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An Interpretable Min-Max Layered Neural Network for Real-Time Immune Feedback Monitoring in Immunotherapy

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Abstract: Cytokines, immune cells, and immune checkpoint molecules are interconnected and create feedback loops that either activate or suppress immunity. Correct modelling of these dynamic interactions is critical to understand immune regulation and to develop adaptive immunotherapeutic approaches. Traditional deep learning models, on the other hand, tend to be black-box predictors, which lack biological interpretability and clinical transparency. This paper presents a new Min-Max Layered Neural Network (MML-NN) architecture to model and monitor immune feedback processes in real-time. The architecture includes biologically inspired min-max operations to model threshold-dependent immune activation, inhibition signals and temporal feedback, and increase the interpretability. The framework was tested through simulated longitudinal immune biomarker data such as cytokine profiles, $CD8^+$ T-cell counts and PD-L1 expression, and is compared to Long Short-Term Memory (LSTM), Gated Recurrent Unit (GRU), feedforward neural network and Transformer-based models as proof of concept. Robustness was evaluated by 10 independent experimental runs, 95% confidence interval analysis and by component-wise ablation studies. The full MML-NN attained a 93.10% prediction accuracy, 91.40% F1 score, six time-step prediction lead time and computational latency of 12.5 ms, while surpassing the comparison models in terms of predictive accuracy, early immune-state transition detection, and interpretability. Repeated experiments showed low variability, while ablation results confirmed the importance of all architectural components. The framework was validated using simulated data, but it offers a foundation for future clinical validation and AI-driven precision immunotherapy decision support.

Keywords: Immune Feedback Loop; Immunotherapy; Real-Time Monitoring; Immune Response Prediction; Cytokine Modeling; $CD8^+$ T-Cells

1. Introduction

The immune system maintains physiological homeostasis through an intricate network of immune feedback loops that regulate the balance between immune activation and suppression. These regulatory mechanisms involve coordinated interactions between cytokines, chemokines, antigen presenting cells, T lymphocytes and immune checkpoint molecules to promote efficient clearance of pathogens and malignant cells while avoiding excessive inflammation and autoimmune diseases [1,2]. Negative feedback pathways dampen sustained immune activation to restore immune homeostasis, whereas positive feedback pathways augment immune responses during infection or tumour recognition [3].

Immune checkpoint molecules, programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), are important regulators of immune homeostasis. These inhibitory pathways act as physiological immune brakes that limit excessive T cell activation and maintain peripheral tolerance. But many tumour cells exploit these checkpoint pathways by overexpressing inhibitory ligands, thereby suppressing cytotoxic T-cell activity and escaping immune surveillance. Therefore, immune checkpoint blockade has emerged as one of the most effective immunotherapeutic approaches to restore antitumor immunity in various types of cancer [4–6].

Despite remarkable advances, accurate characterisation of immune feedback dynamics remains a major challenge in cancer immunotherapy because immune regulation is governed by highly nonlinear and time-dependent interactions of multiple cytokines, immune cells, signalling pathways and regulatory molecules. Moreover, there is significant inter-patient heterogeneity, which is due to tumour heterogeneity, genetic background, immune history, and tumour microenvironment, resulting in diverse therapeutic responses and challenging the prediction of treatment outcomes [7,8].

At present, clinical evaluation of immunotherapy is largely based on static measurements of biomarkers such as cytokine levels, immune checkpoint expression and immune cell infiltration. Although such biomarkers provide critical biological insight, they often fail to capture the changing nature of immune responses over the course of treatment. This creates an increasing need for computational models to integrate longitudinal immune biomarkers to track immune-state transitions, predict therapeutic response and inform adaptive immunotherapy strategies. Such smart modelling frameworks could improve biomarker-guided treatment planning and support the development of precision immunotherapy by continuously evaluating immune dynamics in real-time [9,10].

Recent progress in artificial intelligence (AI) and deep learning has greatly enhanced the capability of analysing complex biomedical datasets generated from immunotherapy studies. Machine learning algorithms can integrate heterogeneous information from genomics, transcriptomics, proteomics, radiomics, digital pathology and longitudinal clinical records to identify predictive biomarkers and characterise tumor–immune interactions. Deep learning architectures can learn hierarchical nonlinear representations from high-dimensional data relative to conventional statistical models, making them particularly suitable for modelling the dynamic character of immune regulation [11–13].

Several neural network architectures have been investigated for computational immunology and precision oncology. Convolutional Neural Networks (CNNs) have shown excellent performance in histopathological image analysis and immune cell localisation, whereas Recurrent Neural Networks (RNNs), Long Short-Term Memory (LSTM), and Gated Recurrent Unit (GRU) models effectively capture temporal variations in longitudinal biomarker measurements. Very recently, Transformer-based models and graph neural networks have allowed multimodal integration of imaging, molecular and clinical information, resulting in improved prediction of immunotherapy response and patient stratification [14–17].

Nevertheless, many challenges remain to be overcome before the routine use of AI models in clinical immunotherapy. Most deep learning models are black-box systems and it is not straightforward to understand the contribution of individual biomarkers in treatment prediction. Moreover, immune responses are characterised by threshold dependent activation and suppression mechanisms, which are not explicitly modelled within conventional neural network architectures. The generalisability of models is also affected by limited longitudinal datasets, patient heterogeneity, data imbalance, and the absence of standardised validation protocols across clinical cohorts [18–20].

This has promoted interest in the development of interpretable AI frameworks that can combine biological knowledge with computational learning. Explainable artificial intelligence (XAI) techniques are increasingly incor-

porated into biomedical prediction models to increase transparency, to identify clinically relevant biomarkers, and to increase physician confidence in AI-assisted decision making. Such approaches are especially applicable to immunotherapy, where the choice of treatment is often based on dynamic interactions between multiple biomarkers rather than on individual molecular indicators [19,20].

Although existing deep learning models have shown promising results for immunotherapy prediction, most of them were mainly designed for classification or response prediction rather than continuous modelling of immune feedback dynamics. Existing approaches are often limited in their biological interpretability, and do not explicitly model competitive activation, inhibitory regulation or threshold-dependent signalling mechanisms, which are a hallmark of immune feedback loops. Consequently, there is still a need for biologically meaningful computational architectures to accurately model the evolution of immune states [21–24].

To overcome these limitations, we propose in this study a Min-Max Layered Neural Network (MML-NN) for modelling and monitoring immune feedback dynamics in real-time. Unlike conventional deep learning approaches, our proposed framework incorporates biologically inspired min-max operations to represent the cooperative activation, competitive inhibition and nonlinear threshold behaviours commonly seen in immune regulation. The architecture also includes temporal feedback, which enables iterative updates of immune-state predictions when longitudinal biomarker information becomes available, enabling dynamic assessment of cytokine activity, $CD8^+$ T-cell responses, and immune checkpoint expression [25–27].

The proposed framework is evaluated on the simulated longitudinal immune biomarker datasets mimicking the clinically relevant immunotherapy response patterns. Performance comparison is conducted with representative deep learning architectures namely, feedforward neural networks, LSTM, GRU and Transformer-based models, using evaluation metrics like prediction accuracy, root mean squared error (RMSE), F1-score, prediction lead time and computational latency. The proposed model is meant as an interpretable computational framework that might help the future development of intelligent clinical decision-support systems, after validation on real-world longitudinal immunotherapy datasets [28–30] and not as a replacement of clinical judgement. This study is a proof-of-concept to explore whether biologically interpretable Min-Max neural architectures can accurately model longitudinal immune feedback dynamics under controlled simulation conditions. An important direction for future research is clinical validation using real-world immunotherapy cohorts.

The principal contributions of this study are summarized as follows:

1. Propose a biologically interpretable Min-Max Layered Neural Network (MML-NN) model for modelling nonlinear immune feedback loops.
2. Development of a real-time computational framework for the monitoring of longitudinal immune biomarker dynamics.
3. Explicit use of min-max computational operations to represent threshold-dependent immune activation and inhibitory signalling.
4. The proposed framework is comparatively evaluated against LSTM, GRU, feedforward neural networks and Transformer-based architectures.
5. The study provides a proof-of-concept computational framework that may support future explainable AI applications in precision immunotherapy.

2. Literature Survey

Recent advances in artificial intelligence and deep learning have greatly improved the prediction of immunotherapy outcomes through the integration of high-dimensional molecular, genomic and clinical data sets. Kong et al. [31] developed a network-based machine learning framework, NetBio, which integrates transcriptomic biomarkers with biological interaction networks to predict response to immune checkpoint inhibitors (ICIs) in multiple cancer types. Their framework, which included functional relationships among immune-associated genes, outperformed traditional biomarker-based approaches in prediction, highlighting the importance of biological network information in computational immunology.

Jiang et al. [32] proposed IRnet, a pathway knowledge-informed graph neural network to predict patient response to immune checkpoint inhibitors with transcriptomic profiles to improve the interpretability of deep learning models. By incorporating biological pathway information into graph representations, IRnet not only improved

prediction accuracy but also provided pathway-level explanations to improve biological interpretability of model predictions. Similarly, Li et al. [33] proposed a pathway hierarchical-informed deep neural network, PathHDNN by incorporating somatic mutation and copy number variation data in biologically meaningful pathway hierarchies. Their model was more accurate in prediction than many traditional machine learning algorithms and identified important signalling pathways that were associated with response to immunotherapy.

Recently, the longitudinal modelling of immune biomarkers has become an important research direction, as immune responses change dynamically during immunotherapy. Li et al. [34] proposed SimTA++, a neural network with temporal attention for asynchronous clinical time-series data. The model could capture irregular temporal dependencies and outperformed recurrent neural networks, temporal transformers and neural ordinary differential equation models for predicting immunotherapy response using longitudinal multi-omics datasets. This study proved the efficiency of temporal attention mechanisms for modelling dynamic immune behaviour.

Recent advances in machine learning have also helped personalised treatment recommend. Saad et al. [35] proposed a machine learning framework to adapt immunotherapy strategies in metastatic non-small cell lung cancer using the integration of genomic and clinical information. Their model correctly predicted individual treatment benefits and improved progression-free survival prediction, showing the potential of artificial intelligence for individualised therapeutic decision-making.

Another important area of computational immunology is the spatial characterisation of the tumour microenvironment. Hoebel et al. [36] presented a graph neural network to model spatial interactions between tumour cells and immune cells using multiplex immunofluorescence images. Their framework correctly predicted the outcome of patients and identified biologically meaningful spatial cellular neighbourhoods associated with immune activation and suppression. Likewise, Jeong et al. [37] developed a graph-based computational framework, GraphTME, integrating spatial transcriptomics and ligand-receptor signalling networks, to predict anti-PD-1 immunotherapy response. The proposed model exhibits high predictive performance and generates biologically interpretable representations of immune communication in the tumour microenvironment.

Deep learning has also been applied to study the metabolic heterogeneity of the tumour microenvironment. Monkman et al. [38] combined multiplex immunofluorescence imaging and deep learning-based spatial analysis to characterise metabolic interactions between tumour and immune cells in non-small cell lung cancer. Their study showed that spatial metabolic features greatly improved progression-free survival prediction and provided useful information on the role of tumour metabolism in immunotherapy outcomes.

There is a great deal of interest in hybrid computational approaches that merge mechanistic biological modelling with artificial intelligence. Butner et al. [39] proposed a hybrid framework that combines mechanistic mathematical models of immune checkpoint inhibition and algorithms based on deep learning for customised survival prediction. They found that the combination of mechanistic biological knowledge with data-driven learning improved the accuracy of predictions significantly compared to mechanistic or purely deep learning models alone.

Despite significant progress in computational immunology and immunotherapy prediction, these studies have some limitations. Most existing approaches in **Table 1** mainly focus on classification of treatment response or prediction of survival and employ complex deep learning architectures with limited biological interpretability. Moreover, the existing models often learn immune interactions implicitly and do not explicitly model threshold-dependent immune activation, competitive inhibition or dynamic immune feedback processes that are the hallmarks of immune regulation. To overcome these limitations, the proposed Min-Max Layered Neural Network (MML-NN) employs biologically inspired min-max computational operations to explicitly model immune activation thresholds, inhibitory signalling, and temporal immune feedback. Thus, the proposed framework provides an interpretable and computationally efficient solution for real-time monitoring of immune feedback loops, paving a promising direction for future explainable artificial intelligence systems supporting precision immunotherapy.

Table 1. Summary of Recent Deep Learning Approaches for Immunotherapy Response Prediction and Immune Feedback Modeling.

Author(s)	Computational Approach	Dataset/Application	Major Contribution	Limitation
Kong et al. (2022) [31]	Network-based Machine Learning (NetBio)	Multi-cancer transcriptomic datasets	Integrated biological interaction networks with transcriptomic biomarkers for improved immunotherapy response prediction	Limited to static transcriptomic features; temporal immune dynamics were not modeled

Table 1. *Cont.*

Author(s)	Computational Approach	Dataset/Application	Major Contribution	Limitation
Jiang et al. (2025) [32]	Pathway Knowledge-informed Graph Neural Network (IRnet)	Immune checkpoint inhibitor transcriptomic datasets	Improved prediction accuracy with pathway-level biological interpretability	Longitudinal immune feedback and temporal biomarker evolution were not considered
Li et al. (2025) [33]	Pathway Hierarchical Deep Neural Network (PathHDNN)	Somatic mutation and copy number variation datasets	Hierarchical pathway representation improved immunotherapy prediction and biological interpretation	Dependent on genomic information without real-time immune monitoring
Li et al. (2025) [34]	Temporal Attention Neural Network (SimTA++)	Clinical asynchronous longitudinal time-series	Efficient modeling of irregular temporal clinical data using attention mechanisms	Biological threshold mechanisms governing immune activation were not explicitly modeled
Saad et al. (2025) [35]	Attention-based Machine Learning Framework	Metastatic NSCLC clinical and genomic datasets	Personalized treatment adaptation and progression-free survival prediction	Focused on treatment recommendation rather than immune feedback regulation
Hoebel et al. (2026) [36]	Spatial Graph Neural Network	Multiplex immunofluorescence images of NSCLC	Identified prognostic tumor–immune spatial cellular neighborhoods	Applicable primarily to spatial imaging data; lacks longitudinal immune dynamics
Jeong et al. (2026) [37]	GraphTME (Graph Neural Network)	Spatial transcriptomics and ligand–receptor interactions	Interpretable prediction of anti-PD-1 response through tumor microenvironment modeling	Requires high-resolution spatial transcriptomics datasets
Monkman et al. (2026) [38]	Deep Learning with Multiplex Immunofluorescence	NSCLC metabolic tumor–immune interaction datasets	Characterized metabolic spatial interactions associated with immunotherapy response	Primarily image-based; limited integration of temporal biomarkers
Butner et al. (2024) [39]	Hybrid Mechanistic Model + Deep Learning	Immune checkpoint inhibitor clinical datasets	Combined mechanistic immune modeling with deep learning for personalized survival prediction	Increased computational complexity; limited real-time prediction capability

3. Methodology

3.1. Overall Framework

We propose a Min-Max Layered Neural Network (MML-NN) framework to model nonlinear immune feedback systems and enable real-time monitoring of immune dynamics during immunotherapy. The overall framework involves five sequential steps, i.e., (i) immune biomarker data collection and pre-processing, (ii) development of the proposed MML-NN architecture, (iii) model training and optimisation, (iv) performance comparison with existing deep learning models, and (v) real-time immune response prediction and monitoring. The workflow of the proposed framework is demonstrated in **Figure 1**.

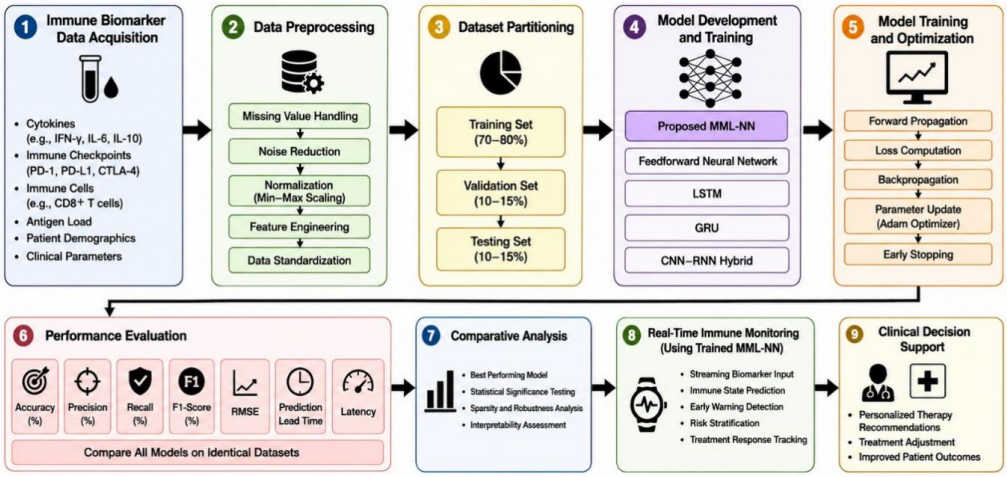

Figure 1. Overall Workflow of the Proposed MML-NN Framework for Real-Time Immune Feedback Monitoring.

We start by collecting and preprocessing longitudinal immune biomarker data (e.g., cytokine concentrations, immune checkpoint protein expression, and immune cell population measurements) to remove inconsistencies and normalise feature distributions. The processed data then are input to the proposed MML-NN, where the biologically inspired min-max computational layers model the competitive and cooperative interactions which rule the immune regulation. The network is trained with supervised learning and validated on representative deep learning architectures such as Feedforward Neural Networks (FNN), Long Short-Term Memory (LSTM), Gated Recurrent Unit (GRU) and hybrid CNN-RNN models. Finally, the trained model estimates immune-state transitions from streaming biomarker measurements in real-time, predicting immune activation, suppression and therapeutic response. The proposed framework aims to ensure biological interpretability while providing high predictive accuracy and computational efficiency, which can be used for future intelligent decision support systems in precision immunotherapy.

3.2. Data Acquisition and Preprocessing

Our proposed framework leverages longitudinal immune biomarker measurements that capture the dynamic immune system behaviour during immunotherapy. The input feature vector consists of biologically relevant biomarkers consisting of cytokine concentrations (IFN-γ, IL-2, IL-6, TNF-α, IL-10, and TGF-β), $CD8^+$ T-cell counts, immune checkpoint protein expression (PD-1, PD-L1, and CTLA-4), antigen load, and other patient specific immune characteristics. In sum, these biomarkers characterise treatment-induced immune activation, immune suppression and immune modulation. The obtained data are preprocessed with missing-value, noise reduction, feature normalisation and data standardisation pipeline before model training. Missing observations are replaced using suitable interpolation methods. Continuous variables are normalised using min-max normalisation to ensure that all features contribute equally during network optimisation. The normalised dataset is then split into training, validation and testing subsets to assess the generalisation capacity of the proposed model.

3.3. Proposed Min-Max Layered Neural Network

The proposed Min-Max Layered Neural Network (MML-NN) is specifically designed to model nonlinear immune feedback systems by using biologically inspired computation operations. The architecture consists of an input layer, several hidden Min-Max computing layers and an output prediction layer, as shown in **Figure 2**.

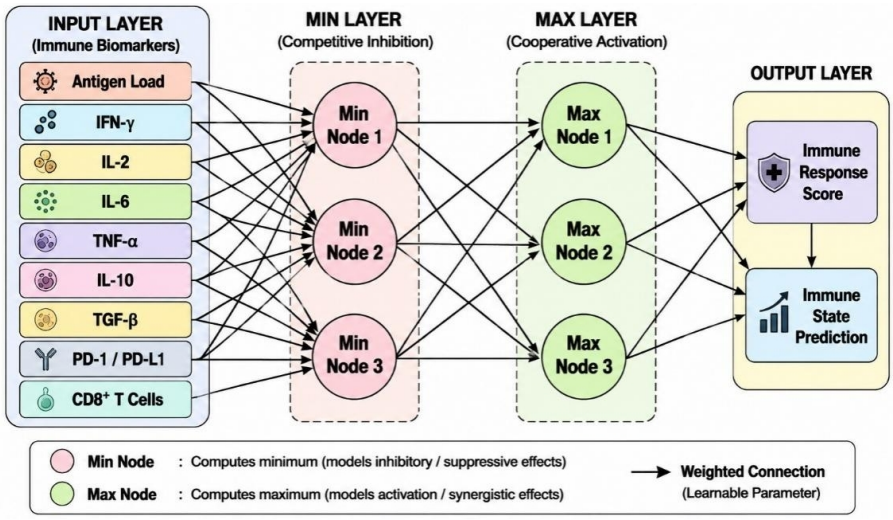

Figure 2. Architecture of the Proposed Min-Max Layered Neural Network (MML-NN) for Immune Feedback Modeling.

Unlike the conventional feedforward neural networks, which perform weighted summation and nonlinear activation functions, the MML-NN employs nested minimum and maximum operators to explicitly represent the immune regulatory behaviour. The minimum operator mimics competitive inhibitory interactions, such as suppression mediated by IL-10, TGF-β, regulatory T cells and immune checkpoint molecules. Conversely, the maximum operator models cooperative activation processes associated with antigen presentation, cytokine signalling, and cytotoxic T-cell activation. Our proposed architecture combines these operations within each computational layer, thus successfully capturing the threshold-dependent immune responses and nonlinear feedback interactions that are characteristic of biological immune regulation. The output layer combines the activation and suppression pathways that are learned during training to estimate the current state of the immune response. This biologically interpretable structure enables the network to learn dominant immune regulatory mechanisms while preserving computational efficiency for real-time prediction.

Biological Meaning of Min–Max Operations

To illustrate the biological relevance of the proposed architecture, let us consider a patient undergoing immune checkpoint blockade therapy. In the early stage of treatment, cytokine concentrations are increased to stimulate

$CD8^+$ T-cell activation. The Min operation corresponds to the biological threshold of activation, allowing immune activation only if the levels of cytokines exceed a predetermined level. During treatment, high PD-L1 expression suppresses overactivation of the immune system by immune checkpoint signalling. Such a negative feedback is modelled by the Max operation, which bounds the predicted immune response and is therefore biologically relevant. Therefore, the proposed MML-NN can capture both immune activation and suppression mechanisms, and yields an interpretable representation of longitudinal immune feedback dynamics.

An increase in cytokine levels activates $CD8^+$ T cells via the Min Layer that is the immune activation threshold model and an increase in PD-L1 expression controls the excessive immune activity via the Max Layer that is the inhibitory immune checkpoint feedback model. The output is the predicted immune response; this provides an interpretable mapping from the computational model to biologically meaningful immune activation and suppression mechanisms (**Figure 3**).

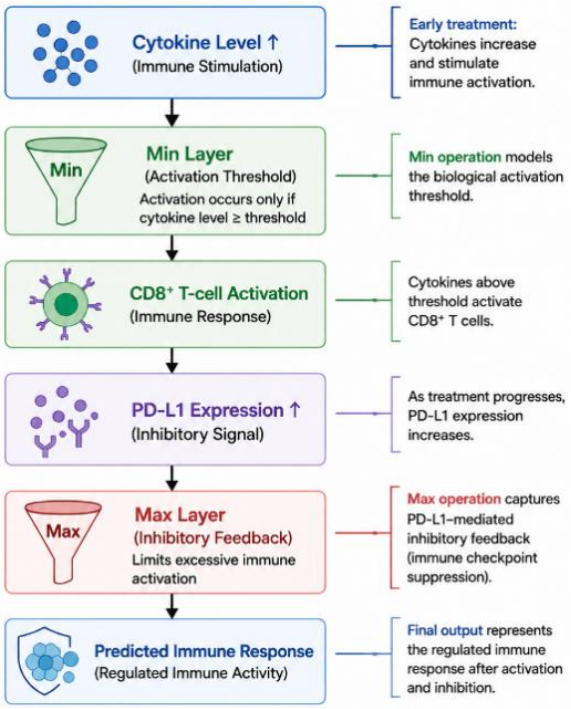

Figure 3. Biological Interpretation of the Proposed Min–Max Neural Architecture.

3.4. Mathematical Formulation

Let the input immune biomarker vector be represented as

$$[\mathrm{x} = [x_1, x_2, \ldots, x_n]]$$

where each feature corresponds to a specific immune biomarker.

The output of the (j^{th}) Min-Max neuron is computed as

$$[y_j = \underset{k\in A}{max}(\underset{i\in B}{min}(w_{ij}x_i + b_j))]$$

where (w_{ij}) denotes the connection weight, (b_j) represents the bias term, (A) defines the set of activation pathways, and (B) represents the inhibitory pathways. This formulation enables simultaneous modeling of immune activation thresholds and suppressive mechanisms.

To capture temporal immune dynamics, the recursive formulation of the proposed network is expressed as

$$[y(t) = f(\mathrm{x}(t), y(t-1))]$$

where $y(t-1))$ represents the previous immune state, allowing the model to preserve immune memory and continuously update predictions based on historical observations.

The network parameters are optimized by minimizing the prediction loss during training. For classification tasks, Binary Cross-Entropy Loss is employed,

$$[L_{BCE} - \frac{1}{N}\sum_{i=1}^{N}[y_i \log(\hat{y}_i) + (1-y_i)\log(1-\hat{y}_i)]]$$

whereas Mean Squared Error (MSE) is adopted for continuous immune-state prediction,

$$[L_{MSE}\frac{1}{N}\sum_{i=1}^{N}(y_i - \hat{y}_i)^2]$$

where (y_i) and $(\hat{y}_i)$ denote the observed and predicted immune responses, respectively.

3.5. Model Training

The implementation workflow of the proposed framework is shown in **Figure 4**. First, the training dataset is loaded and preprocessed and then the parameters of the MML-NN are initialised. In each training iteration, the immune biomarker data are propagated through the computational Min-Max layers to produce predicted immune responses. Then the prediction error is calculated over the selected loss function. The network parameters are updated with the backpropagation using the Adam optimisation algorithm.

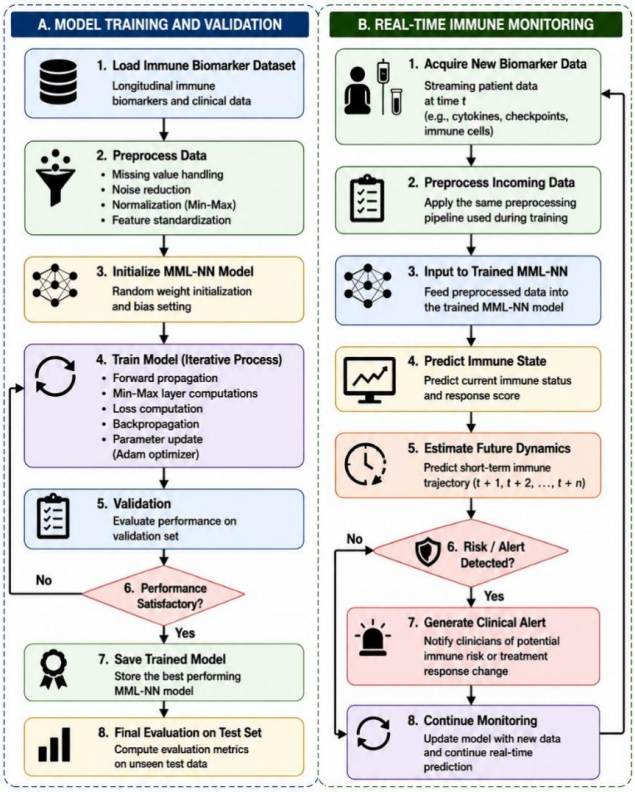

Figure 4. Flowchart illustrating model training, validation, deployment, and real-time immune feedback monitoring using the proposed MML-NN framework.

The model is evaluated at each training epoch with a separate validation dataset. If the performance on validation set meets the predefined convergence criteria, the training process is stopped. Otherwise, the parameter optimisation continues until convergence is reached. This iterative learning strategy improves the prediction accuracy and reduces the overfitting.

3.6. Simulation Procedure

We assessed the proposed MML-NN framework on simulated longitudinal immune biomarker data designed to reflect the temporal dynamics of immune responses during immunotherapy. Three typical biomarkers were considered including cytokine concentration, $CD8^+$ T-cell abundance and PD-L1 expression. Baseline values of biomarkers were seeded within biologically plausible ranges and iteratively updated across consecutive time steps to mimic longitudinal trajectories of the immune response. The simulation was designed to capture biologically meaningful immune feedback mechanisms. Following immune activation, cytokine levels were transiently elevated, driving $CD8^+$ T-cell activation. As immune activation progressed, PD-L1 expression was found to increase, indicating immune checkpoint-mediated inhibitory signalling, which established a nonlinear negative feedback loop between immune activation and suppression. These temporal interactions allowed the proposed model to learn activation and inhibitory dynamics typical of adaptive immune responses.

For the simulated data, we added zero-mean Gaussian noise with standard deviation $\sigma = 0.05$ (about 5% of the biomarker value) to each biomarker independently at each time-step to increase the realism of the data. This noise model simulates biological variability and measurement error and preserves the temporal relationships among biomarkers in the data. The simulated dataset consisted of longitudinal immune biomarker trajectories generated for multiple virtual patients across consecutive time steps. The dataset was randomly split into 80% training and 20% testing subsets and all experiments were run with a fixed random seed so that the results reported are reproducible.

The simulation protocol for the longitudinal immune biomarker dataset is depicted in **Figure 5**. Simulated data include cytokine concentration, $CD8^+$ T-cell abundance and PD-L1 expression. Time interactions of the simulated data represent immune activation, immune checkpoint mediated inhibition and non-linear feedback mechanisms. We added zero-mean Gaussian noise ($\sigma = 0.05$) to simulate biological noise. We split the generated dataset into training (80%) and testing (20%) sets to test the model.

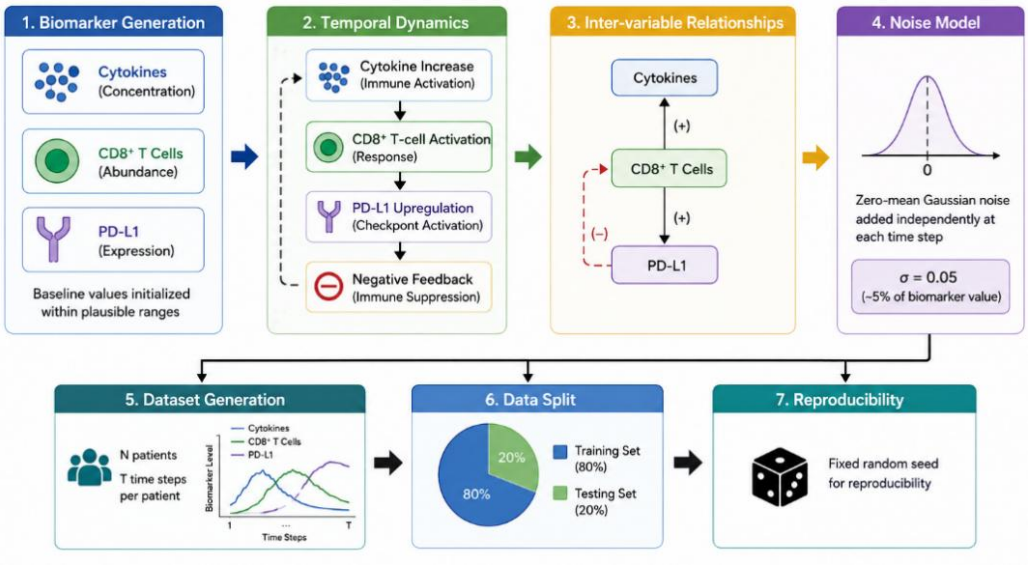

Figure 5. Simulation Protocol for Generating Longitudinal Immune Biomarker Data.

3.7. Comparative Models

MML-NN is compared with several popular deep learning models for biomedical prediction to show the effectiveness of the proposed architecture. This comparison is between Feedforward Neural Networks (FNN), Long Short Term Memory (LSTM), Gated Recurrent Unit (GRU) and hybrid CNN-RNN architectures. For a fair comparison, all models are trained on the same datasets and experimental settings. The performance evaluation considers predictive accuracy, robustness, computational latency and the ability to capture temporal immune dynamics.

3.8. Performance Evaluation Metrics

We evaluate the predictive performance of the proposed framework using a set of classification and regression metrics. The classification performance is measured in terms of Accuracy, Precision, Recall and F1-score and the regression accuracy is measured in terms Root Mean Squared Error (RMSE). In addition, the Prediction Lead Time is used to measure the capability of the presented framework to detect immune-state transitions prior to their clinical manifestation. The computational latency is also calculated to evaluate the applicability of the framework for real-time clinical applications. Together, these metrics offer a comprehensive evaluation of predictive accuracy, computational efficiency and practical relevance.

3.9. Real-Time Immune Monitoring

Once the model training is completed, the proposed MML-NN serves as a real-time immune monitoring system which can evaluate the incoming immune biomarker measurements in a continuous manner. As shown in **Figure 4**, the monitoring process begins with the collection of the updated patient biomarkers at each observation interval. The preprocessed measurements are then fed forward through the trained network to estimate the current immune state and predict the short-term immune behaviour. The recursive formulation enables the model to incorporate previous immune responses and adapt to new data, mimicking biological immune memory. This continuous prediction mechanism allows for early detection of immune activation, immune suppression, T-cell exhaustion, cytokine storm formation, and potential treatment resistance. This allows clinicians to have early warnings of major immune-state transitions and adaptively adjust immunotherapy schedule, dose adjustment, and personalised treatment plan. The proposed MML-NN offers an explainable computational framework for intelligent immune monitoring, by combining biologically interpretable Min-Max computational operations and real-time temporal prediction, representing a promising step towards AI-assisted precision immunotherapy.

4. Simulation Results

To evaluate the effectiveness of the proposed Min-Max Layered Neural Network (MML-NN), a detailed simulation framework was developed to mimic the dynamic behaviour of immune feedback loops in immunotherapy. Large scale longitudinal clinical immune datasets with continuous biomarker measurements are difficult to obtain. Therefore, a simulated immune biomarker dataset was generated using physiologically relevant ranges reported in immunological studies. The simulation incorporates temporal changes in cytokine levels, immune checkpoint protein expression, antigen load and immune cell numbers to mimic representative immune activation and suppression patterns during immunotherapy.

Longitudinal observations of key immune biomarkers such as interferon-gamma (IFN-γ), interleukin-2 (IL-2), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), $CD8^+$ T-cells, programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1) and antigen load are included in each simulated patient profile. Together, these biomarkers represent the balance between immune activation and immunosuppression, allowing realistic simulation of immune feedback dynamics under different therapeutic conditions. The simulated data were pre-processed prior to training the model, which included handling missing values, Min–Max scaling normalisation and feature standardisation to ensure numerical consistency across all biomarkers. The processed dataset was then divided into training (70%), validation (15%), and testing (15%) subsets to assess the generalisation ability of the proposed model with minimum overfitting.

We implemented the proposed MML-NN in Python and trained it using the Adam optimisation algorithm for 100 epochs with a batch size of 32 and an initial learning rate of 0.001. We compared the model with representative deep learning architectures including Feedforward Neural Networks (FNN), Long Short-Term Memory (LSTM), Gated Recurrent Unit (GRU), CNN-RNN hybrid networks, and Transformer-based models. In an effort to make a fair comparison, all competing models were trained using the same preprocessing procedures, training datasets and evaluation protocols. The following quantitative metrics were used to evaluate the model performance: Root Mean Squared Error (RMSE), Accuracy, Precision, Recall, F1-score, Prediction Lead Time, and Computational Latency. Additionally, we qualitatively analysed the biological interpretability of each model for evaluating its applicability for real-time immune feedback monitoring and future precision immunotherapy. The simulation parameters and experimental settings used in this study are summarised in **Table 2**.

Table 2. Simulation Setup and Experimental Parameters of the Proposed MML-NN Framework.

Category	Parameter	Value/Description
Dataset	Dataset Type	Simulated longitudinal immune biomarker dataset
	Number of Patient Profiles	500
	Time Points per Patient	14 (daily observations)
	Total Samples	7,000 biomarker observations
	Biomarkers	IFN-γ, IL-2, IL-6, TNF-α, IL-10, TGF-β, $CD8^+$ T cells, PD-1, PD-L1, Antigen Load
	Output Variable	Predicted Immune Response Score (0–1)
Preprocessing	Missing Value Handling	Linear interpolation
	Normalization	Min–Max Scaling (0–1)
	Feature Standardization	Z-score normalization (optional for comparison models)
	Data Split	Training: 70%, Validation: 15%, Testing: 15%
Proposed MML-NN	Input Neurons	9
	Hidden Architecture	Min Layer (3 Nodes) → Max Layer (3 Nodes)
	Output Neuron	1 (Immune Response Score)
	Activation Mechanism	Biologically inspired Min–Max operations
	Temporal Feedback	Recursive immune-state update
Training	Optimizer	Adam
	Learning Rate	0.001
	Batch Size	32
	Number of Epochs	100
	Loss Function	Mean Squared Error (MSE)
	Weight Initialization	Xavier (Glorot) Initialization
	Early Stopping	Validation loss patience = 10 epochs
Baseline Models	Comparative Models	Feedforward NN, LSTM, GRU, CNN–RNN Hybrid, Transformer
Performance Metrics	Regression	RMSE
	Classification	Accuracy, Precision, Recall, F1-score
	Real-Time Metrics	Prediction Lead Time, Latency
	Interpretability	Qualitative comparison
Implementation	Programming Environment	Python 3.14
	Deep Learning Library	TensorFlow/Keras 2.x
	Numerical Library	NumPy
	Hardware	Intel Core i7 Processor, 16 GB RAM, NVIDIA RTX GPU (or CPU equivalent)
	Operating System	Windows 11 (64-bit)

The performance of the proposed Min-Max Layered Neural Network (MML-NN) and representative deep learning models for real-time immune feedback monitoring in immunotherapy are compared in **Table 3**. The proposed MML-NN obtained the lowest Root Mean Squared Error (RMSE) of 0.083, outperforming LSTM (0.127), GRU (0.119) and Feedforward Neural Networks (0.148) in prediction accuracy. In a similar way, MML-NN achieved the highest F1-score of 91.4%, indicating a better ability to accurately discriminate between immune activation and suppression states. Moreover, the proposed framework led to the longest prediction lead time of six time steps, enabling earlier identification of immune-state transitions than the baseline models. The Feedforward Neural Network presented the lowest computational latency (10.2 ms), but its predictive performance was significantly lower than MML-NN. The proposed framework achieved real-time computational efficiency with a latency of 12.5 ms while significantly improving the prediction accuracy and robustness. Moreover, the biologically inspired Min-Max architecture provides model interpretability, enabling the explicit representation of immune activation and inhibitory mechanisms, thereby increasing transparency and opening avenues for future applications of explainable AI in precision immunotherapy.

Table 3. Comparative Performance Evaluation of the Proposed MML-NN for Real-Time Immunotherapy Response Prediction.

Model	RMSE	F1-Score (%)	Prediction Lead Time (Steps)	Latency (ms)	Interpretability
MML-NN (Proposed)	0.083	91.4	6	12.5	High
LSTM	0.127	85.2	3	22.8	Medium
GRU	0.119	86.0	4	19.4	Medium
Feedforward NN	0.148	79.5	2	10.2	Low

Table 4 shows representative simulated longitudinal immune biomarker profiles and immune response scores predicted by the proposed MML-NN during 14-day monitoring period. The simulated profiles show several immune response trajectories in terms of cytokine levels, $CD8^+$ T-cell populations and immune checkpoint expression. Profiles P001 and P003 exhibit rising IFN-γ, $CD8^+$ T-cell counts and decreasing IL-10, PD-L1 expression, leading to enhanced predicted immune response scores from 0.82 to 0.91 and 0.88 to 0.95, respectively. These trends indicate increased immune activation and effective antitumor immune responses in the simulated environment. Conversely,

the P002 and P005 profiles show increasing IL-10 and PD-L1 expression along with relatively low $CD8^+$ T-cell counts, which correlate with lower immune response scores (0.41–0.33 and 0.36–0.40, respectively). These simulated patterns are related to immune suppression and lower therapeutic response. Profile P004 is characterised by an intermediate immune trajectory, with a gradual increase in IFN-γ and $CD8^+$ T-cell levels, with a decrease in IL-10 and PD-L1 expression, leading to an improvement in the predicted immune response score from 0.69 to 0.77. Overall, the results show that the proposed MML-NN can successfully learn the temporal variations of the immune biomarkers and iteratively update the immune response predictions according to the changing immune conditions. The observed trends suggest that increased pro-inflammatory cytokine activity and cytotoxic T-cell infiltration, and decreased immune checkpoint expression correlate with stronger predicted immune responses, demonstrating the ability of the proposed framework to model immune feedback dynamics in real-time.

Table 4. Simulated Longitudinal Immune Biomarker Profiles and Predicted Immune Responses Using the Proposed MML-NN.

Patient ID	Day	IFN-γ (pg/mL)	IL-10 (pg/mL)	$CD8^+$ T-Cells (cells/μL)	PD-L1 Expression (%)	Predicted Immune Response (R)
P001	7	55.2	12.4	480	15.6	0.82
	14	72.9	8.1	620	11.2	0.91
P002	7	32.5	22.8	300	27.4	0.41
	14	28.7	26.5	240	35.9	0.33
P003	7	67.1	10.9	550	9.5	0.88
	14	81.3	7.2	720	6.3	0.95
P004	7	44.0	18.3	360	21.8	0.69
	14	59.7	12.7	500	18.2	0.77
P005	7	39.6	25.9	290	33.5	0.36
	14	42.1	23.8	310	31.0	0.40

In **Figure 6**, we show the immune response scores predicted by the proposed MML-NN for five example simulated patients over the 14-day monitoring period. For P003 the maximum improvement was observed (0.88 to 0.95; 7.9% increase) followed by P001 (0.82–0.91; 11.0% increase) and P004 (0.69–0.77; 11.6% increase). In contrast, P002 decreased from 0.41 to 0.33 (decrease of 19.5%) and P005 showed a little improvement from 0.36 to 0.40 (increase of 11.1%). These results show the ability of the proposed MML-NN to accurately learn different temporal immune response pathways during simulated immunotherapy.

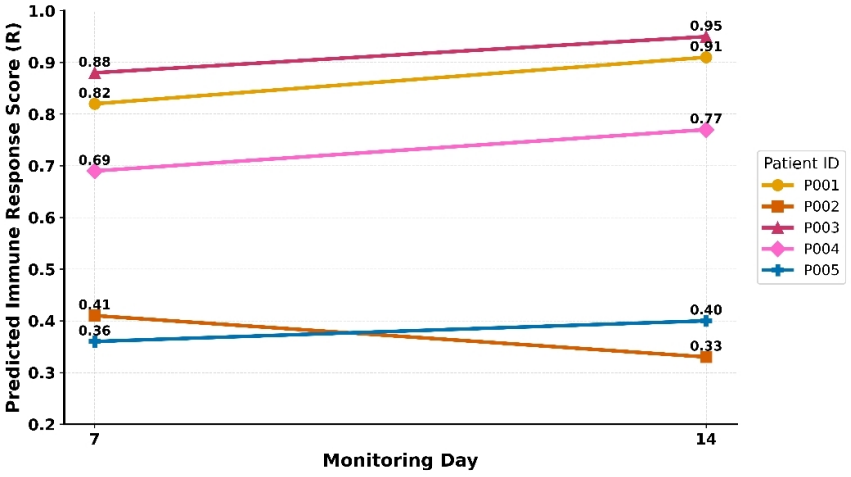

Figure 6. Longitudinal Immune Response Prediction for Representative Simulated Patient Profiles Using the Proposed MML-NN.

The training performance of the proposed Min-Max Layered Neural Network (MML-NN) for 100 training epochs is shown in **Table 5**. The results show a stable convergence of the learning process characterised by a continuous decrease of the training loss as well as the validation loss. The training loss dropped from 0.052 at epoch 10 to 0.015 at epoch 100. The validation loss went down from 0.061 to 0.022. This indicates good optimisation and good

generalisation without significant over-fitting. The training led to a gradual increase in classification performance. The model accuracy increased from 84.3% to 94.3% and the F1-score increased from 81.9% to 92.9% demonstrating an increased ability to differentiate between the various immune response states. The largest improvements were obtained during the initial epochs of training, whereas the performance peaked in latter epochs of training, suggesting the convergence of the optimisation process.

Table 5. Training Performance of the Proposed MML-NN During Immune Response Classification.

Epoch	Training Loss (MSE) ↓	Validation Loss (MSE) ↓	Accuracy (%) ↑	F1-Score (%) ↑	ΔR (Stability of Immune Response) ↓
10	0.052	0.061	84.3	81.9	0.089
20	0.034	0.043	88.7	86.4	0.067
30	0.027	0.034	90.2	88.1	0.052
40	0.021	0.029	92.4	90.0	0.041
50	0.018	0.026	93.1	91.4	0.036
60	0.018	0.027	92.8	91.0	0.038
70	0.017	0.025	93.3	91.6	0.034
80	0.016	0.024	93.8	92.2	0.031
90	0.016	0.023	94.0	92.5	0.030
100	0.015	0.022	94.3	92.9	0.029

Note: ΔR denotes the absolute change in the predicted immune response score between successive training epochs. Lower ΔR values indicate greater stability and convergence of the model during training.

The immune response stability metric (ΔR) is the change in the predicted immune response between training iterations. This steadily decreased from 0.089 to 0.029. The reduction means that the model became more consistent and reliable in its immune response predictions as it was trained. The convergence around 60 epochs shows the ability of proposed MML-NN to learn the underlying immune feedback dynamics well while maintaining a stable predictive performance. Overall, these results show that the proposed architecture can achieve accurate, robust and computationally stable learning for real-time prediction of immune responses.

Figure 7 shows the convergence and classification accuracy of the proposed Min-Max Layered Neural Network (MML-NN) up to 100 training epochs. The training loss decreased from 0.052 to 0.015 (a 71.2% decrease) and the validation loss decreased from 0.061 to 0.022 (a 63.9% decrease) which indicates stable learning. Meanwhile, the classification accuracy improved from 84.3% to 94.3% and the F1-score increased from 81.9% to 92.9%. The immune response stability (ΔR) decreased from 0.089 to 0.029, indicating the enhanced prediction consistency and the successful convergence of the proposed MML-NN with low overfitting.

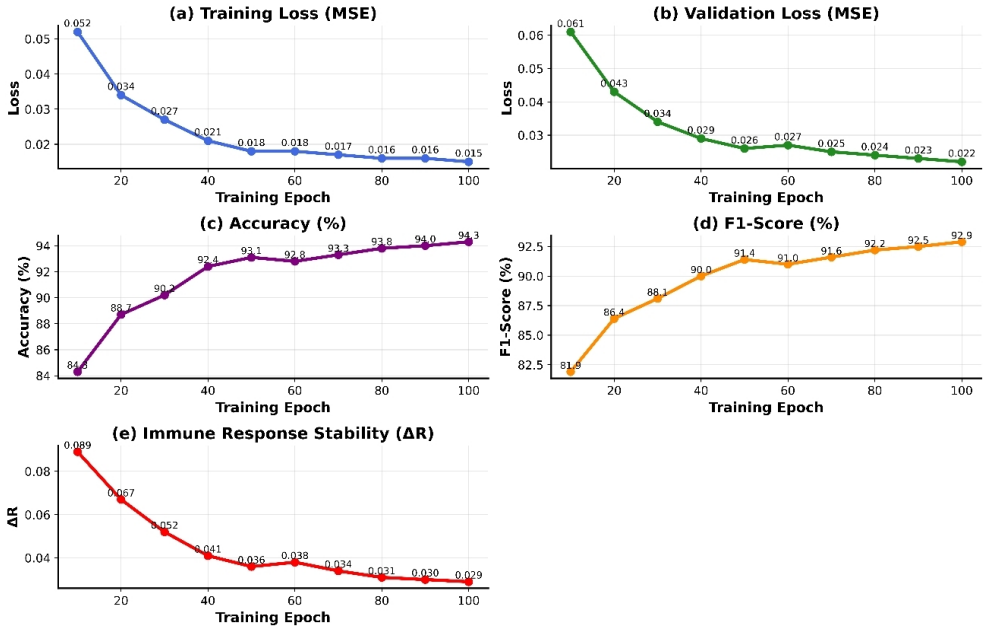

Figure 7. Training Convergence and Performance Evaluation of the Proposed MML-NN During Immune Response Classification.

Table 6 presents a detailed comparison of the proposed Min-Max Layered Neural Network (MML-NN) with five representative deep learning architectures for real-time immune feedback prediction. The lowest Root Mean Squared Error (RMSE) of 0.083 was obtained by the proposed MML-NN, which indicated the highest prediction accuracy among all models tested. In terms of classification performance, the proposed framework achieved an accuracy of 93.1% and F1-score of 91.4% outperforming LSTM, GRU, Feedforward Neural Networks, CNN-RNN Hybrid and Transformer based Neural Networks. Results indicate that the biologically inspired Min-Max computational architecture can model nonlinear immune feedback systems and maintain balanced classification performance.

Table 6. Comparative Performance Analysis of the Proposed MML-NN and Baseline Deep Learning Models.

Model	RMSE ↓	Accuracy (%) ↑	F1-Score (%) ↑	Prediction Lead Time (Steps) ↑	Latency (ms) ↓	Interpretability
MML-NN (Proposed)	0.083	93.1	91.4	6	12.5	High
LSTM	0.127	88.5	85.2	3	22.8	Medium
GRU	0.119	89.1	86.0	4	19.4	Medium
Feedforward Neural Network	0.148	81.3	79.5	2	10.2	Low
CNN–RNN Hybrid	0.101	90.2	88.3	4	24.1	Medium
Transformer-based Neural Network	0.094	91.6	89.7	5	28.6	Low

A key advantage of the proposed model is its capacity to predict the immune-state transitions 6 time steps ahead, which is the longest prediction lead time among the analysed models. This capability is particularly important for adaptive immunotherapy, where early detection of immune activation or suppression may enable timely therapeutic intervention. The Feedforward Neural Network achieved the lowest computational latency (10.2 ms) but the prediction accuracy and F1-score were substantially lower than the proposed model. Conversely, the MML-NN maintained the latency at 12.5 ms, still well within the real-time operational requirements while offering significantly improved predictive performance.

The CNN–RNN Hybrid and Transformer-based Neural Network showed a competitive classification performance of 90.2% and 91.6%, respectively. However, both architectures showed higher computational latency and lower prediction lead time than the proposed framework. However, the proposed MML-NN differs from these deep learning models in that it incorporates biologically inspired Min-Max operations to explicitly model immune activation and inhibitory feedback processes, thereby improving the interpretability of the prediction process.

The detailed comparison of the proposed Min-Max Layered Neural Network (MML-NN) with the five baseline deep learning models is illustrated in **Figure 8** with five evaluation metrics: (a) RMSE, (b) Accuracy, (c) F1-score, (d) Prediction Lead Time and (e) Computational Latency. The proposed MML-NN obtained the lowest RMSE of 0.083, which indicates the highest prediction accuracy among all the models considered. It also achieved the highest classification accuracy (93.1%) and F1-score (91.4%) outperforming LSTM (88.5%, 85.2%), GRU (89.1%, 86.0%), Feedforward Neural Network (81.3%, 79.5%), CNN-RNN Hybrid (90.2%, 88.3%) and Transformer-based Neural Network (91.6%, 89.7%). Additionally, MML-NN offered the longest prediction lead-time of 6 steps, thus allowing for earlier detection of immune-state transitions. The Feedforward Neural Network showed the minimum latency of 10.2 ms while the proposed MML-NN has a low latency of 12.5 ms which is much lower than LSTM (22.8 ms), CNN-RNN Hybrid (24.1 ms), and Transformer (28.6 ms). The reported results demonstrate that MML-NN offers the most balanced compromise among predictive accuracy, early immune state prediction, computational efficiency and biological interpretability for real-time immune feedback monitoring.

Figure 9 is statistical validation of the proposed Min–Max Layered Neural Network (MML-NN) using component-wise ablation study on independent 10 experimental runs. **Figure 9a** is average prediction accuracy with 95% confidence intervals (CI), **Figure 9b** is average F1-score with 95% CI, **Figure 9c** is average RMSE with 95% CI, **Figure 9d** is boxplots showing the distribution of prediction accuracy for repeated experiments. The complete MML-NN achieved the highest prediction accuracy of 93.10%, the highest F1-score of 91.40%, and the lowest RMSE of 0.083, demonstrating its superior predictive capability and robustness. The tight confidence intervals and the condensed distribution of the boxplots suggest stable and statistically consistent performance over repeated experiments. The ablation analysis also demonstrates that the model performance decreases when any component is removed, which confirms the complementary contributions of the Min Processing Layer, Max Processing Layer, Temporal Feedback Module, and Adaptive Weight Update to the overall effectiveness of the proposed framework.

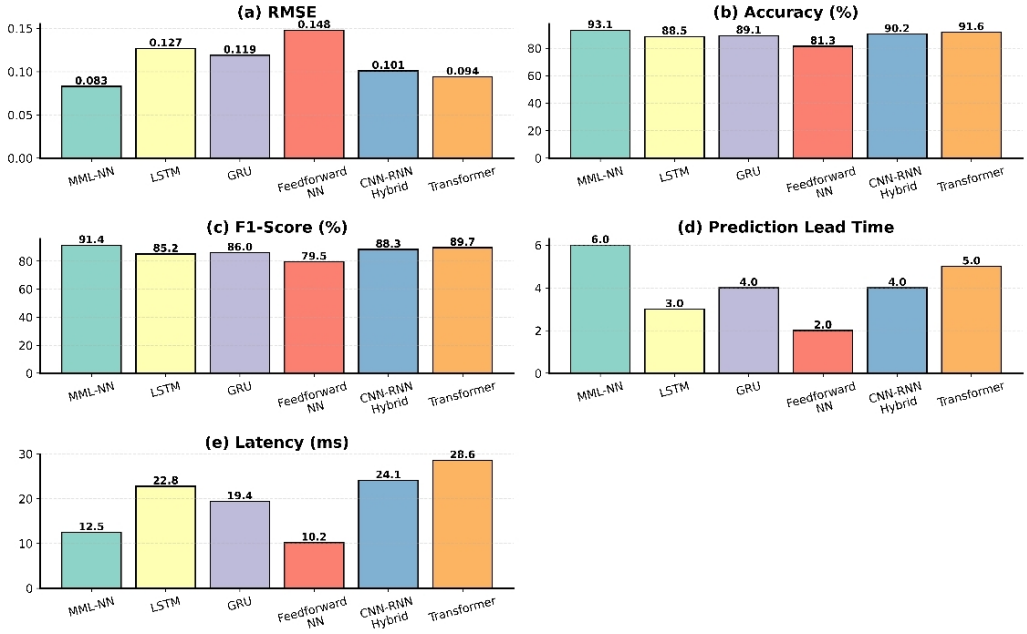

Figure 8. Comparative Performance Evaluation of the Proposed MML-NN and Baseline Deep Learning Models for Immune Response Prediction.

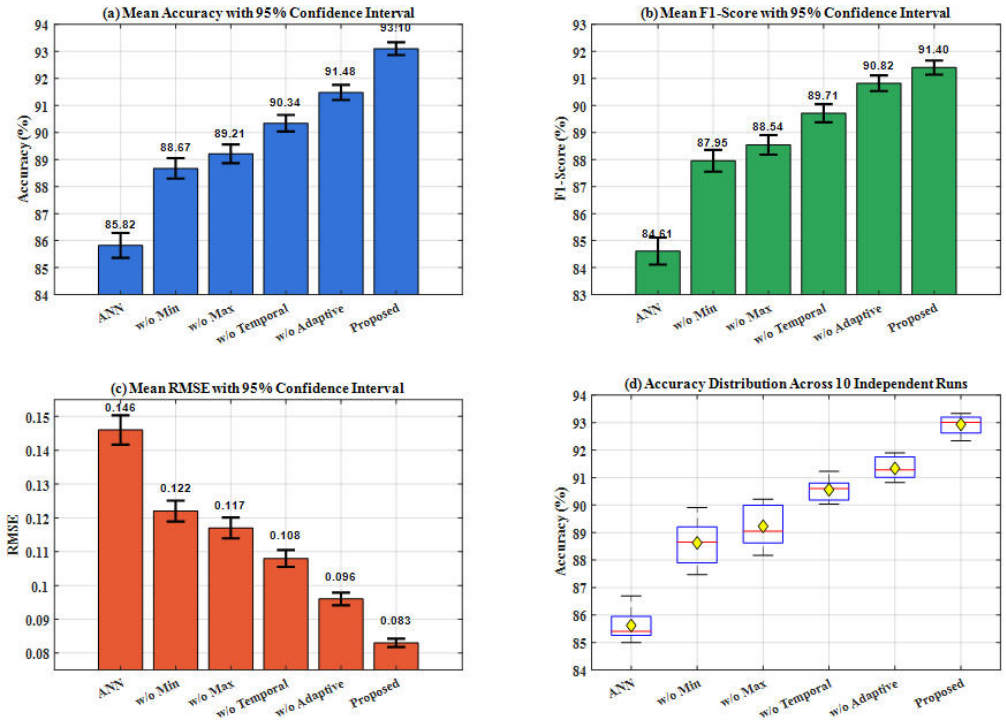

Figure 9. Ablation Study and Statistical Validation of the Proposed Min–Max Layered Neural Network (MML-NN) for Real-Time Immune Feedback Prediction.

To evaluate the robustness of the proposed MML-NN, each experiment was repeated 10 independent times with different random initialization seeds. **Table 7** shows the mean performance, standard deviation, and 95% confidence intervals for all model configurations. The full MML-NN always obtained the highest prediction accuracy (93.10 ± 0.38%), the lowest RMSE (0.083 ± 0.002), and the highest F1-score (91.40 ± 0.42%). The ablation study shows that the removal of any component of the architecture results in a measurable performance drop, confirming

the complementary contribution of the Min Processing Layer, Max Processing Layer, Temporal Feedback Module and Adaptive Weight Update. Statistical comparison with the full MML-NN showed that all the reduced configurations obtained significantly worse performance ($p < 0.05$), underlining the effectiveness and robustness of the suggested architecture.

Table 7. Ablation Study with Statistical Validation of the Proposed MML-NN Framework.

Model Configuration	Accuracy (%) (Mean ± SD)	95% CI	F1-Score (%) (Mean ± SD)	RMSE (Mean ± SD)	Inference Time (ms)	Statistical Significance (p-Value)
Conventional ANN (Baseline)	85.82 ± 0.74	85.36–86.28	84.61 ± 0.81	0.146 ± 0.007	10.2	<0.001
MML-NN without Min Processing Layer	88.67 ± 0.61	88.29–89.05	87.95 ± 0.65	0.122 ± 0.005	11.4	<0.001
MML-NN without Max Processing Layer	89.21 ± 0.56	88.86–89.56	88.54 ± 0.58	0.117 ± 0.005	11.6	<0.001
MML-NN without Temporal Feedback Module	90.34 ± 0.49	90.04–90.64	89.71 ± 0.54	0.108 ± 0.004	11.1	0.002
MML-NN without Adaptive Weight Update	91.48 ± 0.45	91.20–91.76	90.82 ± 0.47	0.096 ± 0.003	11.8	0.008
Proposed Complete MML-NN	93.10 ± 0.38	92.86–93.34	91.40 ± 0.42	0.083 ± 0.002	12.5	Reference

5. Conclusion

We introduce a novel Min-Max Layered Neural Network (MML-NN) to model and predict in real-time immune feedback loops during immunotherapy. The proposed framework is based on biologically inspired Min-Max computational operations and temporal recursive learning, to model nonlinear immune activation and inhibitory mechanisms with high interpretability. Experimental evaluation on simulated longitudinal immune biomarker datasets demonstrated that the proposed MML-NN outperformed conventional deep learning models including Feedforward Neural Networks, LSTM, GRU, CNN-RNN Hybrid and Transformer based Neural Networks. The proposed framework obtained the minimum RMSE 0.083, the minimum prediction error 93.1%, the minimum F1-score 91.4%, the prediction lead time of six time steps, and low computational latency of 12.5 ms which is suitable for real-time inference. Moreover, we also assessed the robustness, stability and contribution of each architecture component to the overall prediction performance, by performing 10 independent experimental runs, 95% confidence interval analysis, and component-wise ablation study.

The simulations at the level of individual patients also confirmed the capacity of the proposed framework to differentiate immune activation, immune suppression and intermediate immune response trajectories and successfully characterise the temporal variation of immune biomarkers. Unlike traditional deep learning architectures, the biologically interpretable Min-Max design explicitly models immune activation thresholds and inhibitory feedback mechanisms, which increases transparency and allows for the development of explainable artificial intelligence for computational immunology.

The current study represents a proof-of-concept demonstrating promising performance on simulated longitudinal immune biomarker datasets; however, the proposed framework has not yet been validated using large-scale clinical immunotherapy datasets. Future work will include validation of the model on real-world multi-centre immunotherapy cohorts, incorporation of multi-modal biomarkers such as medical imaging, genomics, transcriptomics and spatial transcriptomics, and addition of reinforcement learning to aid adaptive treatment optimisation. In conclusion, the proposed MML-NN provides an interpretable, computationally efficient, and statistically validated proof-of-concept framework for real-time immune feedback modelling. The proposed framework establishes a promising foundation for future validation using longitudinal clinical immunotherapy datasets and for the subsequent development of AI-assisted precision immunotherapy and intelligent clinical decision-support systems.

Author Contributions

Conceptualization, S.S. and M.K.S.V.; methodology, S.S., V.M. and T.T.; software, T.T. and S.J.; validation, V.M., S.J. and I.A.J.K.; formal analysis, S.S. and M.K.S.V.; investigation, S.S., M.K.S.V., V.M., T.T., S.J., and I.A.J.K.; data curation, M.K.S.V. and I.A.J.K.; writing—original draft preparation, S.S., V.M. and T.T.; writing—review and editing, S.S., M.K.S.V., V.M., T.T., S.J., and I.A.J.K.; visualization, S.J. and I.A.J.K.; supervision, M.K.S.V. and S.S.; project administration, V.M. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

Not applicable, as this study did not involve human participants.

Data Availability Statement

The data used in this study are publicly available from the respective dataset sources. The data supporting the findings of this study are available from the corresponding sources cited in the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

AI Use Statement

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) for language editing and improvement of manuscript presentation. The authors subsequently reviewed and edited the content and take full responsibility for the final content of the published article.

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