engineering for the detection of SARS-CoV-2 and broader biomedical applications.

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