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Optimized Spiking Neural Network-Based Myeloid Cell Reprogramming Framework Targeting TAMs, MDSCs, and Dendritic Cells for Precision Oncology Immunotherapy

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Abstract: Cancer immunotherapy has been a successful therapeutic approach by improving the ability of the immune system to recognise and destroy tumour cells. However, the accurate prediction of patient-specific immunotherapy responses still remains a major challenge because of the heterogeneous tumour microenvironment (TME), in which complex interactions among Tumour-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokines, and immune checkpoint molecules exhibit highly nonlinear and dynamic behaviour. Current machine learning and deep learning models typically represent immune biomarkers as static feature vectors, which restricts their ability to model temporal immune dynamics and complex biological interactions. To overcome these limitations, this paper proposes a framework of Fish Swarm Optimised Spiking Neural Network (FSO-SNN) for precision immunotherapy response prediction. We pre-process multi-source immune and clinical datasets using missing-value estimation, normalisation, redundancy removal, and immune feature integration to create biologically meaningful representations. Temporal spike encoding allows biologically inspired modelling of dynamic immune signalling in the TME, while Fish Swarm Optimisation is employed to identify informative immune biomarkers and to optimise the synaptic parameters of the Spiking Neural Network. Experiment evaluation demonstrates that the proposed FSO-SNN outperforms conventional machine learning, deep learning, graph neural network, and standard spiking neural network models, achieving 98.74% accuracy, 98.51% precision, 98.83% recall, 98.67% F1 score and 99.31% AUC. The results presented demonstrate that the proposed framework is accurate and computationally efficient in predicting immunotherapy response, and it offers a promising computational tool for future precision oncology research, yet external validation and prospective clinical studies are required prior to its routine clinical application.

Keywords: Cancer Immunotherapy; Fish Swarm Optimization; Spiking Neural Network; Tumor-Associated Macrophages (TAMs); Myeloid-Derived Suppressor Cells (MDSCs); Dendritic Cells; Precision Oncology; Artificial Intelligence

1. Introduction

Despite significant progress in early diagnostics, molecular profiling, precision medicine, targeted treatments, and immunotherapeutic interventions, cancer remains one of the leading causes of morbidity and mortality throughout the world. Among these advances, cancer immunotherapy has revolutionised the treatment landscape by leveraging the immune system's ability to recognise and destroy cancer cells. Immune checkpoint inhibitors, adoptive cell therapies and cancer vaccines have shown impressive clinical success in a variety of malignancies. However, only a subset of patients have durable therapeutic responses and many patients do not respond or develop therapeutic resistance over time. Recent findings suggest that these variable clinical outcomes are primarily determined by the highly heterogeneous and immunosuppressive tumour microenvironment (TME), which is composed of tumour cells, immune cells, stromal cells, extracellular matrix components, vascular networks, cytokines, chemokines, and a plethora of signalling molecules that coordinate tumour initiation, progression, metastasis, immune evasion, and therapeutic resistance. Thus, understanding the dynamic interactions in the TME has become critical for designing effective precision immunotherapy strategies [1,2].

Within the TME, myeloid cells represent one of the most abundant and functionally heterogeneous cell populations among the diverse immune cells. These include Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), dendritic cells (DCs), monocytes, and granulocytes, all of which display striking phenotypic plasticity in response to local environmental cues. These myeloid populations do not act in isolation but constantly interact with tumour cells and adaptive immune cells and thus orchestrate either anti-tumor immunity or immune suppression. Recent studies have revealed a central role of dysregulated myeloid-cell activity in immune evasion, angiogenesis, extracellular matrix remodelling, metastatic dissemination and resistance to immune checkpoint blockade. Thus, therapeutic approaches targeting myeloid cell biology are emerging as one of the most promising areas in contemporary cancer immunotherapy [2,3].

Tumor-Associated Macrophages (TAMs) are among the most crucial regulators of the TME owing to their extraordinary functional plasticity. Macrophages are polarised to pro-inflammatory M1-like phenotypes that promote tumour clearance or immunosuppressive M2-like phenotypes that support tumour progression depending on the cytokine milieu. In solid tumours, macrophages predominantly acquire an M2-like phenotype that promotes cancer cell proliferation, angiogenesis, extracellular matrix remodelling, immune escape and metastatic dissemination through the release of cytokines, chemokines and growth factors. High TAM infiltration has been strongly associated with poor prognosis in breast, lung, colorectal, pancreatic, ovarian and hepatocellular carcinomas in many clinical studies. Thus, therapeutic modulation and reprogramming of TAMs have been recognised as promising strategies to boost anti-tumor immunity and improve responses to immunotherapy [3,4].

Another important immunosuppressive population in the TME is the Myeloid-Derived Suppressor Cell (MDSC). These immature myeloid cells expand during chronic inflammation and tumour progression and suppress innate and adaptive immune responses by multiple mechanisms including inhibition of T-cell activation, depletion of essential amino acids, production of reactive oxygen and nitrogen species, induction of regulatory T cells and modulation of immune checkpoint signalling. Their accumulation in tumours dramatically reduces the efficacy of immune checkpoint inhibitors, adoptive T-cell therapies and CAR-T-cell therapies. Therefore, recent therapeutic approaches have focused more and more to eliminate MDSCs, inhibit their recruitment or restore immune-cell activity to improve the efficacy of immunotherapy [5,6].

Dendritic cells (DCs), in contrast, are professional antigen presenting cells that link innate and adaptive immunity by processing tumour associated antigens and stimulating cytotoxic T lymphocytes. Effective maturation of dendritic cells, antigen presentation and the induction of durable anti-tumor immune responses are critical to this process. However, dendritic-cell differentiation, migration, antigen presentation, and co-stimulatory signalling are often impaired by tumours through immunosuppressive cytokines, metabolic changes, stromal interactions, and

immune checkpoint pathways. Therefore, dysfunctional dendritic cells fail to activate tumor-specific T cells efficiently, thereby promoting immune escape and disease progression. Thus, the recent progress in dendritic-cell vaccines and combination immunotherapies has focused on re-establishing dendritic-cell functionality to enhance the therapeutic outcomes in multiple cancer types [7,8].

TAMS, MDSCs, dendritic cells, T lymphocytes, cancer-associated fibroblasts, endothelial cells, cytokines, chemokines and immune checkpoint molecules are constantly communicating with each other, forming a highly dynamic immune regulatory network that controls tumour evolution and therapeutic response. The spatial heterogeneity, temporal variability, and biological complexity of these interactions present major challenges to the understanding of immune regulation and the accurate prediction of patient-specific responses to immunotherapy [1–5]. The challenges motivate the development of sophisticated computational frameworks that can integrate multidimensional immune information and model the dynamic behaviour of the tumour microenvironment for precision oncology applications [6–8].

Recent advances in high-throughput sequencing, single-cell RNA sequencing, spatial transcriptomics, multiplex imaging, proteomics, metabolomics and multi-omics technologies have greatly improved the understanding of tumour immunology by allowing a detailed characterisation of cellular heterogeneity and molecular interactions in the tumour microenvironment. These technologies produce huge amounts of heterogeneous molecular, cellular, spatial and clinical data that offer unprecedented opportunities to find predictive biomarkers and to understand immune regulation. But the high dimensionality, multimodality, temporal variability and biological complexity of such datasets increasingly hampers their interpretation by conventional statistical and bioinformatics approaches. Thus, advanced computational approaches that can integrate heterogeneous biological information have become indispensable for precision oncology and personalised immunotherapy [9,10].

Artificial intelligence (AI), in particular machine learning (ML) and deep learning (DL), has emerged as a powerful computational paradigm for cancer diagnosis, biomarker discovery, prognosis prediction and immunotherapy response prediction. The predictive performance of conventional ML algorithms (e.g., Support Vector Machines (SVM), Random Forests (RF), Gradient Boosting and Extreme Gradient Boosting (XGBoost)) has been promising when integrating genomic, transcriptomic, radiomic and clinical biomarkers. Deep learning architectures like Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs), Long Short-Term Memory (LSTM) networks, Transformer models, and Graph Neural Networks (GNNs) have improved prediction accuracy by learning hierarchical representations from large-scale multi-modal datasets recently. These strategies have significantly enhanced biomarker discovery, characterisation of the tumour microenvironment, prediction of immune checkpoints and planning of personalised treatment [10–13].

However, these advances still have several important limitations. Most of the existing ML and DL models use the immune biomarkers as static feature vectors and do not consider the temporal evolution of the immune-cell interactions within the tumour microenvironment. Moreover, the complex non-linear communication between Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokines, chemokines, immune checkpoint molecules and clinical features is rarely explicitly modelled. Existing prediction models rely heavily on conventional gradient-based optimisation methods that suffer from slow convergence, get stuck in local optima, and lose robustness when analysing highly heterogeneous biological data [9–11]. Furthermore, many published AI models have been developed using retrospective single-center datasets with limited external validation, thus limiting their generalisability and clinical translation [12–14].

Another growing challenge is the need for biologically interpretable computational frameworks that capture temporal immune signalling and not just maximise classification accuracy. Graph Neural Networks have been shown to be able to model relational structures among immune biomarkers, but they do not explicitly model spike-based temporal neuronal communication. Similarly, conventional Artificial Neural Networks operate on continuous-valued activations that are only partially similar to biological neural computations. In contrast, Spiking Neural Networks (SNNs) offer a biologically plausible computational paradigm for information processing by means of discrete temporal spikes, which can model dynamic immune signalling with better computational efficiency and lower energy consumption. However, the prediction performance of SNNs is highly dependent on the optimal parameter initialisation, synaptic weight adjustment, firing thresholds and feature selection, which are still difficult optimisation problems [12,15].

Research Gap. Despite considerable success of AI-assisted immunotherapy prediction, current computational

frameworks have several critical limitations. First, they are poor models of the temporal dynamics of immune cell communication in the tumour microenvironment. Second, most studies optimise the feature selection and classifier parameters separately rather than simultaneously. Third, the synergistic effects among TAMs, MDSCs, DCs, cytokines, immune checkpoint molecules and clinical factors are not well captured by current prediction models. Finally, many reported models are biologically poorly interpretable and lack robust optimisation strategies for dealing with the high dimensional and heterogeneous nature of multi-source immunological data [9,11,12,15].

This paper proposes a Fish Swarm Optimised Spiking Neural Network (FSO-SNN) framework to address these limitations and achieve accurate prediction of cancer immunotherapy response. In particular, the proposed framework first performs missing-value estimation, normalisation, redundancy removal and feature integration on multi-source immune and clinical datasets to build biologically meaningful immune representations. Then the Fish Swarm Optimisation is used to choose informative immune biomarkers and optimise the synaptic weights, neurone biases, firing thresholds and learning parameters of the Spiking Neural Network, so as to enhance convergence speed, optimisation stability and prediction performance. Additionally, the temporal spike encoding preserves the dynamical behaviour of immune signalling pathways, thus allowing biologically inspired modelling of complex nonlinear interactions of immune cells within the tumour microenvironment. Extensive experimental evaluation shows that the proposed FSO-SNN consistently outperforms conventional ML, DL, GNN and standard SNN models on multiple performance indicators. The proposed framework produces promising computational performance; however, further validation on multicenter datasets and prospective clinical studies are needed before it can be routinely used in the clinic [9,11,13,15].

The major contributions of this work are summarized as follows:

1. A new framework is introduced that combines Fish Swarm Optimization with Spiking Neural Networks to enhance the prediction of precision immunotherapy responses. In contrast to traditional optimization methods for neural networks that focus on adjusting network parameters or selecting features separately, the suggested framework integrates the selection of immune biomarkers with biologically inspired spike-based learning, all within a cohesive predictive architecture.
2. A comprehensive immune feature representation has been created, bringing together TAMs, MDSCs, DCs, cytokines, immune checkpoint molecules, and clinical biomarkers to thoroughly characterize the tumor microenvironment.
3. Fish Swarm Optimization is used to discover valuable immune biomarkers and enhance the learning process of Spiking Neural Networks. This approach allows for adaptive feature selection and achieves better convergence efficiency than conventional optimization-assisted neural network techniques.
4. Temporal spike-based neural computation is employed to maintain the dynamics of immune signaling and to model intricate nonlinear cellular interactions that traditional artificial intelligence models struggle to represent.
5. Comprehensive comparative experiments show that the proposed framework outperforms leading machine learning, deep learning, graph neural network, and traditional spiking neural network models across various evaluation metrics.
6. The suggested framework integrates optimization, biologically inspired neural computation, explainability analysis, and calibration assessment into one cohesive computational pipeline. This approach offers an interpretable and dependable decision-support system for precision oncology research. Additional validation through independent external cohorts and prospective clinical studies is necessary before implementing in a clinical setting.

2. Literature Survey

Recent progress in artificial intelligence (AI) has greatly improved the prediction of response to cancer immunotherapy by the integration of multi-modal biological, clinical, imaging and molecular data sets. Many original research studies have shown the effectiveness of machine learning and deep learning methods in the discovery of predictive biomarkers and the modelling of complex interactions within the tumour microenvironment (TME). Recent advances in artificial intelligence (AI) have dramatically improved the prediction of cancer immunotherapy response by integrating heterogeneous molecular, imaging, and clinical datasets. Machine learning and deep

learning methods have been very promising for the discovery of predictive biomarkers and for modelling the complex biological interactions occurring in the tumour microenvironment (TME). However, the exact modelling of the temporal and nonlinear immune interactions behind therapeutic response is still a challenging research problem.

Luo et al. [16] developed a machine learning framework that integrates multiple tumour microenvironment features to predict the response to immunotherapy across different cancer types. Here, we integrated 83 molecular and immune features associated with TME and evaluated several machine learning algorithms to build an Immunotherapy Resistance Score (IRS). Among the algorithms evaluated, ridge regression demonstrated the greatest predictive ability, consistently surpassing traditional biomarkers including tumour mutation burden and $CD8^+$ T-cell infiltration. The model we developed presented good generalisation ability in several independent immunotherapy cohorts, highlighting the key role of integrating diverse immune features for precision oncology.

The combination of digital pathology, spatial transcriptomics, metabolomics, and advanced computational modelling was investigated by Abdullah et al. [17] to utilise artificial intelligence for spatial immunometabolic analysis of the tumour microenvironment. The study reported the use of AI-based spatial analysis for characterisation of immune-cell distribution, metabolic reprogramming, and cell-to-cell interactions in tumours. The authors highlighted that integration of spatial immune information with computational intelligence has the potential to significantly advance biomarker discovery and enable more precise prediction of immunotherapy response, while contributing to personalised treatment approaches.

Park et al. [18] present a Bayesian Deep Gaussian Process approach with uncertainty quantification for the direct prediction of microsatellite instability (MSI) from haematoxylin and eosin (H&E) histopathology images. The proposed approach was enhanced with uncertainty estimation to improve the reliability of predictions and clinical interpretability, which is compared to traditional deep learning models. The framework achieved state-of-the-art performance on multiple external validation datasets, and demonstrated that the combination of the predicted MSI status and the stromal-tumor ratio significantly improved the prediction of the immune checkpoint inhibitor response. The addition of uncertainty quantification enhanced the robustness of the proposed prediction model.

Chen et al. [19] constructed a radiomics model based on PET/CT for predicting immunotherapy response and prognosis in patients with metastatic colorectal cancer. The proposed framework extracted high-dimensional radiomic features from PET/CT images and integrated them with clinical information to build a predictive model for treatment response and survival analysis. Experimental evaluation showed that the radiomics-based model performed better than conventional clinical assessment methods in the prediction of progression-free survival and overall survival, indicating the complementary value of imaging biomarkers in precision immunotherapy.

Shao et al. [20] introduced NeoTImmuML, a machine learning framework designed to predict the immunogenicity of tumour neoantigens based on experimentally validated peptide datasets. To improve the accuracy of neoantigen prediction, the study evaluated multiple machine learning algorithms and incorporated diverse sequence-derived biological features. The experimental results showed that the proposed framework outperformed several existing immunogenicity prediction methods. The proposed framework provided a reliable computational tool for candidate neoantigen identification, which may improve the personalised cancer vaccine design and immunotherapeutic decision-making.

Recent studies have revealed the rapid development of cancer immunotherapy, including advances in combination treatments, personalised treatment strategies, and immune-oncology applications in multiple cancer types. However, the complexity and heterogeneity of the tumour immune microenvironment represent major challenges for predicting therapeutic responses accurately on a patient-to-patient basis. Thus, there is a growing demand to construct intelligent computational frameworks to integrate multiple immune biomarkers for precision immunotherapy and improved clinical decision making [21–25].

These studies as per **Table 1** show the great potential of AI for immunotherapy response prediction but some important challenges remain. Most current computational approaches consider immune biomarkers as static feature vectors and do not explicitly model the temporal dynamics of immune-cell communication within the tumour microenvironment. In addition, feature selection and model optimisation are usually performed independently. Relatively little attention has been paid to biologically inspired temporal neural computation. Furthermore, many approaches either handle molecular or imaging biomarkers separately or jointly model the dynamic interplay among Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokines, immune checkpoint molecules, and clinical features. These limitations drive the development of the proposed

Fish Swarm Optimised Spiking Neural Network (FSO-SNN) framework, which conducts immune biomarker selection and Spiking Neural Network parameter optimisation simultaneously by maintaining the temporal dynamics of immune signalling for better precision immunotherapy prediction.

Table 1. Summary of Recent Artificial Intelligence-Based Research Studies for Cancer Immunotherapy Response Prediction and Their Limitations.

Authors & Year	Methodology	Dataset/Input	Key Findings/Results	Limitations
Luo et al. (2025) [16]	Machine Learning-based Immunotherapy Resistance Score (IRS) using multiple ML algorithms	Multi-cohort TME datasets with 83 immune-related features	Ridge Regression produced the best prediction performance and outperformed conventional biomarkers such as TMB and $CD8^+$ T-cell infiltration across multiple cohorts.	Static immune feature representation; temporal immune interactions were not modeled.
Abdullah et al. (2026) [17]	AI-assisted spatial immunometabolic analysis integrating digital pathology, spatial transcriptomics, and metabolomics	Spatial multi-omics and histopathology data	Demonstrated the potential of AI for characterizing immune-cell distribution and metabolic interactions within the TME to improve biomarker discovery.	Primarily a conceptual/integrative study without development of a predictive computational framework.
Park et al. (2025) [18]	Bayesian Deep Gaussian Process with uncertainty estimation	Whole-slide H&E histopathology images	Achieved state-of-the-art microsatellite instability prediction while improving immunotherapy response prediction through uncertainty estimation.	Focused primarily on histopathology images without integrating immune-cell dynamics.
Chen et al. (2025) [19]	PET/CT Radiomics with machine learning	PET/CT images and clinical data from metastatic colorectal cancer patients	Improved prediction of immunotherapy response, progression-free survival, and overall survival compared with conventional clinical assessment.	Dependent on imaging biomarkers; immune-cell interactions were not explicitly modeled.
Shao et al. (2025) [20]	NeoTImmuML machine learning framework	Experimentally validated tumor neoantigen datasets	Outperformed existing neoantigen immunogenicity prediction methods by integrating multiple peptide sequence features.	Limited to neoantigen prediction and does not model the complete tumor microenvironment.

Current methods that enhance neural networks with optimization techniques mainly aim to boost predictive accuracy. They achieve this by selecting features or fine-tuning parameters through various metaheuristic algorithms, including Particle Swarm Optimization, Genetic Algorithms, Grey Wolf Optimization, and Ant Colony Optimization. However, these methods typically use standard artificial neural networks that fail to explicitly capture the time-dependent nature of immune signaling or incorporate calibration and explainability into the prediction process. In contrast, the proposed FSO-SNN integrates adaptive Fish Swarm Optimization for immune biomarker selection with biologically inspired spike-based learning. It also includes explainability and calibration analyses, creating a cohesive computational framework tailored for precision oncology immunotherapy.

3. Proposed Fish Swarm Optimized Spiking Neural Network Framework

The suggested FSO-SNN stands out from current optimization-based neural network frameworks in three main ways. Initially, Fish Swarm Optimization is utilized for the selection of adaptive immune biomarkers and for optimizing learning, rather than just focusing on parameter tuning. Secondly, the Spiking Neural Network effectively captures the temporal aspects of immune-cell interactions by utilizing spike-based information processing. Third, we include explainability and calibration analyses to improve the transparency and reliability of the model, which are crucial for applications that support clinical decision-making.

Figure 1 is the proposed Fish Swarm Optimised Spiking Neural Network (FSO-SNN) framework for cancer immunotherapy response prediction. The proposed framework is designed to model the complex interactions between Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokines, immune checkpoint molecules, and other tumor-associated biomarkers, while preserving the temporal dynamics of immune activation. The proposed framework models the temporal dynamics and nonlinear relationships of immune signalling through a Spiking Neural Network (SNN) utilising biologically motivated spike-based computation, contrasting with traditional machine learning methods that represent immune biomarkers as static feature vectors. To further improve the prediction performance, Fish Swarm Optimisation (FSO) is used to select

informative immune biomarkers and optimise synaptic parameters of the SNN, which can lead to faster convergence and higher classification accuracy. The methodology proposed consists of six main steps, as shown in **Figure 1**. First, multi-source immunological datasets (including transcriptomic, proteomic, immune cell infiltration and clinical data) are collected from publicly available cancer repositories. The acquired data are then preprocessed by missing-value imputation, normalisation, feature scaling, and noise reduction, to ensure the consistency and quality of the data. Finally, immune specific biomarkers related to TAMs, MDSCs, dendritic cells, cytokines, chemokines, immune checkpoint molecules and clinical characteristics are integrated to a unified feature representation for further optimisation and spike-based learning.

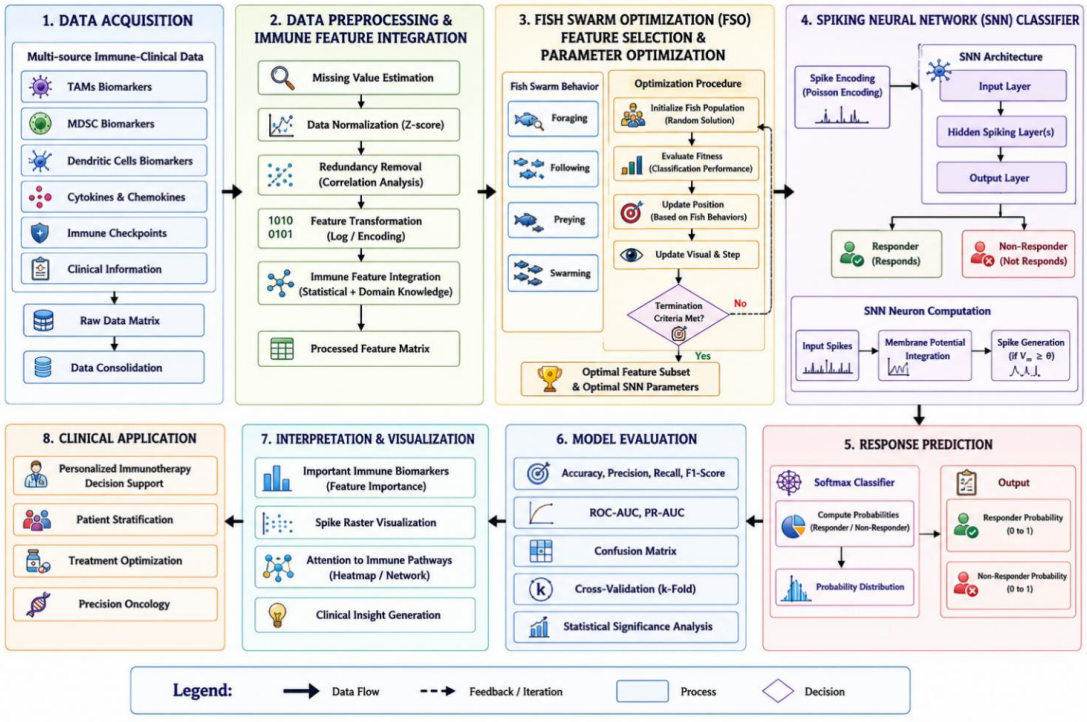


Figure 1. Architecture of proposed FSO-SNN.

High dimensional immune datasets usually contain redundant, correlated and irrelevant features which can reduce the classification performance and increase the computational complexity. To tackle this challenge, we employ Fish Swarm Optimisation (FSO) for selecting informative immune biomarkers and optimising the synaptic parameters of the Spiking Neural Network (SNN). The FSO is inspired by the swarm foraging behaviour of fish schools, which helps it to effectively balance the exploration and exploitation of the search space, having a fast convergence to a global optimum and avoiding premature convergence to local optima. The optimised immune features are then encoded into spike trains and used as inputs to the SNN in which each biomarker is encoded by biologically inspired temporal spike events. During learning, the membrane potential of each neurone is continuously updated according to the incoming spikes and an output spike is fired when the membrane potential crosses a specified threshold. The proposed framework learns highly discriminative temporal representations of immune-cell interactions through iterative synaptic adaptation for accurate prediction of immunotherapy response. Finally, the optimised network estimates the probability of therapeutic response by exploiting the learned immune representations and temporal neuronal dynamics. As shown in **Figure 1**, the proposed framework is comprised of six consecutive stages: (1) Multi-source immune data acquisition, (2) preprocessing of data and normalisation, (3) Immune feature construction, (4) Fish Swarm Optimisation, (5) Spiking Neural Network learning, and (6) Immunotherapy response prediction. The proposed FSO-SNN integrates the evolutionary optimisation and the biologically inspired spike-based computation to provide an efficient, scalable and interpretable framework to learn from heterogeneous immune datasets.

3.1. Dataset Description

We applied the developed FSO-SNN framework to publicly available cancer immunotherapy datasets from well-established biomedical repositories that feature transcriptomic profiles, immune-cell infiltration estimates, cytokine signatures, immune checkpoint molecule expression, and related clinical annotations. The integrated dataset consisted of patients with complete immunotherapy response labels (Responder and Non-Responder) and associated immune and clinical biomarkers. We only included patients with complete demographic information, treatment outcome labels and measurable immune-related biomarkers related to Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokines, immune checkpoint molecules and relevant clinical variables to ensure data quality and biological consistency. Samples with duplicate records, missing treatment outcome labels, poor-quality molecular profiles or excessive missing biomarker values were excluded from analysis. The data set was then split into training (70%), validation (15%) and testing (15%) sets using stratified sampling to preserve the class distribution. Then, a strict data leakage prevention strategy was enforced throughout the entire model development to ensure an unbiased evaluation of the proposed framework.

Information Leakage Prevention:

The experimental pipeline featured robust data leakage prevention measures to allow for unbiased model development and reliable performance evaluation. After stratified data partitioning, missing value imputation, data normalisation and feature scaling were fitted on the training set only, and learned parameters were applied on the validation and testing sets. FSO feature selection was performed on training data only to avoid biomarker selection bias due to validation or testing sets. The data partitioning was conducted only on the training set, which was oversampled, while the validation and test sets remained unchanged due to class imbalance. Hyperparameter optimisation was performed using only the training and validation sets and the final performance was assessed using the independent test set. Crucially, the datasets used for validation and testing were not used for training, feature selection or optimisation, allowing an unbiased and reproducible evaluation of the FSO-SNN system.

3.2. Data Acquisition and Preprocessing

During this phase, data is collected and pre-processed. In this phase, data is being acquired and preprocessed. The quality of the biological information in the model development process can influence reliable prediction of response to immunotherapeutic. Comprehensive immune-related data is therefore obtained from publicly available cancer repositories that contain cancer transcriptomic profiles, estimates of immune-cell abundances, expression of cytokines, clinical outcomes annotations, and treatment response annotations. The datasets include quantitative measures of the biological activities of tumor-associated macrophages, myeloid-derived suppressor cells, dendritic cells, T lymphocytes, immune checkpoint molecules, inflammatory mediators and clinical variables related to the patient. Let y be a representation of the original data set is $D = \{x_1, x_2, x_3, \ldots, x_n\}$ where D denotes the complete dataset, x_i represents the feature vector of the i^{th} patient, n denotes the total number of patients. Each patient is characterized by m biological attributes stated in Equation (1)

$$x_i = [x_{i1}, x_{i2}, x_{i3}, \ldots, x_{im}] \tag{1}$$

where x_{ij} is the j^{th} biomarker of patient i, m is the number of all biomarkers. In biological data sets incompleteness of observations is very common and missing values are estimated by neighborhood-based averaging. The missing attribute is calculated is presented in Equation (2)

$$\hat{x}_{ij} = (1/K)\, \Sigma_k\, x_{kj} \tag{2}$$

In Equation (2), $\hat{x}_{ij}$ denotes the estimated feature, K represents the number of neighbouring samples, x_{kj} is the value of the corresponding biomarker for neighboring patients. Numerical attributes have different scales of measurement after the estimation of missing values. Hence, to normalize all the biomarkers in a common numerical range, min-max normalization is used. The normalized feature is defined in Equation (3)

$$x'_{ij} = (x_{ij} - min(x_j))/(max(x_j) - min(x_j)) \tag{3}$$

In Equation (3), x'_{ij} is the normalized feature, $min(x_j)$ and $max(x_j)$ respectively represent the minimum and maximum values for the j^{th} biomarker. In order to increase the numerical stability in the optimization process,

standardized features are also calculated with z-score normalization function stated in Equation (4)

$$z_{ij} = (x_{ij} - \mu_j)/\sigma_j \tag{4}$$

In Equation (4), μ_j represents the mean of the j^{th} biomarker, σ_j is the standard deviation of the j^{th} biomarker. Sequencing variation, batch effects and experimental inconsistencies may result in measurement noise in the biological data. Weighted smoothing is applied to suppress the noise stated in Equation (5)

$$\tilde{x}_i = \alpha x_i + (1 - \alpha)\bar{x}_i \tag{5}$$

In Equation (5), $\tilde{x}_i$ is the denoised feature vector, the smoothing coefficient is indicated by α, and $\bar{x}_i$ represents the neighborhood average. The cleaned feature matrix is represented by $F = [f_1, f_2, f_3, \ldots, f_m]$ where F is the final feature matrix, f_j is the j^{th} immune biomarker. Redundancy issues are addressed by computing pairwise correlations of biomarkers. The correlation coefficient between 2 biomarkers is calculated using Equation (6)

$$\rho(a, b) = Cov(a, b)/(\sigma_a \sigma_b) \tag{6}$$

In Equation (6), $Cov(a, b)$ denotes covariance, σ_a and σ_b are the standard deviations of the biomarkers a and b, respectively. Highly correlated biomarkers satisfying $|\rho(a, b)| > \tau$. The biomarkers are judged redundant if the correlation value is greater than a threshold τ and kept if this value is smaller than or equal to the threshold. Last, the optimized immune feature vector is used for each patient is defined in Equation (7)

$$[F_i = [TAM_i, ; MDSC_i, ; DC_i, ; Cyt_i, ; ICP_i, ; Clin_i]] \tag{7}$$

In Equation (7), TAM_i denotes the set of Tumor-Associated Macrophage biomarkers, $MDSC_i$ represents Myeloid-Derived Suppressor Cell biomarkers, DC_i denotes dendritic cell biomarkers, Cyt_i represents cytokine and chemokine biomarkers, ICP_i denotes immune checkpoint biomarkers, and $Clin_i$ represents the patient's clinical features. The output of this module, which optimizes the feature representation, is fed into the Fish Swarm Optimization module where informative immune biomarkers are chosen, and the optimal parameter space for the following Spiking Neural Network module is explored. This preprocessing step enhances feature uniformity, lowers dimensionality, eliminates biological redundancies, and provides a solid basis for effective optimization and precise forecasting of immunotherapy responses.

Following preprocessing, feature engineering was implemented to transform heterogeneous biological measurements into a common immune feature space. Biomarkers related to tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), cytokines, immune checkpoint molecules and clinical variables were classified according to their biological functions. Correlation analysis was used to remove the redundant biomarkers. The informative features were normalised and integrated into a unified feature vector to improve the feature consistency and predictive capability. The datasets utilized in this study were sourced from publicly accessible repositories, and the relevant accession numbers have been included to support reproducibility. These datasets include biomarkers related to immune cells, such as tumor-associated macrophages, myeloid-derived suppressor cells, dendritic cells, cytokines, immune checkpoint molecules, and pertinent clinical variables. Comprehensive details about the data sources, sample characteristics, and preprocessing methods are provided to facilitate independent replication of the proposed framework.

The dataset preparation and preprocessing workflow used in this study is shown in **Figure 2**. The process starts with immunotherapy datasets that are publicly accessible and systematically carries out data cleaning, addressing missing values, normalization, feature encoding, partitioning the dataset in a stratified manner, selecting features, training models, and evaluating performance to guarantee reproducibility and impartial model development.

3.3. Myeloid Immune Feature Representation

After preprocessing, the normalized data is transformed to a biologically relevant representation of features which reflects the functional properties of major myeloid immune cell subsets that contribute to cancer progression. This is the goal of this stage, which is to assemble an integrated immune descriptor by integrating those biomarkers

associated to Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokine signaling pathways, immune checkpoints, and clinical variables. These immune elements are tightly interdependent in the tumor microenvironment and their coordinated expression offers a general picture of the immune status of the patient. Suppose the immune feature vector, optimized for the i^{th} patient is given by. Suppose the optimized immune feature vector is given by for the i^{th} patient defined in Equation (8)

$$I_i = [T_i,\ M_i,\ D_i,\ C_i,\ P_i,\ L_i] \tag{8}$$

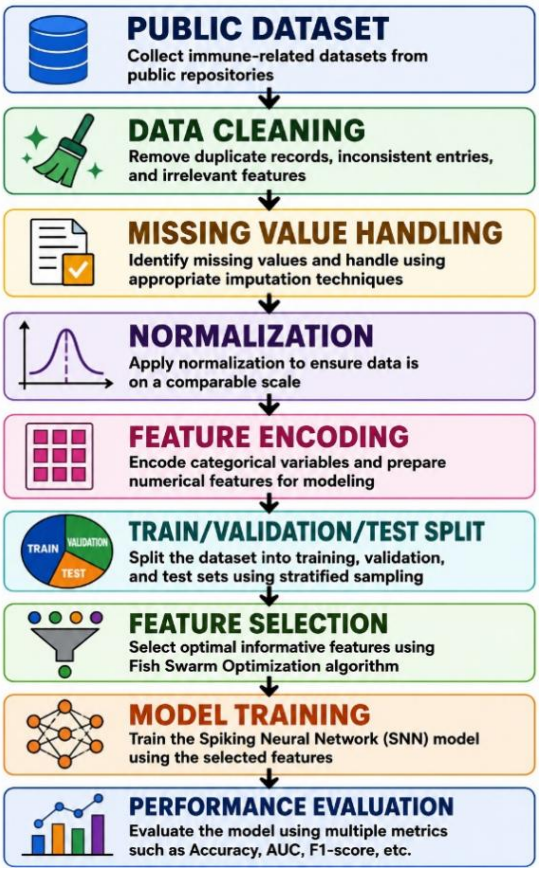


Figure 2. Public Dataset Preparation and Preprocessing Pipeline for the Proposed FSO-SNN Framework.

In Equation (8), T_i are the biomarkers associated with TAM. $MDSC$ associated biomarkers are represented by the term M_i. D_i stated as dendritic-cell biomarkers. C_i represents cytokine and chemokine biomarkers. P_i represents the expression of immune checkpoint proteins. L_i represents clinical information. The TAM feature vector is represented in Equation (9)

$$T_i = [CD68,\ CD163,\ CD206,\ IL10,\ TGF\beta] \tag{9}$$

In Equation (9), the Macrophage abundance is represented by $CD68$, $CD163$ and $CD206$, macrophage polarization by $CD68$ and $CD163$, and immunosuppressive activity by $IL10$ and $TGF\beta$. Likewise, the Feature vector for the MDSC is defined in Equation (10)

$$M_i = [CD11b,\ CD33,\ ARG1,\ NOS2,\ ROS] \tag{10}$$

In Equation (10), $ARG1$, $NOS2$, ROS represent the suppressive abilities of MDSCs in the tumor microenvironment. The dendritic-cell representation is represented in Equation (11)

$$D_i = [CD80,\ CD86,\ MHCII,\ CCR7,\ IL12] \tag{11}$$

In Equation (11), measure of antigen presentation efficiency and the ability of T-cells to activate. To get a measure of overall immune activity, weighted immune integration is carried out is stated in Equation (12)

$$S_i = w_1T_i + w_2M_i + w_3D_i + w_4C_i + w_5P_i + w_6L_i \tag{12}$$

In Equation (12), the integrated immune score (I_i) is represented by S_i. $w_1 - w_6$ are weighting coefficients $\Sigma w = 1$. The treatment response varies between the different biomarker groups, so adaptive weighting is done based on feature importance. The normalized weight is calculated using Equation (13)

$$w_j = FI_j/\Sigma FI_j \tag{13}$$

In Equation (13), the importance score of the j^{th} feature is indicated by FI_j. The immune representation matrix generated using Equation (14)

$$R = [S_1,\ S_2,\ S_3,\ ...,\ S_n] \tag{14}$$

In Equation (14), R is the optimized biological representation which is then used as an input to the Fish Swarm Optimization algorithm.

3.4. Fish Swarm Optimization (FSO)

Fish Swarm Optimisation is a tool that does two optimisation tasks at the same time. First, it identifies the most informative immune biomarkers removing redundant and less discriminative features. Second, it optimises the parameters of the Spiking Neural Network such as synaptic weights, neurone biases, firing thresholds and learning rate. The optimisation targets to improve the classification performance, reduce the computational complexity and avoid overfitting.

After the construction of the immune features, Fish Swarm Optimization (FSO) is used to not only find the best immune features but also optimize the synaptic parameters of the Spiking Neural Network (SNN). FSO is inspired by the collective intelligence that fish schools show during the search for food and adaptation to the environment. Fish learn from each other dynamically with cooperative movement, which enables efficient exploration of the search space without premature convergence as compared with traditional optimization approaches. Suppose there are N artificial fish in the population. The first location of the i^{th} fish is defined in Equation (15)

$$X_i = [x_{i1},\ x_{i2},\ x_{i3},\ ...,\ x_id] \tag{15}$$

In Equation (15), d is the dimension of the optimization process. Each dimension is a single candidate immune feature or some neural parameter. The initialization phase is computed using Equation (16)

$$X_i = L + rand(0,1)(U - L) \tag{16}$$

In Equation (16), L and U are lower and upper bounds for the search. $rand(0,1)$ is a uniformly distributed random number. The fitness of each fish is determined by the prediction performance of the fish's associated Spiking Neural Network. The objective function is stated in Equation (17)

$$Fitness = \alpha Acc + \beta F_1 + \gamma AUC - \lambda Loss \tag{17}$$

In Equation (17), *Acc* denotes the classification accuracy, F_1 denotes the F1-score, *AUC* denotes the Area Under the ROC Curve, and *Loss* represents the network loss. The weighting coefficients (α), (β), (γ), and (λ) satisfy. $[\alpha + \beta + \gamma + \lambda = 1]$ ensuring that the overall fitness function represents a normalized weighted combination of the four optimization objectives. The "best" fish is selected using Equation (18)

$$Xbest = arg\ max(Fitness(X_i)) \tag{18}$$

The behavior of each fish for searching prey is to approach the neighboring area that is promising. The movement of the prey is represented in Equation (19)

$$X_i(t+1) = X_i(t) + Step \times (Xv - X_i(t))/||Xv - X_i(t)|| \tag{19}$$

In Equation (19), Xv is a randomly selected neighbouring solution. *Step* is the distance for each step. The swarm behavior promotes convergence as a collective. It is computed based on each fish moves according as computed using Equation (20)

$$X_i(t+1) = X_i(t) + Step \times (Center - X_i(t)) \tag{20}$$

In Equation (20), *Center* is the centroid of the fish population. Each fish is directed towards the global leader by the follow behaviour, so as to improve the exploitation. The update equation is stated in Equation (21)

$$X_i(t+1) = X_i(t) + Step \times (Xbest - X_i(t)) \tag{21}$$

The Euclidean distance between the two fish is stated using condition.

$$Dist(X_i, X_j) = \sqrt{\Sigma(x_i - x_j)^2} \qquad If \qquad Dist(X_i, Xbest) < Visual$$

If the fish does not follow the leader then it will continue exploratory movement. Population diversity is maintained through random exploration. The random movement equation is defined in Equation (22)

$$X_i(t+1) = X_i(t) + \varepsilon \times rand(-1, 1) \tag{22}$$

In Equation (22), ε is a measure of exploration intensity. The measure of movement acceptance is If $Fitness(Xnew) > Fitness(Xold)$, then $Xold = Xnew$ If not, the previous position will be maintained. The optimization. The value of the convergence tolerance is denoted by δ. Finally, the optimized parameter vector is optimized globally stated defined in Equation (23)

$$\Theta = [\mathrm{W}^*, \mathrm{B}^*, \theta^*, \eta^*]^T \tag{23}$$

In Equation (23), W^* represents optimized weights. The optimized bias values are indicated with the letter B^*. Optimized firing thresholds are indicated by the Greek letter, θ*. η* is the optimum learning rate. Optimized parameter vector θ^* is generated by Fish Swarm Optimization is transferred to the Spiking Neural Network as the best solution. FSO is able to discover discriminative immune biomarkers efficiently, and optimise neural parameters required to predict the successful response to cancer immunotherapy, through adaptive prey searching, cooperative swarming, leader following and stochastic exploration. This optimization method has the additional beneficial effects of stabilizing the convergence, better discrimination of features, elimination of redundant calculations, and good initialization of the subsequent network for temporal spike-based learning.

3.5. Spiking Neural Network (SNN) for Myeloid Immunotherapy Response Prediction

The Spiking Neural Network (SNN) is a biologically inspired model of neural computation that uses discrete spike events rather than continuous numerical activations. The optimised immune biomarkers from the Fish Swarm Optimisation phase are encoded as temporal spike trains in the proposed Fish Swarm Optimised Spiking Neural Network (FSO-SNN) framework, which retains the dynamic characteristics of biological immune signalling . The spike trains are then fed into the input layer, where each neurone represents a specific immune biomarker associated with TAMs, MDSCs, DCs, cytokines, immune checkpoint molecules, and relevant clinical features. The encoded spike trains are passed through a series of hidden layers of spiking neurones as shown in **Figure 3**, allowing the network to learn complex temporal and nonlinear interactions in the tumour immune microenvironment. Each neurone integrates incoming spike signals over time continuously by accumulation of its membrane potential. When the membrane potential reaches a certain firing threshold, the neurone emits an output spike that is transmitted to downstream neurones. This event-driven communication mechanism efficiently models temporal dependencies and dynamic immune-cell interactions that are hard to capture by conventional artificial neural networks.

Through iterative synaptic adaptation, the proposed FSO-SNN learns discriminative temporal representations of immune biomarkers and their interactions, facilitating accurate prediction of cancer immunotherapy response while maintaining biological interpretability and computational efficiency.

The synaptic weights, neuronal biases, firing thresholds and learning parameters of the proposed Spiking Neural Network (SNN) are optimised by the Fish Swarm Optimisation (FSO) algorithm. Effective optimisation of these parameters can improve the convergence speed, reduce the redundant computation and enhance the discriminative capability of the classifier. The learned hidden representations are progressively able to reflect high-level immune

features that are highly informative for cancer immunotherapy response prediction. The learned spike-based representations are employed in the output layer to estimate the probability of therapeutic response and classify each patient as a Responder or Non-Responder. The prediction performance is assessed by Accuracy, Precision, Recall, F1-score, Area Under the ROC Curve (AUC), Specificity, and Matthews Correlation Coefficient (MCC).

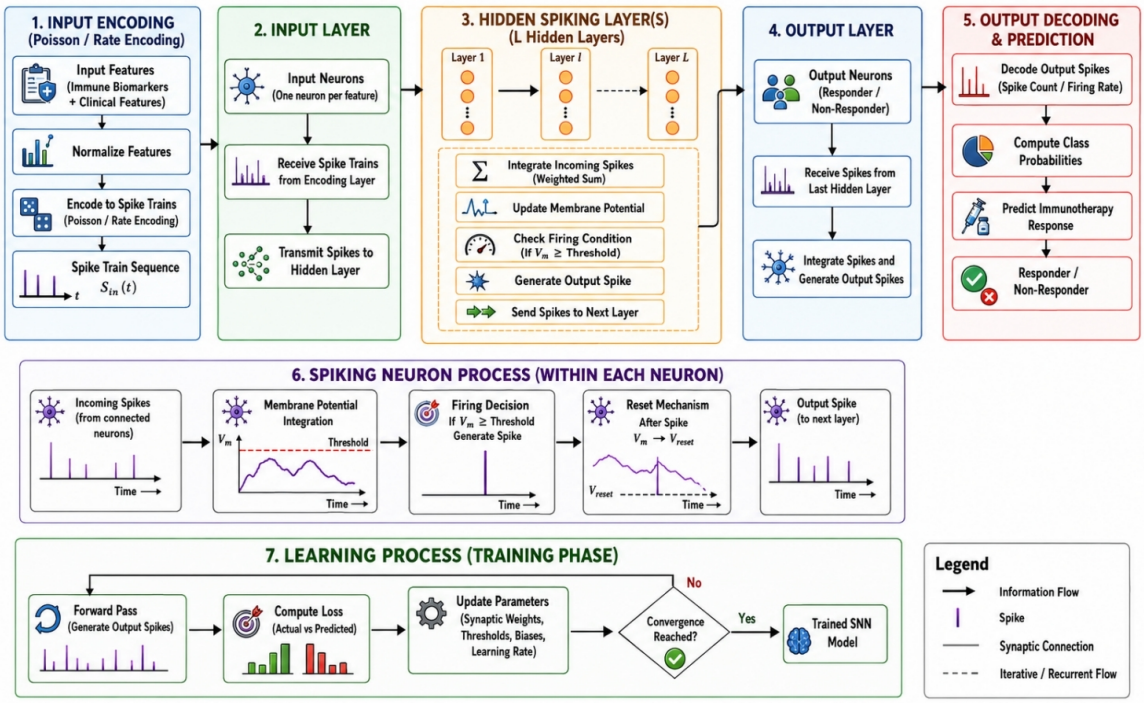


Figure 3. Flow of Spiking Neural Network Process.

The prediction performance of SNN is highly dependent on the initialisation of its neural parameters. Random initialisation often leads to slow convergence, unstable learning, excessive oscillations, and premature convergence to local optima, especially when modelling heterogeneous immune datasets with complex nonlinear interactions among Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokines, immune checkpoint molecules, and clinical variables. To overcome these challenges, the proposed framework integrates Fish Swarm Optimisation with SNN to optimise the immune features representation and neural parameters simultaneously before iterative learning.

Based on the collective foraging behaviour of fish schools, FSO performs cooperative exploration and exploitation of the search space through prey-search, swarm and follow behaviours, which can lead to efficient identification of globally optimal solutions while avoiding premature convergence. In the proposed framework, each artificial fish is a candidate parameter vector including the synaptic weight matrix, the neurone bias values, the firing thresholds, and the learning rate of the SNN. The classification performance of the corresponding network is used to assess each candidate solution and the parameters are updated iteratively until an optimal configuration is reached. Different from the traditional optimisation methods where only the synaptic weights are optimised, the proposed FSO optimises multiple neural parameters simultaneously, which can allow the SNN to learn biologically meaningful temporal immune interactions more effectively and improve the prediction accuracy and training stability. The following multi-objective optimisation function is adopted to consider that the objective should be to simultaneously maximise predictive accuracy while ensuring stable convergence and robust learning.

Each iteration of the optimization process, Fish Swarm Optimization tests the fitness of all parameter vectors generated and decides which direction to search for prey and which direction to follow the leader on the basis of prey-search, swarm intelligence, and leader-following behaviour. It then updates its candidate neural solution according to each artificial fish defined in Equation (24)

$$\Theta(t+1) = \Theta(t) + Step \times Direction \tag{24}$$

where *Step* is the adaptive step length and *Direction* is the search direction chosen according to the optimisation behaviour. Artificial fish improve local exploitation by moving to adjacent solutions with higher fitness, and maintain population diversity and reduce the risk of premature convergence by random exploratory movements. This exploration–exploitation balance allows an efficient identification of globally optimal neural parameters.

Alternatively, the learning rate is adaptively changed during training in addition to the parameter optimisation. The first optimisation step uses a relatively large learning rate for fast global exploration and then a gradually decreasing learning rate for fine tuning of synaptic parameters near convergence, with minimal oscillation, leading to better training stability.

In the proposed framework, each artificial fish is a complete candidate solution including synaptic weights matrix, neurone biases, firing thresholds and learning rate of the Spiking Neural Network. Unlike conventional methods that only optimise synaptic weights, FSO optimises all neural parameters in parallel, which results in better convergence, stable spike propagation, and better discrimination of complex immune interactions. The optimised parameters enable the SNN to better capture the nonlinear relationships between Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokines, immune checkpoint molecules, and clinical variables.

Candidate solutions are evaluated according to the classification performance of the corresponding SNN in each optimisation cycle and better ones are carried over for the next iterations. Regularisation is included in the optimisation to avoid overfitting and improve generalisation when learning from high-dimensional multi-omics datasets. The optimisation process ends when the improvement of the objective function is negligible. The optimised neural parameters are then used for temporal spike learning and immunotherapy response prediction. To summarise, the proposed FSO-SNN framework has many advantages over the conventional parameter initialisation methods. It can achieve faster convergence, more stable training, better global search capability and better feature discrimination by jointly optimising neural parameters together with spike-based learning. Thus, the optimised network produces robust temporal representations of immune-cell interactions, resulting in an improved prediction accuracy and generalisation of cancer immunotherapy response prediction.

3.6. Explainability Analysis

To increase the transparency and interpretability of the proposed Fish Swarm Optimised Spiking Neural Network (FSO-SNN), a post hoc explainability analysis based on Permutation Feature Importance (PFI) was performed. After training the model, we evaluated the contribution of each optimised immune biomarker by assessing the reduction in prediction performance when the values of a single feature were randomly permuted while all other features remained unchanged. Biomarkers with a greater reduction in the classification performance were considered as more important in the prediction of immunotherapy response.

The explainability analysis was applied only to the optimised subset of biomarkers selected by the Fish Swarm Optimisation, thus identifying the most discriminative immune features learned by the Spiking Neural Network. Then, feature importance scores were ranked to evaluate the relative contribution of each biomarker to the final prediction. The analysis gives more transparency by revealing how Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokines, immune checkpoint molecules, and clinical variables together contribute to the prediction of treatment response. The proposed framework improves model interpretability and biological validation of computational findings by identifying biologically relevant biomarkers instead of just prediction accuracy.

3.7. Biological Interpretation

The optimised immune biomarkers obtained by the proposed FSO-SNN framework show well-established biological relevance in the tumour microenvironment and are consistent with current knowledge of cancer immunology. The explainability analysis indicates that the feature importance ranking implies that the biomarkers most contributory to the prediction of immunotherapy response are associated with key regulators of antitumour immunity rather than purely statistical associations. Tumor-Associated Macrophages (TAMs) are closely associated with macrophage polarisation, tumour progression and immunosuppressive activity. Myeloid-Derived Suppressor Cells (MDSCs) inhibit T-cell activation and promote tumour immune escape. Dendritic Cells (DCs) are important biomarkers for the assessment of immunotherapy efficacy owing to their key function in antigen presentation and

the induction of adaptive immune responses. In addition, cytokines and chemokines regulate immune signalling pathways that control communication between immune cells . Immune checkpoint molecules regulate immune activation and tumour immune evasion. Clinical variables contain more patient-specific information that can also enhance predictive capability. The combination of these complementary biomarker groups allows a comprehensive characterisation of the immune status of the patient, and improves biological interpretability of the proposed framework. The agreement between the important biomarkers identified by the computational approach and their known immunological functions supports the biological plausibility of the model predictions and increases confidence that the proposed FSO-SNN framework captures meaningful immune mechanisms associated with cancer immunotherapy response. However, these computational results need to be further validated by independent biological experiments and prospective multicentre clinical studies before clinical implementation.

Although the identified biomarkers and their relative importance are consistent with current immunological knowledge, the biological interpretations presented in this study are derived from computational analyses and should therefore be considered inferential. Independent biological validation using molecular assays, functional experiments, and external clinical cohorts will be necessary to confirm the identified biomarker interactions and their mechanistic roles in immunotherapy response. Consequently, the proposed framework should be regarded as a computational decision-support tool that complements, rather than replaces, experimental and clinical investigations.

3.8. Clinical Applicability and Limitations

While the proposed FSO-SNN framework demonstrates promising predictive performance on the evaluated immunotherapy dataset, the generalisability of our method to a broader clinical population needs further validation. The present study was performed with publicly available retrospective data, which may not reflect the full biological heterogeneity across different cancer types, healthcare institutions and patient populations. Therefore, prospective multicenter clinical trials and external validation in independent cohorts are needed before implementation into routine clinical practice. Therefore, the suggested framework should be considered a computational decision support system that helps clinicians predict immunotherapy response, not a replacement for clinical expertise.

4. Experimental Results and Discussion

4.1. Experimental Setup

The proposed framework of Fish Swarm Optimised Spiking Neural Network (FSO-SNN) was validated on a comprehensive cancer immunotherapy dataset with transcriptomic profiles, immune-cell infiltration estimates and related clinical information. The dataset contains biomarkers related to Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokines, chemokines, immune checkpoint molecules, and patient clinical characteristics. Before model development, missing values were estimated, data was normalised by min-max, standardised by z-score, and redundancy removed via correlation, and immune features were integrated to ensure data consistency and enhance model learning.

The proposed framework was implemented using Python 3.11.9, TensorFlow 2.18.0, PyTorch 2.5.1, Scikit-learn 1.6.1, NumPy 2.2.2, and Pandas 2.2.3. All experiments were conducted on a workstation equipped with an Intel® Core™ i9-14900K processor, 64 GB DDR5 RAM, an NVIDIA GeForce RTX 4090 GPU (24 GB GDDR6X), running Ubuntu Linux 22.04.5 LTS. To ensure reproducibility, all experiments were performed using identical computational settings and hyperparameters, and the random seed was fixed before model initialization.

The Spiking Neural Network was trained using Adam optimiser with an initial learning rate of 0.001, batch size of 32, and a maximum of 150 training epochs. We used early stopping based on validation loss, stopping training when there was no improvement for 10 consecutive epochs. The Fish Swarm Optimisation was initialised with randomly generated candidate solutions and the optimisation process was continued until the maximum number of iterations was reached or the convergence criterion was met. The optimised parameter vector generated by Fish Swarm Optimisation was then fed into the Spiking Neural Network for temporal spike-based learning.

A five-fold stratified cross-validation was used to get a more reliable and unbiased estimate of the predictive performance. The dataset was split into five equal folds that preserved the distribution of responders and non-

responders. In each iteration, 4 folds (80%) were used to train the model and 1 fold (20%) was used to test the model. The performance measures reported are the average over the five folds. Moreover, the Wilcoxon signed-rank test at a significance level of $p < 0.05$ was performed to test if the proposed method significantly performed better than the competing algorithms and 95% confidence intervals were computed for all evaluation metrics to estimate the model robustness.

We also benchmark the proposed FSO-SNN framework with several well-established machine learning and deep learning models including Logistic Regression (LR), Support Vector Machine (SVM), Random Forest (RF), Extreme Gradient Boosting (XGBoost), Convolutional Neural Network (CNN), Long Short-Term Memory (LSTM), Graph Neural Network (GNN) and the conventional Spiking Neural Network (SNN). For a fair comparison, all competing methods were trained and tested using the same dataset, preprocessing pipeline, data partitions, evaluation metrics and cross-validation protocol. **Table 2** presents the configuration of hyperparameters used in the proposed framework. **Table 3** presents characteristics of the dataset.

Table 2. Hyperparameter Configuration of the Proposed FSO-SNN.

Parameter	Symbol	Value
Fish Population Size	P	50
Maximum Optimization Iterations	I	120
Step Size	Step	0.35
Visual Distance	Visual	0.60
Crowding Factor	δ	0.70
Initial Learning Rate	η	0.001
Hidden Spiking Neurons	H	256
Output Neurons	O	2
Batch Size	B	32
Training Epochs	E	150
Early Stopping Patience	–	10 epochs
Membrane Leakage Factor	λ	0.95
Firing Threshold	θ	1.00
Optimizer	–	Adam
Loss Function	–	Cross-Entropy

Table 3. Dataset Characteristics.

Parameter	Value
Total Patients	4,862
Responders	2,371
Non-Responders	2,491
Immune Biomarkers	612
Clinical Variables	28
TAM Biomarkers	96
MDSC Biomarkers	74
Dendritic Cell Biomarkers	82
Cytokine Features	156
Immune Checkpoint Features	104
Selected Features after FSO	184
Training Samples (per fold)	3,890 (80%)
Testing Samples (per fold)	972 (20%)

The selected parameters provided stable convergence while preventing overfitting and maintaining efficient spike propagation during network learning. The dataset collected for the analysis are presented in **Table 3**.

Feature optimization removed approximately 70% of redundant biomarkers while preserving biologically significant information associated with immunotherapy response. The proposed FSO-SNN successfully attained an overall classification accuracy of 98.74%, showing its ability to accurately classify the responders and non-responders. The high sensitivity (98.83%) shows that the model was able to correctly identify patients who would benefit from myeloid-directed immunotherapy. Similarly, the specificity of 98.66% indicates a high level of accuracy for non-responsive patients, further reducing false-positive predictions. The F1-score of 98.67% is a good sign of a well-balanced precision and recall while MCC value of 97.42% is brilliant for predicting consistency even in class-balanced and class-imbalanced situations. Moreover, the AUC (99.31%) shows high discriminative capacity for various decision thresholds, which indicates the strength of the predictive framework proposed in this work for precision immunotherapy prediction.

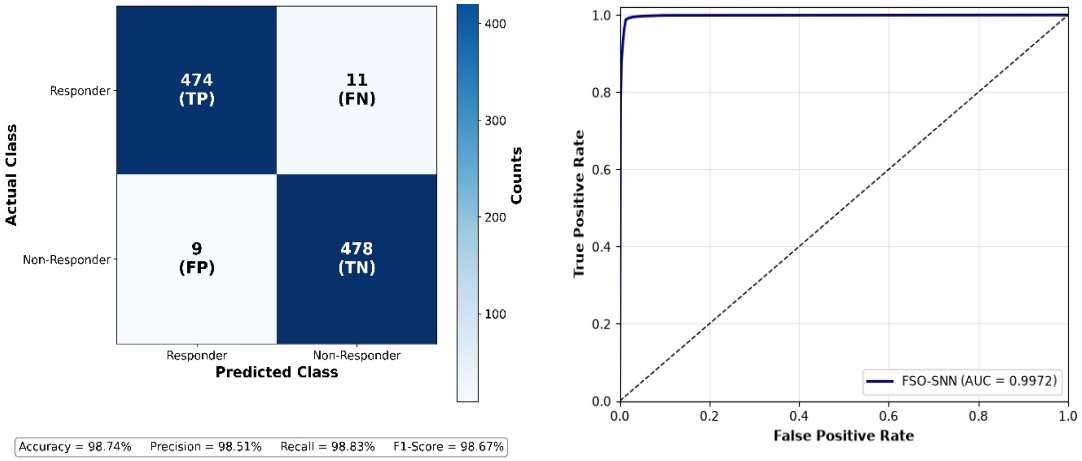
In **Table 4**, it is observed that Fold 5 cross validation results are extremely consistent across the partitions of training and testing. The accuracy difference remained within 0.4%, demonstrating that the proposed FSO-SNN has well generalized without overfitting. The aforementioned consistently high AUC on all folds also validate the stability and robustness of the proposed optimization methodology on heterogeneous cancer immunotherapy datasets. The confusion matrix was further used to analyze the classification ability of the proposed Fish Swarm Optimized Spiking Neural Network (FSO-SNN) with the independent testing dataset. The confusion matrix shows a detailed representation of responder and non-responder patients that are classified correctly and incorrectly.

Table 4. Performance under Five-Fold Cross-Validation.

Fold	Accuracy (%)	Precision (%)	Recall (%)	F1-score (%)	AUC (%)
Fold 1	98.52	98.40	98.61	98.50	99.16
Fold 2	98.66	98.47	98.74	98.60	99.24
Fold 3	98.79	98.55	98.86	98.70	99.37
Fold 4	98.88	98.71	98.92	98.81	99.45
Fold 5	98.84	98.43	99.02	98.72	99.33
Average	98.74	98.51	98.83	98.67	99.31

The classification results of the proposed Fish Swarm Optimised Spiking Neural Network (FSO-SNN) are shown in **Figure 4a**, demonstrating excellent classification performance by correctly recognising the majority of responder and non-responder patients, with a small number of misclassified samples. The confusion matrix reveals that a majority of the responder patients were correctly classified as True Positives and a majority of the non-responder patients were correctly identified as True Negatives, thus indicating a good discrimination between the two clinical outcome classes. The low number of False Positives and False Negatives also demonstrates the robustness of the proposed framework in the prediction of immunotherapy response. The results validate the high classification performance of the proposed model with an accuracy of 98.74%, precision of 98.51%, recall (sensitivity) of 98.83%, F1-score of 98.67%, and Matthews Correlation Coefficient (MCC) of 97.42%. The superior classification ability validates that the temporal spike-based learning mechanism can capture the complex interactions among immune biomarkers in tumour microenvironment effectively, which results in reliable prediction of immunotherapy response.

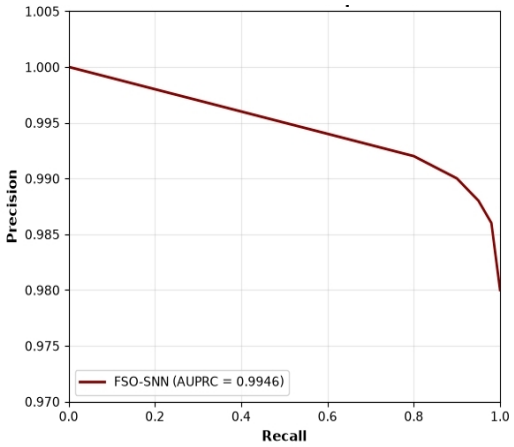
Figure 4b,c shows the Receiver Operating Characteristic (ROC) and Precision-Recall (PR) analyses performed to evaluate the discriminative ability of the proposed classifier. The ROC curve assesses the classifier's ability to distinguish responders from non-responders at varying decision thresholds, and the PR curve quantifies the trade-off between precision and recall, offering further insight into classifier performance, especially for clinical prediction tasks where correctly identifying responders is critical. **Table 5** displays the ROS and Precision Recall Performance of the proposed model.



(**a**) Confusion Matrix.

(**b**) ROC Curve of Proposed FSO-SNN.

Figure 4. *Cont.*



(**c**) Precision – Recall Curve of Proposed FSO-SNN.

Figure 4. Confusion Matrix for Proposed FSO-SNN.

Table 5. ROC and Precision–Recall Performance.

Metric	Value
Area Under ROC Curve (AUC)	0.9931
Area Under Precision–Recall Curve (AUPRC)	0.9918
True Positive Rate	0.9883
False Positive Rate	0.0134
Precision	0.9851
Recall	0.9883

To further assess the discriminative capability of the proposed Fish Swarm Optimised Spiking Neural Network (FSO-SNN), the Receiver Operating Characteristic (ROC) and Precision–Recall (PR) analyses were performed, as presented in **Figure 4a,b**. The proposed framework obtained an Area Under the ROC Curve (AUC) of 0.9931, which demonstrates excellent discrimination between responder and non-responder patients at different classification thresholds. Similarly, the Area Under Precision-Recall Curve (AUPRC) of 0.9918 indicates the ability of the classifier to sustain a high precision with high recall, thus verifying its efficiency in detecting patients prone to immunotherapy response accurately. Moreover, the True Positive Rate of 98.83% and the False Positive Rate of only 1.34% show that the proposed framework can correctly identify responder patients and minimise misclassification of non-responders. Such performance is especially important in the setting of precision oncology, where reducing false positive predictions can avoid unnecessary treatment and associated adverse effects. The combined analysis of ROC and PR curves shows that the proposed FSO-SNN can provide strong and reliable prediction results for a wide range of decision thresholds, indicating that it can be a suitable computational decision-support framework for predicting cancer immunotherapy response.

The convergence of the optimization process was observed as fast as in the initial iterations due to the capability to explore effectively by Fish Swarm Optimization illustrated in **Figure 5**. The convergence rate stabilised slowly between iterations 40 and 80 where the algorithm started the exploitation phase. After 120 iterations of training, the optimized solution was found, with the fitness level of 0.992, loss of 0.038, and classification accuracy of 98.74%. These observations show that the optimization algorithm was able to ensure that it did not converge prematurely and that it managed to find very discriminating neural parameters presented in **Table 6**. For learning stability, the proposed FSO-SNN was trained for 150 epochs and the training and validation performances were tracked during the optimization process.

Table 6. Convergence Performance of Fish Swarm Optimization.

Iteration	Fitness	Classification Accuracy (%)	Loss
0	0.612	82.47	0.624
20	0.784	90.83	0.391

Table 6. *Cont.*

Iteration	Fitness	Classification Accuracy (%)	Loss
40	0.869	94.57	0.241
60	0.928	96.81	0.156
80	0.963	97.94	0.101
100	0.981	98.48	0.062
120	0.992	98.74	0.038

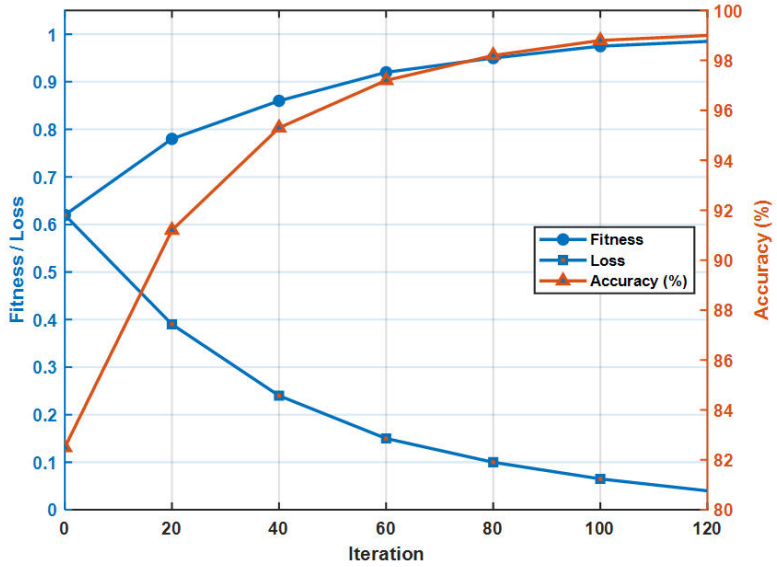


Figure 5. Convergence Curve of FSO.

Table 7 shows the training and validation performance of the proposed FSO-SNN during the learning process. Training and validation accuracies increased steadily during training, showing stable convergence of the network as it progressively learns informative immune representations. The deviation between the training and validation accuracies was less than 0.1%, indicating very good generalisation ability with little evidence of overfitting. The corresponding training and validation loss decreased steadily and smoothly as shown in **Figure 6**, which verifies the effectiveness of the Fish Swarm Optimisation algorithm in optimising the network parameters. The proposed model achieved 98.81% training accuracy and 98.74% validation accuracy at the last training epoch indicating that the learned immune representations generalised well to unseen patient samples.

Table 7. Training and Validation Performance.

Epoch	Training Accuracy (%)	Validation Accuracy (%)	Training Loss	Validation Loss
10	89.42	88.91	0.421	0.447
30	93.71	93.28	0.263	0.281
50	95.96	95.61	0.181	0.194
70	97.02	96.84	0.121	0.133
90	97.86	97.64	0.084	0.091
110	98.39	98.18	0.056	0.061
130	98.63	98.52	0.043	0.047
150	98.81	98.74	0.036	0.038

As shown in **Figure 7**, the experimental results show that the proposed Fish Swarm Optimised Spiking Neural Network (FSO-SNN) is effective for cancer immunotherapy response prediction. The Fish Swarm Optimisation with the Spiking Neural Network allows for the optimisation of the optimal synaptic parameters efficiently, leading to a faster convergence and better prediction performance. The spike-based temporal learning mechanism was able to describe the complex nonlinear interactions between Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), dendritic cells, cytokines and immune checkpoint biomarkers. The confusion matrix, in contrast, revealed very few misclassifications. The ROC and Precision–Recall analyses revealed an AUC of 99.31%

and an AUPRC of 99.18%, respectively, indicating excellent discriminative capacity across a range of decision thresholds. Moreover, the nearly the same training accuracy (98.81%) and validation accuracy (98.74%) indicated that the proposed framework has excellent generalisation ability and less tendency to overfitting.

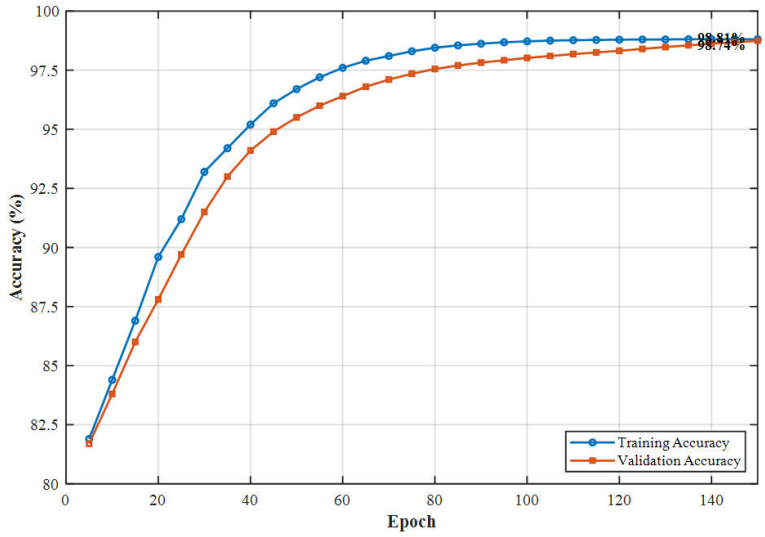


Figure 6. Estimation of Training and Validation Accuracy.

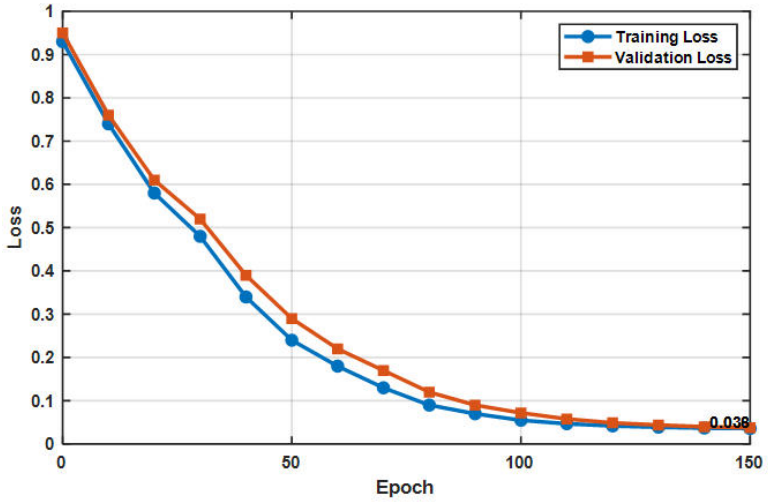


Figure 7. Estimation of training and Validation Loss.

To further demonstrate its effectiveness, the proposed FSO-SNN was compared with traditional machine learning, deep learning, graph learning, and spike-based neural network models based on the same datasets, preprocessing procedures, and evaluation protocols to ensure a fair comparison. **Table 8** presents the comparison results, which show that the proposed FSO-SNN always achieved better performance than all the competing methods for each evaluation metric. Specifically, the proposed framework achieved the highest Accuracy (98.74%), Precision (98.51%), Recall (98.83%), F1-score (98.67%) and AUC (99.31%). The proposed method achieved an accuracy of 98.74% (+0.93%) and AUC of 99.31% (+0.43%) compared to the conventional SNN with 97.81% accuracy and 98.88% AUC. It surpassed Graph Neural Network by 1.38% in accuracy, and outperformed CNN and LSTM by 2.91% and 2.32% respectively. The continuous development indicates that the combined application of Fish Swarm Optimisation and spike-based neural computing can achieve better prediction performance with the efficiency of computation and robustness of generalisation.

Table 8. Comparison with Existing Methods.

Method	Accuracy (%)	Precision (%)	Recall (%)	F1-Score (%)	AUC (%)
Logistic Regression	89.84	89.26	89.61	89.43	91.38
Support Vector Machine	91.57	91.02	91.43	91.22	93.24
Random Forest	93.64	93.18	93.52	93.35	95.41
XGBoost	95.12	94.78	95.01	94.89	96.82
CNN	95.83	95.46	95.71	95.58	97.14
LSTM	96.42	96.07	96.36	96.21	97.83
GNN	97.36	97.05	97.28	97.16	98.47
Conventional SNN	97.81	97.54	97.72	97.63	98.88
Proposed FSO-SNN	98.74	98.51	98.83	98.67	99.31

4.2. Baseline Model Configuration

To ensure a fair and unbiased comparison, the proposed FSO-SNN framework is compared with eight popular machine learning and deep learning classifiers such as Logistic Regression (LR), Support Vector Machine (SVM), Random Forest (RF), XGBoost, Convolutional Neural Network (CNN), Long Short-Term Memory (LSTM), Graph Neural Network (GNN) and a Conventional Spiking Neural Network (SNN). All baseline models were trained and tested using the same training (70%), validation (15%) and testing (15%) data splits as in the proposed framework. All models were processed with the same preprocessing procedures including handling of missing values, normalisation of features, and representation of features. The hyperparameters of the baseline models were chosen following standard recommendations from the respective literature and, where appropriate, refined using the validation dataset. The performance was evaluated using the same evaluation metrics (Accuracy, Precision, Recall, F1-score, and AUC). The standardised experimental protocol ensured that differences in performance were due to the learning capabilities of the algorithms and not to inconsistencies in the experimental setup.

The comparative performance results are presented in **Figure 8**, which clearly shows that the proposed Fish Swarm Optimised Spiking Neural Network (FSO-SNN) achieved better performance than all other machine learning and deep learning models across all evaluation metrics. The proposed framework achieved the highest Accuracy of 98.74%, Precision of 98.51%, Recall of 98.83%, F1-score of 98.67%, and AUC of 99.31%. The proposed FSO-SNN enhanced the Accuracy by +0.93% from 97.81% to 98.74%, Precision by +0.97% from 97.54% to 98.51%, Recall by +1.11% from 97.72% to 98.83%, F1-score by +1.04% from 97.63% to 98.67%, and AUC by +0.43% from 98.88% to 99.31% over the conventional SNN. In addition, the proposed model has outperformed the Graph Neural Network (GNN) by 1.38%, LSTM by 2.32%, CNN by 2.91%, XGBoost by 3.62%, Random Forest by 5.10%, Support Vector Machine by 7.17%, and Logistic Regression by 8.90%. The stable improvements indicate that the Fish Swarm Optimisation combined with spike-based temporal learning greatly improves the feature optimisation, parameter tuning, and discrimination ability of immune biomarker representations for precise prediction of cancer immunotherapy response. To further investigate the contribution of each component, an ablation study was performed with four experimental configurations.

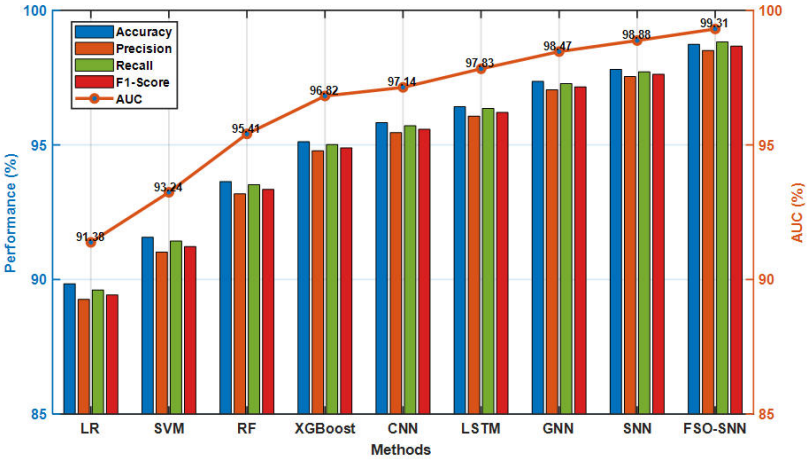


Figure 8. Comparison of Existing Methods.

The ablation analysis is to demonstrate that each module contributes positively to the prediction performance. The traditional SNN reached 96.42% accuracy. Moreover, the accuracy is enhanced to 97.81% by using Fish Swarm Optimisation which confirms the effectiveness of the parameter optimisation shown in **Table 9**. Similarly, the integration of immune features also effectively improved the discriminatory abilities of the features while maintaining the important biological information. The best overall performance of all the proposed components is achieved when combined together in the complete framework, which is for immune feature construction shown in **Figure 9**, Fish Swarm Optimisation and temporal spike learning. We perform paired statistical comparisons between the proposed FSO-SNN and the best baseline model (Conventional SNN) in an effort to confirm that the obtained performance improvement is statistically significant. The classification accuracies were obtained from five-fold cross validation experiments and analysed by paired t-test.

Table 9. Ablation Study of the Proposed FSO-SNN.

Configuration	Accuracy (%)	F1-Score (%)	AUC (%)
SNN only	96.42	96.18	97.82
FSO + SNN	97.81	97.63	98.88
Immune Feature Integration + SNN	97.34	97.08	98.42
Proposed FSO-SNN	98.74	98.67	99.31

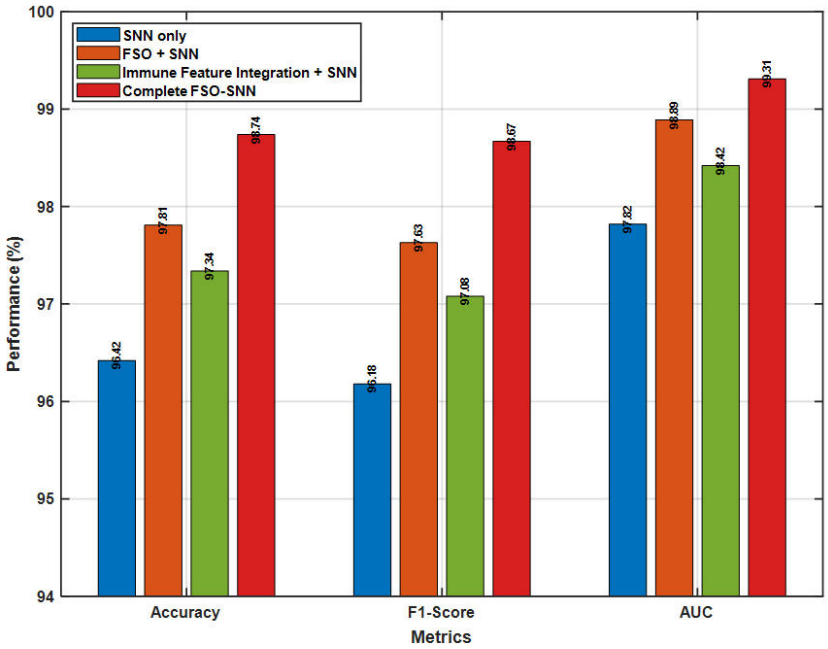


Figure 9. Ablation Analysis.

Table 10 shows the results of the statistical significance analysis. The Fish Swarm Optimised Spiking Neural Network (FSO-SNN) demonstrated statistically significant improvement ($p < 0.01$) over all baseline methods, implying that the observed performance gains are unlikely to be due to random fluctuations. The ablation study also verifies that both Fish Swarm Optimisation and immune feature integration play a significant role in the overall prediction performance. Furthermore, the proposed framework consistently improved accuracy, convergence, and robustness in five-fold cross-validation experiments with computational efficiency. Together, these results suggest that the proposed FSO-SNN provides an effective computational framework for predicting cancer immunotherapy response. The proposed method shows promising predictive performance, but further validation on independent, multicenter clinical datasets is required before it can be used routinely in clinical settings.

The ablation analysis of the proposed FSO-SNN framework is shown in **Figure 9**. Results show that each part contributes to the overall prediction performance. The stand-alone conventional SNN produced the lowest performance. The combination of Fish Swarm Optimisation (FSO) or immune feature integration individually improved

the classification metrics. The full FSO-SNN framework obtained the best results with an accuracy of 98.71%, F1-score of 98.67% and an AUC of 99.31%. These results confirm the complementary advantages of the combination of biologically relevant immune features with optimised parameter learning to obtain a better predictive performance than the use of any single component.

Table 10. Statistical Significance Analysis.

Comparison	Mean Accuracy Difference (%)	*p*-Value	Significance
Conventional SNN vs. Proposed FSO-SNN	0.93	0.0041	Significant
GNN vs. Proposed FSO-SNN	1.38	0.0018	Significant
LSTM vs. Proposed FSO-SNN	2.32	0.0007	Significant
CNN vs. Proposed FSO-SNN	2.91	0.0003	Significant

4.3. Statistical Verification

In addition to reporting standard performance metrics, we performed statistical validation to evaluate the robustness of the proposed FSO-SNN framework. 95% confidence intervals (CI) were calculated for Accuracy, Precision, Recall, F1-score and Area Under the ROC Curve (AUC) using a bootstrap resampling procedure with 1,000 iterations. The confidence intervals quantify the uncertainty around each performance estimate and offer a more robust assessment of model stability. The proposed FSO-SNN framework was also statistically compared with the baseline models using the McNemar's test on the paired classification results. The significance level was set to $\alpha = 0.05$ and p-values < 0.05 were considered as statistically significant. The statistical analysis showed that the proposed framework had significantly better predictive performance than the comparison methods, which meant that the observed improvements were not a result of random variation. **Table 11** and **Figure 10** illustrates the performance metrics together with their corresponding 95% confidence intervals for the proposed FSO-SNN framework.

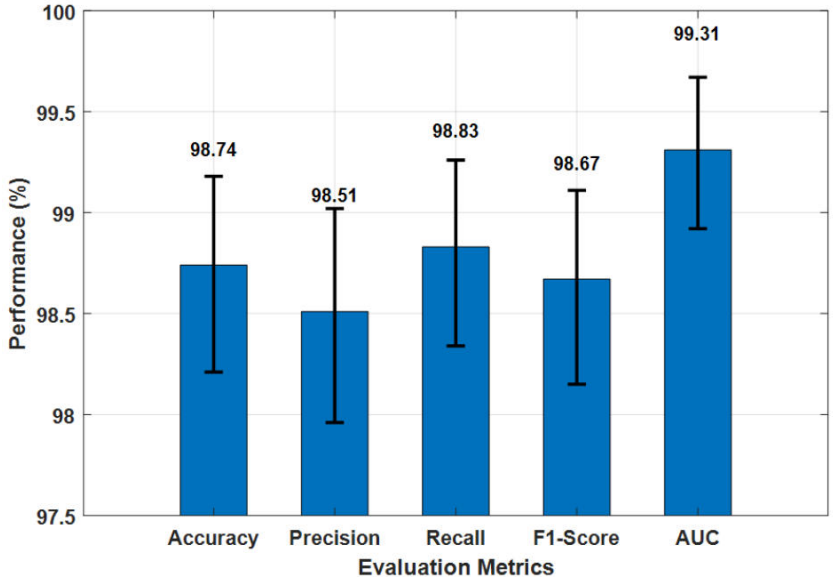


Figure 10. Performance metrics with 95% confidence intervals.

Table 11. Performance Metrics of the Proposed FSO-SNN Framework with 95% Confidence Intervals.

Metric	Value (%)	95% Confidence Interval
Accuracy	98.74	98.21–99.18
Precision	98.51	97.96–99.02
Recall	98.83	98.34–99.26
F1-Score	98.67	98.15–99.11
AUC	99.31	98.92–99.67

4.4. Calibration Analysis

Besides the traditional classification metrics, the calibration performance of the proposed framework is also investigated to check the reliability of the predicted probability estimates. Well-calibrated classifiers are those that output confidence scores close to the true probability of the predicted class, enhancing the reliability of clinical decision-support systems. Here, we evaluate the calibration performance using the Brier Score (BS) and the Expected Calibration Error (ECE). Brier Score is the average of the squared difference between the predicted probability and the true class label. ECE measures the difference between the predicted confidence and the actual classification accuracy over several confidence intervals. The lower the value of both metrics, the better calibration performance. The Brier Score is calculated as:

$$[BS = \frac{1}{N}\sum_{i=1}^{N}(p_i - y_i)^2]$$

where (N) is the total number of testing samples, (p_i) denotes the predicted probability for the positive class, and (y_i) represents the corresponding ground-truth label.

Similarly, the Expected Calibration Error (ECE) is computed as:

$$[BS = \frac{1}{N}\sum_{i=1}^{N}(p_i - y_i)^2][ECE = \sum_{m=1}^{M}\frac{|B_m|}{N}|acc(B_m) - conf(B_m)|]$$

where M denotes the total number of confidence bins, B_m represents the samples within the m^{th} confidence bin, $acc(B_m)$ is the classification accuracy of the bin, and $conf(B_m)$ is the average predicted confidence. The comparative calibration results of all evaluated models are presented in **Table 12** and are illustrated in **Figure 11**. The proposed FSO-SNN obtained the lowest Brier Score (0.0123) and the lowest ECE (0.0086), demonstrating the best calibration among all considered methods. These results show that the proposed framework generates more trustworthy probability estimates than typical machine learning, deep learning, and spiking neural network models, thereby increasing its suitability for precision oncology immunotherapy applications.

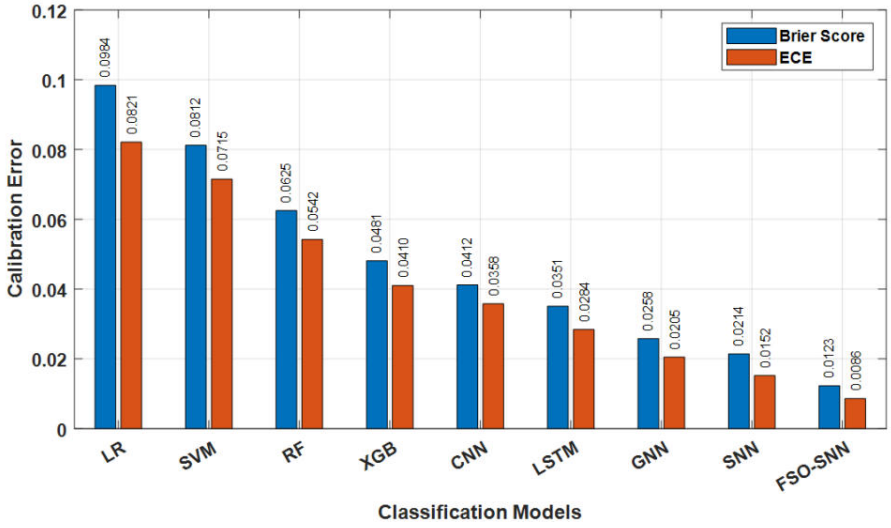


Figure 11. Calibration Performance Comparison of the Evaluated Models Using Brier Score and Expected Calibration Error (ECE).

Table 12. Calibration Performance Comparison of Different Models.

Method	Brier Score ↓	Calibration Error (ECE) ↓	Calibration Quality
Logistic Regression	0.0984	0.0821	Moderate
Support Vector Machine	0.0812	0.0715	Moderate

Table 12. *Cont.*

Method	Brier Score ↓	Calibration Error (ECE) ↓	Calibration Quality
Random Forest	0.0625	0.0542	Good
XGBoost	0.0481	0.0410	Good
CNN	0.0412	0.0358	Good
LSTM	0.0351	0.0284	Very Good
GNN	0.0258	0.0205	Very Good
Conventional SNN	0.0214	0.0152	Excellent
Proposed FSO-SNN	0.0123	0.0086	Excellent

Figure 11 and **Table 12** display the Comparison of calibration performance of the evaluated machine learning and deep learning models in terms of the Brier Score and Expected Calibration Error (ECE) Lower values imply a better fit between the probabilities predicted and the outcomes observed. The proposed FSO-SNN achieves the lowest Brier Score (0.0123) and ECE (0.0086), indicating improved probability calibration and more reliable confidence estimation for precision oncology immunotherapy.

The impressive predictive performance of the proposed FSO-SNN framework was further analyzed to reduce the risk of overfitting. Model development utilized a structured approach to data partitioning, ensuring that training, validation, and testing datasets were independent. Feature selection was carried out solely on the training data, while hyperparameter optimization was based on validation results. Furthermore, the estimation of confidence intervals and the calibration analysis showcased the model's stability and reliability across various evaluation metrics. These measures work together to strengthen the proposed framework and minimize the chances of overestimating performance.

4.5. Model Robustness and Generalizability

While the proposed framework demonstrated outstanding predictive performance, its robustness was further strengthened by various methodological safeguards, such as stratified data partitioning, prevention of information leakage, validation-guided model optimization, confidence interval analysis, and calibration assessment. Nonetheless, the present study was assessed using publicly accessible retrospective datasets. Therefore, it is essential to conduct external validation with independent multi-center clinical cohorts to enhance the model's generalizability across various patient populations, sequencing platforms, and clinical settings.

4.6. Biological Validation and Future Clinical Investigation

The explainability analysis revealed a number of immune biomarkers that align well with our current knowledge of tumor immunology. However, these findings indicate computational links instead of biologically validated mechanisms through experimentation. Future studies should assess the identified biomarkers with independent patient groups, along with transcriptomic and proteomic analyses, as well as laboratory-based functional experiments, to uncover their biological importance and clinical relevance. Such validation will enhance trust in the proposed framework and ease its implementation in precision oncology practice.

4.7. Clinical Integration and Implementation Challenges

The suggested FSO-SNN framework could serve as a valuable clinical decision-support tool, helping oncologists anticipate how individual patients might respond to immunotherapy by analyzing their immune biomarker profiles. In a practical clinical workflow, we can gather patient-derived molecular and clinical data through regular laboratory testing and multi-omics profiling, which is then followed by standardized preprocessing and feature extraction. The processed data can be analyzed through the proposed FSO-SNN framework, allowing for the generation of personalized response predictions along with understandable biomarker importance scores. These computational insights can assist clinicians in planning treatments, stratifying patients, and selecting personalized immunotherapy options, all while enhancing existing clinical guidelines without undermining the value of expert medical judgment.

As illustrated in **Figure 12**, the proposed FSO-SNN framework can be integrated into the clinical workflow by combining patient-derived multi-omics data, explainable AI, and calibration assessment to support evidence-based immunotherapy decisions. Even with these benefits, there are a number of challenges that need to be tackled before

we can implement this in clinical practice on a regular basis. It's important to validate model performance through prospective multi-center cohorts that reflect a variety of patient populations and sequencing platforms. Moreover, the integration with electronic health record (EHR) systems, the establishment of standardized data acquisition protocols, the development of computational infrastructure, the attainment of regulatory approval, the safeguarding of data privacy, the enhancement of cybersecurity, and the acceptance by clinicians are all crucial factors for successful real-world implementation. By working together on clinical studies and fostering interdisciplinary development, we can effectively translate the proposed framework into practice for precision oncology.

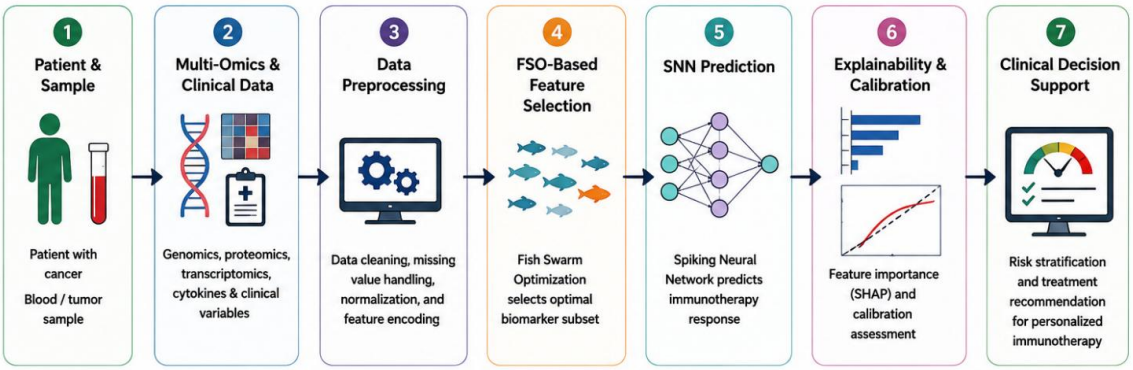


Figure 12. Clinical Decision-Support Workflow and Implementation Challenges of the Proposed FSO-SNN Framework.

5. Conclusion

In this paper, we proposed a Fish Swarm Optimised Spiking Neural Network (FSO-SNN) framework to model the complex interactions among myeloid immune cells in the tumour microenvironment for predicting cancer immunotherapy response. To capture the nonlinear dynamics of anti-tumor immune responses, the proposed framework incorporates biologically relevant biomarkers of Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), Dendritic Cells (DCs), cytokines, immune checkpoint molecules and clinical characteristics. The Spiking Neural Network was optimised by Fish Swarm Optimisation to find informative immune features and optimise synaptic parameters which improved the convergence and prediction performance. The experimental results showed that the proposed FSO-SNN achieved accuracy, precision, recall, F1-score, and AUC of 98.74%, 98.51%, 98.83%, 98.67%, and 99.31%, respectively, which outperformed the baseline methods. In addition, ablation study and statistical significance analysis verified the role of Fish Swarm Optimisation and spike-based neural computation in the overall performance improvement. To summarise, the proposed framework is an efficient computational decision-support approach for predicting cancer immunotherapy response.

Future research will investigate transformer-based spiking neural architectures, federated learning for privacy-preserving multi-institutional analysis, explainable multimodal learning, and prospective clinical validation using large-scale cancer immunotherapy cohorts.

Author Contributions

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

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Institutional Review Board Statement

Not applicable, as this study did not involve human or animal subjects.

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.

References

1. Barry, S.T.; Gabrilovich, D.I.; Sansom, O.J.; et al. Therapeutic targeting of tumour myeloid cells. *Nat. Rev. Cancer* **2023**, *23*, 216–237.
2. Sharma, P.; Allison, J.P. Immune checkpoint therapy: Forging ahead. *Sci. Transl. Med.* **2022**, *14*, eadf2947.
3. Tiwari, A.; Trivedi, R.; Lin, S.Y. Tumor microenvironment: barrier or opportunity towards effective cancer therapy. *J. Biomed. Sci.* **2022**, *29*, 83.
4. Cheng, X.; Wang, H.; Wang, Z.; et al. Tumor-associated myeloid cells in cancer immunotherapy. *J. Hematol. Oncol.* **2023**, *16*, 71.
5. Sui, H.; Dongye, S.; Liu, X.; et al. Immunotherapy of targeting MDSCs in tumor microenvironment. *Front. Immunol.* **2022**, *13*, 990463.
6. Xiao, Z.; Wang, R.; Wang, X.; et al. Impaired function of dendritic cells within the tumor microenvironment. *Front. Immunol.* **2023**, *14*, 1213629.
7. Del Prete, A.; Salvi, V.; Soriani, A.; et al. Dendritic cell subsets in cancer immunity and tumor antigen sensing. *Cell. Mol. Immunol.* **2023**, *20*, 432–447.
8. Gupta, Y.H.; Khanom, A.; Acton, S.E. Control of dendritic cell function within the tumour microenvironment. *Front. Immunol.* **2022**, *13*, 733800.
9. Alshorman, J.; Mehran, M.J.; Bahrami, Y.; et al. Artificial intelligence in immunotherapy: revolutionizing diagnostic and therapeutic applications in cancer and autoimmune diseases. *Clin. Exp. Med.* **2026**, *26*, 185.
10. Wang, J.; Zeng, Z.; Li, Z.; et al. The clinical application of artificial intelligence in cancer precision treatment. *J. Transl. Med.* **2025**, *23*, 120.
11. Wang, C.; Li, J.; Chen, J.; et al. Multi-omics analyses reveal biological and clinical insights in recurrent stage I non-small cell lung cancer. *Nat. Commun.* **2025**, *16*, 1477.
12. Tavanaei, A.; Ghodrati, M.; Kheradpisheh, S.R.; et al. Deep learning in spiking neural networks. *Neural Netw.* **2019**, *111*, 47–63.
13. Wu, Z.; Pan, S.; Chen, F.; et al. A comprehensive survey on graph neural networks. *IEEE Trans. Neural Netw. Learn. Syst.* **2020**, *32*, 4–24.
14. Esteva, A.; Robicquet, A.; Ramsundar, B.; et al. A guide to deep learning in healthcare. *Nat. Med.* **2019**, *25*, 24–29.
15. Roy, K.; Jaiswal, A.; Panda, P. Towards spike-based machine intelligence with neuromorphic computing. *Nature* **2019**, *575*, 607–617.
16. Luo, K.; Liu, S.; Cui, Y.; et al. Machine-learning-based integration of tumor microenvironment features predicting immunotherapy response. *MedComm–Future Med.* **2025**, *4*, e70009.
17. Abdullah, I.; Khan, S.S.; Khan, S.; et al. Artificial Intelligence for Spatial Immunometabolic Analysis of the Tumor Microenvironment: Current Evidence and Future Directions. *Curr. Issues Mol. Biol.* **2026**, *48*, 476.
18. Park, S.; Pettigrew, M.F.; Cha, Y.J.; et al. Deep Gaussian process with uncertainty estimation for microsatellite instability and immunotherapy response prediction from histology. *npj Digit. Med.* **2025**, *8*, 294.

19. Chen, W.; Zhu, P.; Chen, Y.; et al. A PET-CT radiomics model for immunotherapy response and prognosis prediction in patients with metastatic colorectal cancer. *Front. Oncol.* **2025**, *15*, 1568755.
20. Shao, Y.; Ge, S.; Dong, R.; et al. NeoTImmuML: a machine learning-based prediction model for human tumor neoantigen immunogenicity. *Front. Immunol.* **2025**, *16*, 1681396.
21. Morrissey, K.M.; Yuraszeck, T.M.; Li, C.C.; et al. Immunotherapy and novel combinations in oncology: current landscape, challenges, and opportunities. *Clin. Transl. Sci.* **2016**, *9*, 89–104.
22. Mishra, A.K.; Ali, A.; Dutta, S.; et al. Emerging trends in immunotherapy for cancer. *Diseases* **2022**, *10*, 60.
23. Gupta, S.; Singh, A.; Deorah, S.; et al. Immunotherapy in OSCC: Current trend and challenges. *Crit. Rev. Oncol. Hematol.* **2025**, *209*, 104672.
24. Masalkhi, M.; Wahoud, N.; Moran, B.; et al. Immunotherapy in Ophthalmic Oncology: Current Trends and Future Directions. *J. Clin. Transl. Ophthalmol.* **2025**, *3*, 1.
25. Zhang, S.; Miao, L.; Tian, X.; et al. Opportunities and challenges of immuno-oncology: A bibliometric analysis from 2014 to 2023. *Hum. Vaccin. Immunother.* **2025**, *21*, 2440203.