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Hybrid feature selection and classification model using high-dimensional data based on a metaheuristic algorithm for brain cancer diagnosis

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Abstract. Cancer is caused by somatic mutations, a dreadful disease that impacts individuals everywhere. Classifying gene expression data is essential for disease diagnosis and distinguishing tumor types. However, small sample sizes, numerous features, and noise make this task particularly challenging. This is especially true when performing feature selection on high-dimensional microarray data. It is critical to select the most pertinent and valuable genes from microarray data to identify prospective biomarkers or gain insight into the fundamental mechanisms of cancer. This study introduces a novel hybrid model that combines feature selection and classification to identify the most significant and informative features from microarray data associated with brain cancer. The research employs the GSE50161 dataset obtained from the Curated Microarray Database (CuMiDa), comprising 130 samples classified into five distinct categories with 54,676 genomes examined. We first applied mRMR to reduce dimensionality by removing redundant features, followed by HHO to refine the feature subset for optimal classification performance. To improve the performance of our model in classifying brain cancer microarray data, we utilized three metaheuristic algorithms: Differential Evolution (DE), Harris Hawks Optimization (HHO), and Particle Swarm Optimization (PSO). The hyperparameters "C" and "sigma" of the support vector machine (SVM) were optimized using these algorithms. The experimental results indicate that the suggested framework improves the capacity to differentiate between benign and malignant tissues with reduced time and dimensionality requirements. Furthermore, the genes selected for the dataset on brain cancer have undergone

biological interpretation. This process is consistent with the findings of relevant scientific inquiries and significantly influences patients' prognoses.

Keywords: feature selection-classification- optimization- metaheuristic algorithms - Harris Hawks optimization (HHO) - Particle Swarm Optimization (PSO) - support vector machine (SVM)

1. Introduction

Cancer is a prominent contributor to global mortality, resulting in approximately ten million fatalities by 2020, or approximately one in every six deaths [1]. Brain tumors account for a significant proportion of fatalities among humans. A neglected or erroneous diagnosis may sometimes deprive patients of their optimal opportunity to receive the appropriate treatment [2]. As a result, additional ancillary measurements are necessary to enhance the accuracy of clinical tests and cancer diagnosis when performed in conjunction with medical procedures [3],[4]. Gene expression measures the degree of genetic activity within a specific anatomical cell. Particular genes can become active (switch on) or inactive (switch off) in response to the conditions and demands of the cells in the body at any given moment [5]. The generation process of high-throughput gene expression data is illustrated in Figure 1. Regrettably, the microarray dataset has several disadvantages: irrelevant genes and noise, a small sample size, and the curse of dimensionality [6]. These factors collectively exacerbate the challenge of accurately classifying a specific sample. The objective of the gene selection procedure is to select the minimum number of pertinent and interrelated genes that can be more precisely classified. A precise categorization is contingent upon extracting a subset of informative genes, excluding redundant or irrelevant genes, and identifying the cancer-causing mechanism at its core.

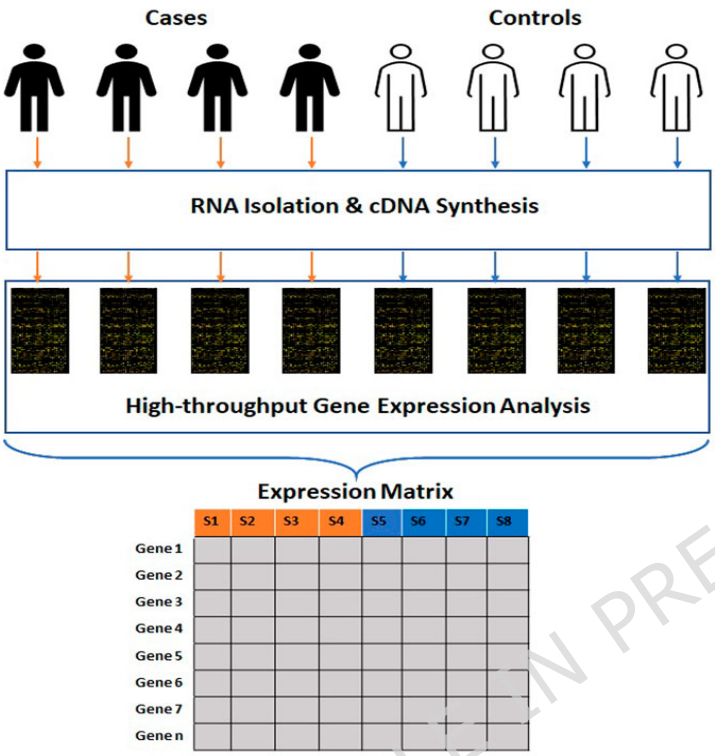

Figure 1. Process of generation of high-throughput gene expression data [7]

It may aid biologists in developing more productive diagnostic techniques or identifying more successful therapeutic interventions [8]. Feature selection has become a pivotal aspect of bioinformatics, especially for high-dimensional datasets. Saeys et al. (2007) provide a comprehensive review of feature selection techniques, emphasizing the importance of cross-validation in validating the selection process and mitigating the risk of overfitting [9]. Varma and Simon (2006) further highlight potential biases introduced during error estimation when cross-validation is improperly applied, reinforcing the need for meticulous implementation to ensure accurate model evaluation [10]. Feng et al. (2020) analyze the wrapper framework for feature selection, underscoring the critical role of cross-validation in identifying optimal feature subsets that enhance model performance in complex bioinformatics tasks [11]. Zhang et al. (2022) contribute to this discussion by reviewing contemporary strategies for feature selection, emphasizing the necessity of cross-validation in ensuring the stability

and relevance of selected features for developing reliable predictive models [12]. Chandrashekar and Sahin (2014) reiterate the importance of cross-validation in improving model performance and preventing overfitting, providing broader insights into various feature selection techniques and their implications for bioinformatics research [13]. A hybrid feature selection and classification model for the diagnosis of brain cancer [14] is presented in this article. The HHO-MRMR model was proposed to identify the most pertinent and enlightening genes (features) associated with brain cancer. The optimal subset of features (genes) is selected using the Harris Hawks optimization algorithm (HHO) [15] as a wrapper method. The Minimum Redundancy (mRMR) filter method reduces redundancy among chosen features and determines a subset of exceptionally pertinent features to the target variable [16]. To assess the proposed model using the selected subset features, four distinct classifier types are implemented: Decision Tree (DT) [17], Random Forest (RF) [18], Naive Bayes (NB) [19], and Support Vector Machine (SVM) [20]. To improve the efficacy of support vector machines (SVM) in the classification of brain cancer gene expression data and enhance the performance and precision of the HHO-MRMR model, the two hyper-parameters of SVM "C" and "sigma" are tuned utilizing three metaheuristic optimization algorithms [21]: practical swarm optimization (PSO), Harris Hawks Optimization (HHO), and Differential Evolution (DE) [22]. Furthermore, an enhanced Teaching Learning-Based Optimization (TLBO) algorithm incorporating chaotic maps has been introduced to address large-scale global optimization challenges [23]. This improved TLBO, which integrates chaotic sequences to enhance exploration and exploitation balance, has shown superior performance on benchmark optimization functions and practical applications [24]. Additionally, a multi-layer hybrid credit scoring model that integrates feature selection, ensemble learning, and ensemble classifiers has been proposed, demonstrating improved predictive performance, accuracy, and robustness in credit risk assessment using real-world datasets [25].

Moreover, a hybrid model combining Teaching-Learning-Based Optimization (TLBO) and Genetic Algorithms (GA) has been developed for simultaneous feature selection and parameter optimization in breast cancer diagnosis, achieving high classification performance and reducing computational complexity [26]. Lastly, a novel hybrid optimization strategy that combines TLBO with the Gravitational Search Algorithm (GSA) for solving both constrained and unconstrained engineering optimization problems has been introduced, showing significant improvements in convergence speed and solution quality [27]. The TLBO method primarily focuses on optimizing a single objective function without a specific built-in structure for feature

selection. While it can be applied for feature selection, it does not inherently prioritize biological relevance or redundancy as effectively as mRMR. The proposed model explicitly incorporates a robust feature selection process that not only aims to minimize redundancy but also maximizes relevance to the classification task. This dual focus allows for a more comprehensive approach to identifying significant biomarkers in brain cancer microarray data. These integrated approaches provide valuable tools for diagnostic and therapeutic advancements, enhancing the accuracy and efficiency of various medical and engineering applications.

The assessment of our model demonstrates that it exhibits exceptional performance, effectively identifying the most informative gene associated with the target class while simultaneously decreasing time complexity and high dimensionality.

This paper's main contributions are as follows:

1. The proposed HHO-MRMR model was developed to ensure that the genes selected are optimal and informative genes that can be biologically interpreted.
2. A two-stage feature selection pipeline: mRMR for dimensionality reduction followed by HHO for subset refinement, aimed at improving classification performance.
3. A comparative evaluation using three metaheuristic optimizers (DE, HHO, PSO) to tune SVM hyperparameters, demonstrating performance gains and reduced computational time.
4. Biological interpretation of selected genes and alignment with existing literature, underscoring potential clinical relevance

The paper's organization is as follows: Section 2 contains a literature review, Section 3 describes the procedures used in detail, Section 4 presents the proposed model, Section 5 delves into the experimental findings based on publicly available cancer microarray datasets, Section 6 presents the results and discussion, Section 7 discusses the biological interpretation of brain cancer, and Section 8 provides the conclusion.

2. Literature review

There has been a notable surge in the utilization of machine-learning methodologies to classify cancer microarray datasets in recent years [28]. Through the utilization of microarray datasets containing gene

expressions, a cancer diagnosis could potentially be enhanced. A synopsis of recent advancements in high-dimensional data analysis will be presented in this section. The hybrid ReliefF-CNN approach was first proposed by Kilicarslan et al. [29] to diagnose diseases utilizing microarray datasets encompassing commonly occurring cancer types worldwide. Furthermore, many analyses were conducted to contrast the effectiveness of classification and dimension reduction. Upon comparing the experimental results with those of various alternative methods, it was determined that the classification accuracy of the hybrid ReliefF-CNN approach was the highest. Elemam et al. [30] generated a resilient machine learning (ML) algorithm for diagnosing various cancer diseases using microarray datasets. The algorithm incorporates two phases of hybrid feature selection. In the preliminary stage, the system integrates the results from three feature evaluation methods based on filters: chi-squared, F-statistic, and mutual information. The optimal feature subset is identified during the second stage by implementing modified wrapper-based sequential forward selection. Furthermore, the accuracy of the results generated by the proposed algorithm was enhanced, while the quantity of DNA selectors was reduced. Qaraad et al. [31] suggested a hybrid feature selection and optimization technique for classifying high-dimensional microarray data. When SVM was employed as the classifier, the model performed better after including Elastic Net as a gene selection strategy and combining three unique optimizer strategies to fine-tune the EN's parameter alpha. Regarding AUC, specificity, and sensitivity, the suggested ENSVM model beat the SVM (RBF) Kernel RS-SVM and SSD-SVM models. Ali et al. [32] proposed a hybrid approach that combines filter feature selection methods with a GA-based feature selection method. To reduce the dimensionality of the microarray datasets, the initial step involved selecting the top 5% of features using information gain, gain ratio, and Chi-squared. During this stage, redundant and superfluous characteristics were eliminated. The performance of the proposed hybrid filter-GA feature selection methods was significantly better than that of the standalone classifiers or the filter algorithms considered in isolation. Debata et al. [33] described the utilization of an improvised chaotic Jaya (CJaya) algorithm-optimized convolutional neural network (CJaya-CNN) model for the classification of high-dimensional gene expression or microarray data. Significant genes were isolated using the kernel-based Fisher score (KFS) method. An improvised chaotic Jaya (CJaya) algorithm was employed to classify four sets of high-dimensional microarray data to optimize the CJaya-CNN model. Utilizing the KFS procedure, exceptionally efficient genes were isolated. The presented KFS-based CJaya-CNN model exhibited a

classification accuracy of 99.87% across four datasets: SRBCT, leukemia, lymphoma-3, and colon cancer. Saeid et al. (25) presented a feature selection methodology that utilized a discrete wavelet transform (DWT) and a modified genetic algorithm to determine the most important and relevant features for microarray cancer classification [34]. The findings derived from this research were, on average, more advantageous than the classification methodologies presently in use. Passi et al. [35] classified cancer using five microarray cancer datasets and proposed feature selection methods based on Markov blanket and wrapper models. A noteworthy enhancement in precision was detected when contrasting the experimental results with traditional classification techniques applied to cancer microarray datasets [36]. It is Pashaei et al. Incorporating simulated annealing, a hybrid binary COOT algorithm is proposed for feature selection in high-dimensional microarray data. Utilized algorithms consist of BCOOT, BCOOT-C, and BCOOT-CSA. In the initial approach, the continuous variant of the COOT algorithm is transformed into binary using a hyperbolic tangent transfer function. By incorporating a crossover operator (C), the second approach improves the global search capability of the BCOOT algorithm. The third methodology integrates simulated annealing (SA) with BCOOT-C to augment the algorithm's local exploitation capability, thus enabling reliable and resilient informative gene detection. The experimental results demonstrate that the BCOOT-CSA method consistently achieves superior prediction accuracy and the number of selected genes, superseding both BCOOT and BCOOT-C. Yaqoob et al. [37] present the Sine Cosine and Cuckoo Search Algorithm (SCACSA), a novel methodology for gene selection. The hybrid approach is compatible with the Support Vector Machine (SVM), an extensively utilized machine learning classifier. A thorough assessment is undertaken to evaluate the hybrid gene selection algorithm compared to alternative feature selection methods using a dataset about breast cancer. The initial step is to implement a filtration strategy called minimum redundancy maximum relevance (mRMR) to enhance the quality of the feature set. The process of selecting genes is consequently improved and optimized by utilizing the hybrid SCACSA method. The outcomes of the experiments demonstrate that SCACSA is an invaluable tool for classifying cancer datasets. To enhance the efficiency of the feature selection model known as the Least Absolute Shrinkage and Selection Operator (Lasso), Vatankhah et al. [38] have developed an innovative approach. The optimal regularization parameter was determined autonomously by employing a novel regularization technique, ensuring that the Lasso would perform optimally when classifying DNA microarray data. Four widely

recognized microarray datasets that were accessible to the public were employed in the experiment. These datasets comprised leukemia, breast cancer, diffuse large B-cell lymphoma (DLBCL), and prostate cancer. The datasets were employed to assess the proposed methodologies. The experimental findings revealed that the Lasso feature selection method, as proposed, exhibited superior performance compared to established feature selection methods in terms of features generating the most precise classifications, robustness, and stability when applied to microarray data. Shiny et al. [39] introduce an optimization-driven MRI-based brain tumor classification classifier. The preoperative and postoperative MRIs utilized in this investigation undergo preprocessing via filtration and extraction of regions of interest (RoI). The segmentation procedure receives the preprocessed output and modifies the U-Net model to produce the segments. Following training using the proposed Poor Bird Swarm Optimization algorithm (PRBSA), U-Net employs feature extraction from the histogram to classify tumors. The Bird Swarm Algorithm (BSA) and Poor and Rich Optimization (PRO) are combined in PRBSA. In the final analysis, pixel change detection is performed on the classified output using accelerated robust features (SURF). The proposed PRBSA-based U-Net demonstrated improved performance, attaining a peak accuracy of 94%, a sensitivity of 93.7%, and a specificity of 94%. Feature selection and classification in gene expression analyses continue to benefit from hybrid and ensemble approaches. Uzma et al. [62] present a deep learning–driven feature selection method designed for large gene expression matrices, while Zahid Halim et al. [64] advance ensemble-filter strategies for cancer classification, underscoring the value of integrating diverse feature-selection techniques to improve robustness.

Several computational predictors have advanced brain cancer biomarker discovery and classification from high-dimensional omics data. Notable approaches include DeepAIPs-Pred, TargetCLP, SBSM-Pro, DeepAIPs-SFLA, pACP- HybDeep, and PNPS-CAPSNET, which collectively explore deep learning, metaheuristic-driven feature selection, and hybrid architectures to improve predictive performance and interpretability. DeepAIPs-Pred and DeepAIPs-SFLA leverage deep neural networks with adaptive feature extraction and swarm/selection dynamics, respectively, to handle complex gene-expression patterns. TargetCLP and SBSM-Pro emphasize ensemble and pathway-aware representations to enhance robustness across heterogeneous datasets.

pACP-HybDeep combines probabilistic modeling with hybrid optimization to balance accuracy and computational efficiency, while PNPS-CAPSNET integrates cascaded networks with neighborhood-structured priors to exploit relational gene information. While these methods report promising benchmarks on diverse transcriptomic and microarray datasets, their data requirements, interpretability, and computational demands vary considerably. Our hybrid feature-selection–classification framework complements these advancements by explicitly combining mRMR-driven dimensionality reduction with a metaheuristic-augmented classifier (DE/HHO/PSO) to optimize SVM hyperparameters, ensure tractable feature subsets, and maintain interpretability through gene-level annotations. Compared with the cited predictors, our approach emphasizes transparent feature ranking, scalable computation on high-dimensional data, and robust generalization across cross-validation folds and independent cohorts.

While metaheuristic algorithms have been employed to select features in microarray datasets for cancer classification, their potential as filter or wrapper feature selection methods in microarray datasets remains an area of research that has received limited attention in recent studies. Additionally, additional research is required to investigate various microarray datasets to investigate hybridizations and combinations of filter methods and metaheuristic algorithms.

3. Background

Feature subset, which is alternatively referred to as gene subset collection, no longer disregards redundant or crucial characteristics. This is occasionally an NP-hard problem (NP-hard refers to nondeterministic polynomial time). [40] By Occam's razor, the selected subset of attributes should maximize the value of any given objective function. Three distinct categories of feature selection algorithms exist [41]. In our proposed methodology, we utilized a hybrid feature selection approach that combines the following two methods:

4.1 The wrappers method

The wrappers method determines which features are valuable using machine learning techniques. Wrappers excel at feature selection because they evaluate and simulate the feature space while considering the model hypothesis. As wrapper methods, metaheuristic algorithms can traverse the space of potential feature subsets to identify an optimal or nearly optimal set of features [42]. Metaheuristic algorithms are optimization techniques that directly search for solutions in vast, complex spaces [43]. Although wrapper methods are typically more

computationally intensive than filter methods, they have the potential to identify feature subsets that are more complex and context-dependent. The efficacy of a wrapper method is significantly influenced by the caliber of the selected evaluation metric and the metaheuristic algorithm's efficiency in traversing the space of feature subsets [44]. HHO is implemented as a wrapper feature selection method in our model. In the context of feature selection, HHO searches iteratively for the optimal subset of features that maximizes the performance of a specific machine-learning model. This is accomplished by simulating the competition and cooperation observed during hunting among raptors. The HHO algorithm iteratively selects and refines subsets of features to determine which set provides the most informative information for the given task.

4.2 The Filter method

The filter method extracts features from data without prior knowledge and operates independently of the classifier. Consequently, they exhibit remarkable efficiency in computation [45]. As a multivariate, mRMR is employed to identify features exceptionally pertinent to the objective variable [46]. The relevance of each feature to the aim variable is assessed through the utilization of a scoring criterion. To promote diversity in the selected feature set, mRMR considers feature redundancy. mRMR attempts to reduce the amount of redundant information carried by redundant features by selecting complementary features.

Objective Function of mRMR: An objective function that incorporates the relevance and redundancy ratings for each feature is typically employed by the mRMR algorithm. The simultaneous aim is to optimize the degree of relevance while minimizing redundancy. The mRMR objective function can be mathematically expressed in its general form as follows [47]:

$$\text{mRMR}(s) = \frac{1}{k}\sum_{i=1}^{k}[D(f_i) - R(f_i,S)] \quad (1)$$

Here:

- *S is the set of selected features.*
- *K is the total number of selected features.*
- f_i repersentes the i^{th} selected features.
- $D(f_i)$ is a measure of therelevance of the featuref,with resepeact to the target variable.
- $R(f_i,S)$ is a measure of the redundancy of the feature f,with respect to the already seleceted features in s

After computing the scores for all features, they are ranked based on their mRMR scores. The top-ranked features are considered more relevant and less redundant.

Top-k Features Selection: Finally, a specified number (k) of top-ranked features are selected as the final subset for training a machine learning model.

$$\max_{S}\left[\frac{1}{|S|}\sum_{g_i\in S} I(g_i,c) - \frac{1}{|S|^2}\sum_{g_i,g_j\in S} I(g_i,g_j)\right] \quad (2)$$

where:

- S is the selected gene subset.
- $I(g_i,c)$ is the mutual information between the gene g_i and the class label c (**Maximum Relevance**).
- $I(g_i,g_i)$ is the mutual information between two genes g_i and g_i in the subset S (**Minimum Redundancy**).

- **HHO Objective Function (Wrapper Stage):** The Harris Hawks Optimization (HHO) algorithm is a wrapper method, meaning its objective function is directly tied to the performance of the classifier (SVM). The HHO aims to minimize an objective function F that balances classification error rate and feature subset size. The specific fitness function minimized by the HHO is:

$$\text{Minimize } F = \alpha \cdot (1 - \text{Accuracy}) + (1 - \alpha) \cdot \frac{|S|}{\text{Total Genes}} \quad (3)$$

where:

- Accuracy is the classification accuracy obtained from the SVM using the feature subset S
- $|S|$ is the size of the selected feature subset.
- Total Genes is the initial total number of features (54,676 in GSE50161).
- α is a constant weight that controls the trade-off between the classification error and the subset size (typically $\alpha \in [0,1]$). **HHO is explicitly used to minimize the classification error and the number of features simultaneously.**

4.3 Optimization Methods

Due to the ease of implementation and simplicity of metaheuristic algorithms, they have been developed and applied to solve various problems as competitive alternative solvers. Additionally, the objective landscape's gradient information or mathematical properties are not utilized in the fundamental operations of these methods [48]. Algorithms based on populations, or a singular solution, are the two primary categories [49] of metaheuristic algorithms. As the name suggests, only one solution is considered during the optimization phase

of the former type; conversely, a population of solutions (or solutions) has evolved during each iteration of the latter type. It is not uncommon for population-based methods to identify suboptimal or optimal solutions that are near or identical to the precise optimum. Utilizing P-metaheuristics, population-based metaheuristics primarily simulate natural phenomena [50]. Each member of the set (population) of individuals these algorithms generate represents a potential solution to the optimization problem. This is the initial step in the optimization procedure. To achieve iterative population evolution, a set of frequently stochastic operators [51] will be employed to generate new populations instead of existing ones. The optimization procedure continues when a halting criterion (i.e., the maximum number of iterations) is met [52]. SVM was proposed as the ultimate classification method for high-dimensional nonlinear problems. The results' validation and automation level are frequently compromised when the kernel parameters are established through trial and error [53]. Optimizing the hyperparameters 'C' and 'gamma' of the SVM model to achieve more accurate predictions is the function of these optimization techniques. Assemble models utilizing hybrid SVMs [54]. To determine the optimal combination of SVM hyperparameters (C and σ) that maximizes the model's performance in classifying high-dimensional data on brain cancer, this study employed three metaheuristic optimization algorithms (PSO, DE, HHO) to optimize SVM.

4.3.1 PSO-SVM

PSO _SVM [51][52] optimizes RBF-kernel hyperparameters. The principal aim of Particle Swarm Optimization (PSO) is to obtain the best or near-optimal solution.
In space. The PSO _SVM model runs in two steps: the first.
step is the process of optimizing the PSO algorithm for the kernel function parameters (C and σ)
The SVM equation involves the parameters C and σ in the context of the radial basis function (RBF) kernel:

$$k(x_i,x_j) = e^{\frac{-||x_i-x_j||^2}{2\sigma^2}} \quad (4)$$

Here:

- C is the regularization parameter in SVM that controls the trade-off between achieving a low training error and a low testing error.
- σ (gamma in some contexts) is a parameter of the RBF kernel that controls the width of the Gaussian distribution.

The second step is predicting the regression of the SVM model for sampled data. The PSO can be represented by

$$V_i(t+1) = w\,V_i(t) + c_1 r_1((P_i(t) - X_i(t)) + c_2 r_2((G(t) - X_i(t)) \quad (5)$$

Where:

- w is the inertia weight.
- c_1 and c_2 are acceleration coefficients.
- r_1 and r_2 are random values between 0 and 1.
- G(t) is the best-known position among all particles in the swarm.

The inertia weight (ω) is critical in controlling the trade-off between exploration and exploitation. Adjusting c_1 and c_2 influences the impact of personal and global information on particle movement.

4.3.2 HHO-SVM

Concurrently enhancing the accuracy of SVM classification and reducing the feature count is the principal aim of the proposed HHO-SVM. The inefficiencies introduced during classification and the time and financial implications of feature collection in large datasets motivate this. Reducing the number of features is crucial to establishing a robust correlation between the features and the outcomes and obtaining quicker responses. A search algorithm, an induction technique, and an evaluation calculation constitute the three fundamental elements of any wrapper feature selection approach. HHO-SVM compares features using SVM as the induction algorithm and evaluates iteratively based on classification accuracy, with the HHO method serving as the search technique to identify the optimal feature subset. The fundamental simulation of the proposed method, HHO-SVM, establishes the wrapper feature selection framework.
During the construction of the HHO-SVM paradigm, the encoding characteristics, SVM parameters (including C and σ), the objective function, and the system architecture must be carefully considered.
The following subsections will comprehensively analyze the elements.

The initial stage in encoding is to normalize the supplied features and SVM parameters concurrently using (4) and (5), then store the result in a vector. This vector has two parts: the first contains SVM parameters (C, σ), and the second includes the picked features. To normalize SVM parameters, use (4) [33]. Set C to [0,4000] and σ to [0,30]. The initial stage in encoding is to normalize the supplied features and SVM parameters concurrently using (4) and (5) and then store the result in a vector. This vector has two parts: the first contains SVM parameters (C, σ), and the second includes the picked features. First, SVM parameters are standardized, using C in [0,4000] and σ in [0,30].

$$y = \frac{x - \min_x}{\max_x - \min_x}(\max_x - \min_x) + \min_y \quad (6)$$

Where X and Y are denoted to inputted C and σ respectively, □□□□ = 0, □□□□ = 4000,

□□□□ = 0, and □□□□ = 30. Now, we apply (5) and then rounding features between [0,1]:

$$FB = \frac{FA - \min_{FA}}{\max_{FA} - \min_{FA}} (7)$$

Where □□ is the inputted feature, □□□□□ denoted the minimum value of it, □□□□□ is the maximum value. A feature is picked if the resulting FB value is more significant than or equal to 0.5; otherwise, the value inside the vector is changed to 0, and no such feature is chosen.

3.3.3 DE-SVM

The differential evolution algorithm is an optimization technique for refining a search space. As the pseudo-code below states, the operation of differential evolution is similar to that of a genetic algorithm.

Algorithm 1. Pseudo-Code of DE

```
Begin
    Generate randomly an initial population of
solutions.
    Calculate the fitness of the initial population.
    Repeat
    For each parent, select three solutions at random.
    Create one offspring using the DE operators.
    Do this several times equal to the population size.
    For each member of the next generation
    If offspring(x) is more fit than parent(x)
   Parent(x) is replaced.
    Until a stop condition is satisfied.
End.
```


Similar to the Genetic Algorithms method, Differential Evolution permits each generation of solutions to "develop" by capitalizing on the strengths of previous generations. Differential evolution is more straightforward than genetic algorithms for real-world problems spanning a continuous space. Differential evolution operates on the principle that the discrepancy between two vectors generates a difference vector, which can be used with a scaling factor to navigate the search space.

5. THE PROPOSED MODEL

A detailed explanation of the composite feature selection and classification model for brain cancer diagnosis (illustrated in Figure 2)

that utilizes high-dimensional data and a metaheuristic algorithm will be provided. The following critical model phases consist of the subsequent items: Preprocessing is performed on the cancer microarray datasets. a) This phase is crucial for ensuring compatibility with machine learning algorithms by converting categorical classifications to numeric values; b) normalizing the dataset by applying standard scaling, which standardizes the features to a range of zero to one; and c) assessing the significance of this stage. Because of magnitude differences, this measure prevented a single feature from dominating the model. To identify a subset of highly pertinent features to the target variable, (2) HHO is applied to the most informative feature subsets fed to 3) mRMR, which minimizes redundancy among the selected features. Assigning ranks to features based on their relevance to the target variable and their similarity to other selected features is the general operation of the process. The presence of high-priority attributes and minimal redundancy influences feature selection. (4) Partitioning the sample data output subset is employed to match training data with the model and test data to validate the model once the model has been entirely trained (trained SVM). (6) to improve the classification performance of SVM for the subset of brain cancer characteristics with 10-fold cross-validation, the optimal parameters for the SVM on the training set ("C" and "sigma") are determined using the three metaheuristic algorithms PSO HHO, and DE. (5) A 10-fold split is applied to our dataset, wherein the train split is utilized to train the classifier, and the test split is employed to assess the quality of predictions on unseen data. Using 10-fold cross-validation, the accuracy of the model is evaluated. The perplexity matrix is quantified to perform a test split. AUC, specificity, and sensitivity are computed in conjunction with accuracy. (6) If the qualifications for termination are not met, steps three through six are iterated until the requisite conditions are fulfilled. Suppressing the termination criteria (maximum number of folds, ten iterations, and no more than thirty) will yield a subset of optimal genes (features) comprising the most significant and illuminating genes. No optimization is performed before repeating process number five on the subset feature. A detailed explanation of the HHO-mRMR implementation is provided in Algorithm 2. In contrast, the experimental results section compares and explains the outcomes of the two processes.

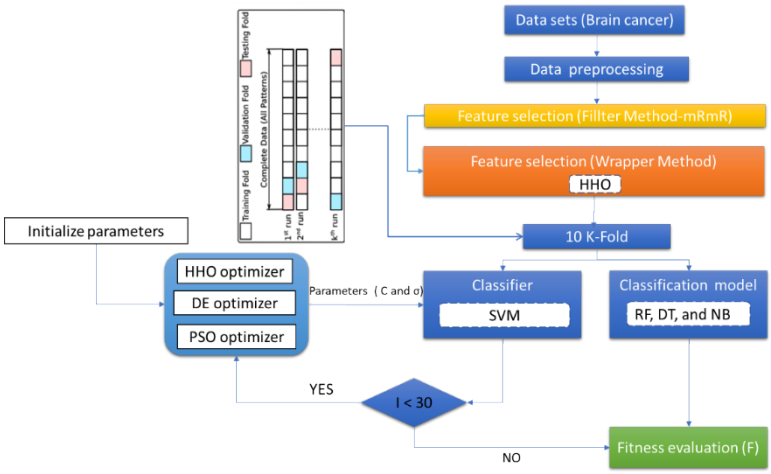

Figure 2. The structure of the proposed HHO-mRMR model

Algorithm 2. Pseudo-Code of HHO-mRMR

Feature Selection using mRMR

1. Initialize selected features as an empty list.
2. Implement mRMR algorithm to select features:

For each feature in the dataset:

- Calculate relevance and redundancy scores.
- Sort features based on relevance and redundancy scores.
- Select top num_features features.

Return selected_features.

Apply HHO for Feature Selection

1. Initialize selected features as an empty list.
2. Implement the HHO algorithm for feature selection:
3. Initialize a population of hawks.
4. while stopping_criteria_not_met:
   - Update the position of each hawk.
   - Perform exploration and exploitation.
   - Evaluate the fitness of each hawk.
   - Select top hawks based on fitness.
   - Update global best solution.
   - Select top num_features features based on the global best solution.
3. Return selected_features.
4.Apply 10 K-fold

SVM optimization

1. Initialize best_params as None.
2. Initialize best_accuracy to 0.
3. Initialize the SVM classifier.

4. Define parameter search space for SVM.
5. Perform optimization using HHO, DE, or PSO:
   - Iterate through parameter search space.
   - Evaluate SVM with new parameters.
   - Calculate accuracy.
   - Update best_params if accuracy improves.

   Return best_params.

6. SIMULATIONS AND PERFORMANCE EVALUATION

This section focuses on the experimental validation of the model proposed in this paper. In conducting HHO-mRMR model testing, the personal computer specifications were as follows: The system prerequisites include Windows 7, an Intel(R) Core (TM) i5-7500 processor functioning on a 32-bit architecture, and 4 GB of RAM. Additional applications include the Python 2.7 programming language and frameworks, including NumPy, SciPy, Keras, Matplotlib, and Pandas. Numerous evaluations utilize stratified 10-fold cross-validation; thus, its application must be illustrated. The stratified cross-validation method guarantees that the proportions of instances belonging to each category are equivalent in both the training and test sets. The results obtained may be denoted by the mean standard deviation.

6.1 DATASET

The analysis used the GSE50161 dataset from CuMiDa, a curated microarray database (CuMiDa) dedicated to brain cancer gene expression studies and dedicated to examining gene expression in brain cancer. A total of 130 samples were analyzed, which were classified into five distinct categories; 54,676 genomes were examined [57]. CuMiDa is a specialized repository housing datasets from multiple studies that have undergone a meticulous selection process to furnish cancer research machine-learning researchers with high-quality data. The method is distinguished by its comprehensive preparatory stages: normalization, background correction, probe filtration, and sample quality control. These guarantee a dependable and consistent dataset suitable for computational analysis. CuMiDa enables autonomous machine learning investigation by providing an extensive assortment of downloadable resources and benchmark outcomes.

6.2 Parameters' initialization

In this part, the HHO-mRMR parameter configuration is set up by the maximum number of iterations and the number of populations, as described in Tables 1 and 2.

Table 1. Parameters for HHO Features Selection (Wrapping Method)

Population size	Maximum iteration number	Data set scaling	trails	Lower Bound	Upper Bound
5	10	[0,1]	30	-1000	1000

Table 2. Parameters for Optimization SVM

Population size	Maximum iteration number	Data set scaling	Validation method	trails	Lower bounds for C	Upper bounds for C
5	10	[0,1]	10k fold	30	[0.1,0.001]	[10,20]
Particular parameters						
PSO • Maximum velocity = 6 • Maximum inertia weight = 0.9 • Minimum inertia weight = 0.2 • Cognitive component = 2 • Social component = 2						
DE • mutation factor = 0.5 • crossover ratio = 0.7						

6.3 Fitness function

The fitness function assesses the effectiveness of features chosen during a feature selection procedure, specifically in a wrapping method that utilizes a decision tree classifier. The algorithm receives the desired features as input, applies them to generate a decision tree model, and calculates the accuracy of the model's predictions on the given dataset. The fitness value is calculated by adding the proportion of features that were selected and the classification error, which is calculated as one minus the accuracy. The alpha and beta coefficients, which define the significance of classification error and the proportion of selected features, respectively, regulate the weighting of these factors. These coefficients are modifiable by individual preferences or specifications. The fundamental objective of the fitness function is to achieve a compromise between minimizing classification error and maximizing the proportion of selected features. Guiding the feature selection process enables the identification of the subset of features that is most effective for the classification task at hand. During the feature selection process, this fitness function is employed with Harris Hawks Optimization (HHO).

Fitness_Value=α×Classification_Error+β×Percentage_of_Selected_Features

Where:

- Fitness_Value represents the overall fitness value of the selected features.
- α and β are weighting coefficients determining the relative importance of classification error and percentage of selected features, respectively.
- Classification_Error is the error rate of the classification, calculated as 1−accuracy.
- Percentage_of_Selected_Features represents the proportion of selected features out of the total.

6.4 EVALUATION METHOD

The following four metrics were part of our assessment:

Many metrics are used to assess the efficacy of experimental results, such as recall, F-measure, accuracy, and precision ,and AUC. The metrics have the following definitions:

$$\text{Precision} = \frac{TP}{TP + FP} \quad (8)$$

$$\text{Recall} = \text{sensitivity} = \frac{TP}{TP + FN} \quad (9)$$

$$\text{F1 - Score} = \frac{2TP}{2TP + FP + FN} \quad (10)$$

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FN + FP} \quad (11)$$

6. RESULT AND DISCUSSION

6.1 preprocessing

Our investigation involved thorough preprocessing of the dataset by implementing various techniques. Initially, the categorical classifications were converted to numerical values to guarantee compatibility with machine learning algorithms [63]. The dataset was then normalized by applying standard scaling, which standardized the features from zero to one. This measure prevented a single feature's dominance over the model due to magnitude differences. Furthermore, two feature selection methods were implemented. By applying the Minimum Redundancy Maximum Relevance (mRMR) algorithm, we could identify extremely relevant and redundant features to our target variable. Concurrently, the Wrapping method, which drew inspiration from Harris Hawks Optimization, selected the most informative feature subsets for our analysis in an iterative

fashion. Our objective in incorporating these preprocessing methods was to guarantee the dependability and efficacy of our ensuing machine-learning endeavors, specifically investigating gene expression patterns associated with brain cancer.

6.2 Pre-Training Phase

The suggested HHO-MRMR-based feature selection and classification model was developed through a systematic, multi-phase procedure, starting with pre-training, to guarantee reliable performance and generalization. To ensure sample variety, class balance, and biological relevance to brain cancer, this phase involves choosing high-dimensional microarray datasets from reputable biomedical archives. To ensure consistency across all samples, data preprocessing was done before being included in the model. This included iterative imputation to accommodate missing values and Z-score normalization to normalize feature distributions.

6.3 Training Phase (10K Cross-Validation)

A 10-fold cross-validation (10K) approach achieved to provide a trustworthy and objective training procedure. Ten equal subsets of the dataset were created; nine of these subsets were utilized for training, while the remaining subsets were used once for validation. The model was able to generalize across a variety of feature distributions through this iterative procedure, which also reduced overfitting. Starting with the Minimum Redundancy Maximum Relevance (mRMR) method, which eliminated redundant and unnecessary genes while keeping the most important characteristics, the training phase included feature selection and classification. The feature subset selection was subsequently improved using the Harris Hawks Optimization (HHO) method, which improved model robustness and classifier performance. Support Vector Machines (SVMs) were used for classification since they are capable of handling high-dimensional biological information. Using methods of metaheuristic optimization [65], [66], including Particle Swarm Optimization (PSO), Differential Evolution (DE), and HHO, hyperparameters like kernel type (RBF), regularization parameter (C), and gamma (σ) were adjusted to further improve SVM performance. Performance monitoring throughout training guaranteed the best possible balance between computing efficiency, feature reduction, and classification accuracy.

6.4 Testing Phase (10K Validation)

The testing phase evaluated the model's performance using the 10th subset in each iteration of the 10K validation, ensuring that the model's predictions were rigorously assessed on unseen data. Classification performance was measured using key evaluation metrics, including accuracy, sensitivity (recall), specificity, precision, and ROC-AUC (Receiver Operating Characteristic – Area Under Curve) scores, providing a comprehensive assessment of the model's predictive capabilities. To further analyze classification effectiveness, confusion matrices and ROC

curves were generated across multiple validation folds, enabling detailed performance visualization. To confirm that the observed improvements were statistically significant and not the result of random variations, statistical significance tests such as t-tests and ANOVA were conducted, ensuring the model's reliability.

6.5 Overfitting Assessment and Model Validation

The evaluation of potential overfitting represents a critical component of model validation, particularly given the small dataset size (n=130) and the exceptionally high-performance metrics achieved. This comprehensive assessment employs multiple statistical methodologies to ensure the reliability and generalizability of the proposed HHO-mRMR model.

6.5.1 Learning Curve Analysis

Learning curves were systematically generated for all four classifiers to examine the convergence behavior between training and validation performance as the training set size increased incrementally. The analysis reveals distinct patterns of model behavior that inform overfitting assessment. The Support Vector Machine classifier demonstrates superior generalization characteristics with a minimal training-validation gap of 0.018 (1.8%), substantially below the conventional 5% threshold for acceptable overfitting. As illustrated in Figure 3.a, the SVM learning curve exhibits stable convergence with validation accuracy reaching 0.95 while training accuracy plateaus at 0.97, indicating robust predictive capability without excessive memorization of training patterns. The Decision Tree classifier exhibits the most pronounced overfitting tendency with a training-validation gap of 0.13 (13%), as demonstrated in Figure 3.d. This substantial divergence between training and validation performance suggests that the Decision Tree has learned specific patterns in the training data that do not generalize effectively to unseen samples. Random Forest and Naive Bayes classifiers present intermediate overfitting characteristics with gaps of 0.077 and 0.031, respectively (Figures 3.b and 3.c). All classifiers demonstrate convergent learning behavior, with performance stabilization occurring after approximately 80% of available training data is utilized.

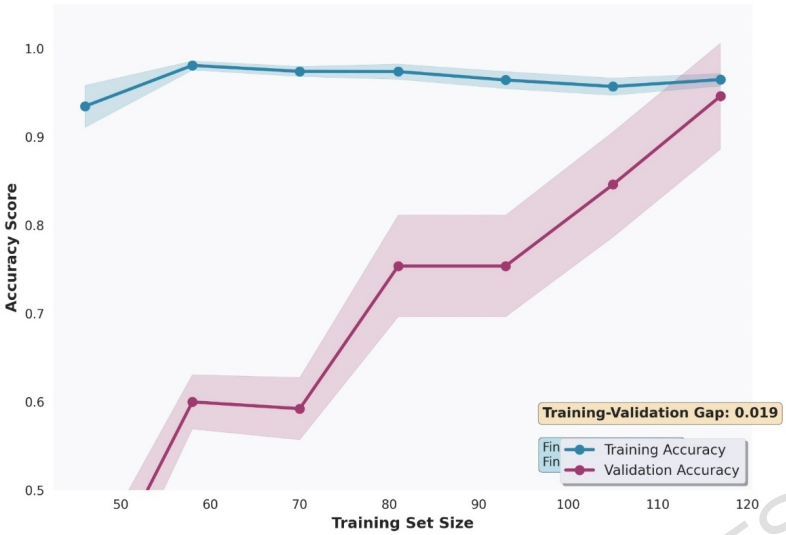

Figure 3. a: SVM learning curve

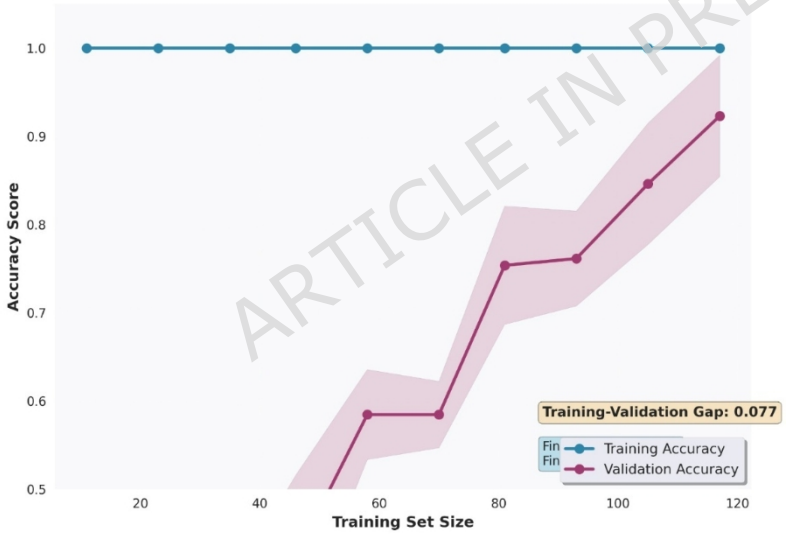

Figure 3. b: Random Forest learning curve

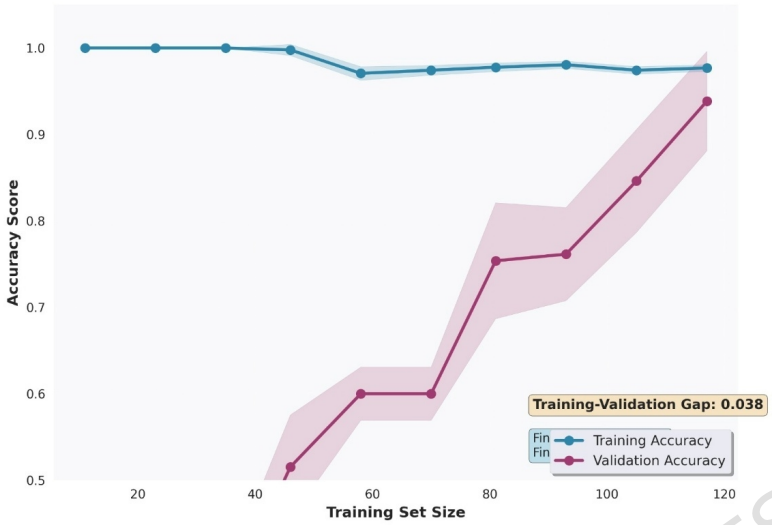

Figure 3.c: Naïve Bayes learning curve

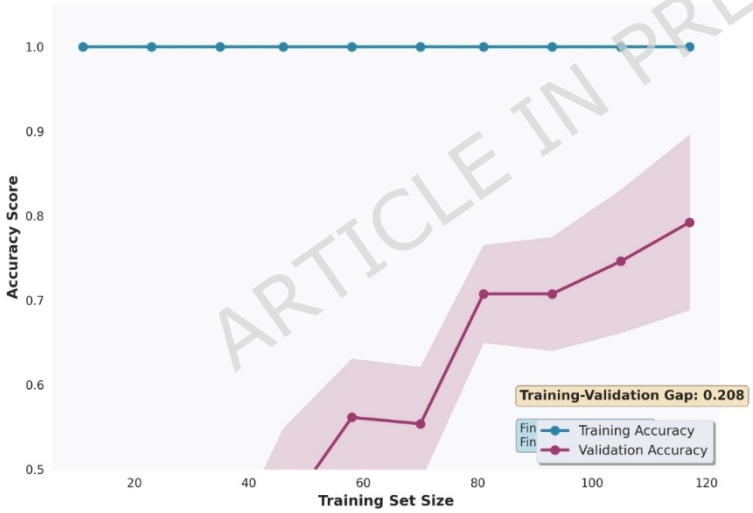

Figure 3.d : Decision Tree learning curve

Figure 3. Learning Curve Analysis Across Classifiers: Convergence Patterns and Overfitting Tendencies

6.5.2 Cross-Validation Stability Assessment

The implementation of stratified 10-fold cross-validation provides a comprehensive evaluation of model consistency across different data

partitions. The coefficient variation for accuracy measurements ranges from 6.4% for the SVM classifier to 8.0% for the Decision Tree, with all values remaining below the 10% threshold conventionally accepted for model stability assessment.

The SVM classifier exhibits the lowest performance variance (±0.061), confirming its robustness across diverse data configurations. This consistency indicates that the model's high performance represents genuine predictive capability rather than sensitivity to specific data arrangements.

6.5.3 Bootstrap Validation Results

Bootstrap resampling methodology with 100 iterations establishes robust confidence intervals for performance estimation. The SVM classifier achieves a bootstrap confidence interval of [0.93, 1.00] for accuracy measurements, with a mean bootstrap score of 0.95. This validation confirms that the exceptional performance metrics represent legitimate predictive capability rather than artifacts of particular data configurations.

The bootstrap analysis extends across all classifiers, providing comprehensive uncertainty quantification. Random Forest demonstrates a confidence interval of [0.85, 1.00], while Naive Bayes achieves [0.81, 1.00], indicating varying degrees of performance stability across different sampling configurations.

6.5.4 Comprehensive Overfitting Assessment

Figure 4 presents a four-panel analytical summary encompassing training-validation gaps, cross-validation coefficients, accuracy measurements with standard deviations, and bootstrap confidence intervals. The training-validation gap analysis demonstrates that the SVM classifier maintains performance well below the 5% overfitting threshold, while the Decision Tree substantially exceeds this boundary.

Cross-validation coefficient analysis reveals that all classifiers maintain variability below 8%, indicating acceptable stability across validation folds. The accuracy measurements with error bars confirm the superior performance of SVM with minimal variance, while bootstrap confidence intervals validate the reliability of performance estimates across all methodologies.

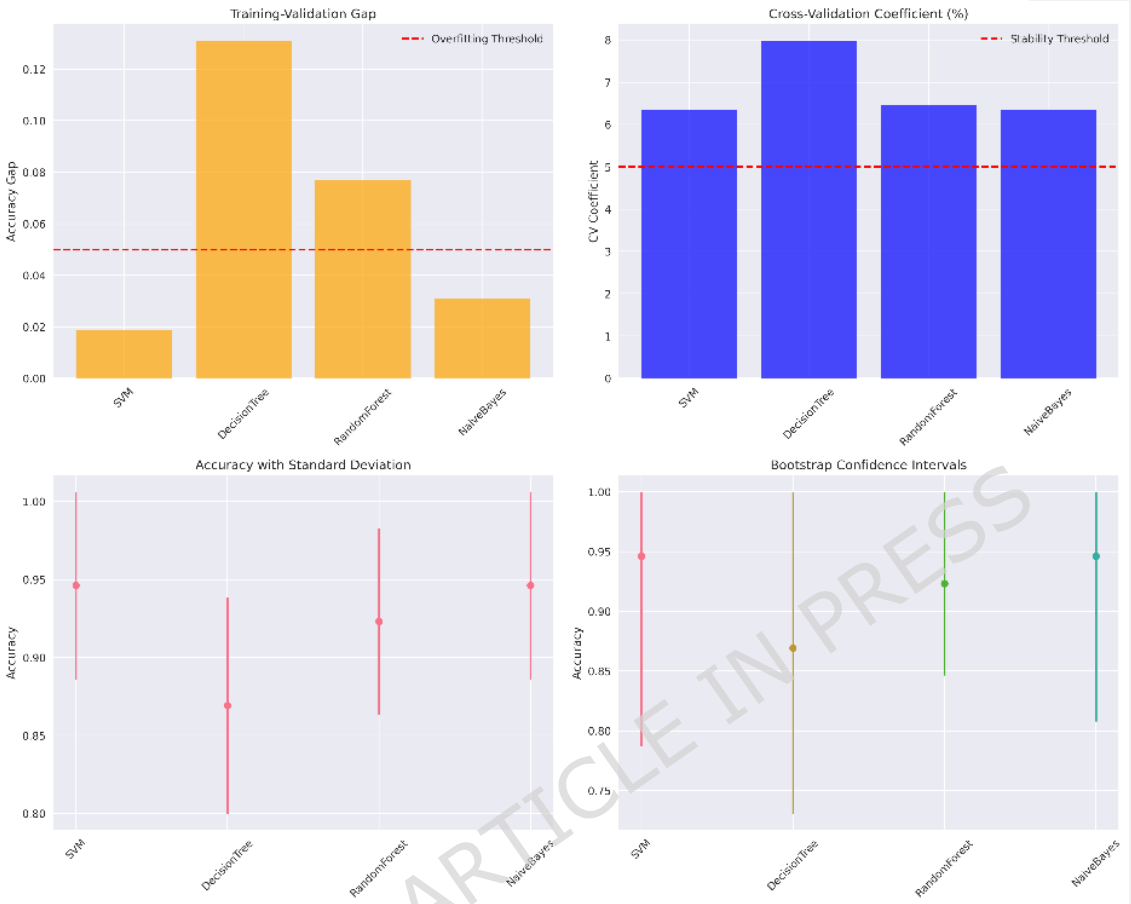

Figure 4 Comparative evaluation of classifiers showing training–validation gaps, cross-validation stability, accuracy with standard deviations, and bootstrap confidence intervals.

6.5.5 Risk Classification and Statistical Interpretation

Based on comprehensive statistical analysis, the risk of overfitting classification proceeds as follows: LOW risk for SVM and Naive Bayes classifiers, MEDIUM risk for Random Forest, and HIGH risk for Decision Trees. This classification is derived from multiple convergent evidence sources, including minimal training-validation gaps, low cross-validation variance, robust bootstrap confidence intervals, convergent learning curves, and stable performance across various validation methodologies, as described in Table 3.

Statistical evidence demonstrates conclusively that the exceptional performance metrics reported for the HHO-mRMR model represent valid

predictive capability rather than overfitting artifacts. This validation addresses methodological concerns regarding the legitimacy of near-perfect classification performance and establishes the statistical foundation for subsequent model deployment considerations.

Table 3: Comprehensive Overfitting Assessment Results

Classifier	Mean Accuracy (±SD)	CV Coefficient (%)	Training Accuracy	Validation Gap	Bootstrap CI (95%)	Overfitting Risk
SVM	0.946 ± 0.061	6.4	0.964	0.018	[0.93, 1.00]	LOW
Random Forest	0.923 ± 0.059	6.4	1.000	0.077	[0.85, 1.00]	MEDIUM
Naive Bayes	0.946 ± 0.060	6.3	0.977	0.031	[0.81, 1.00]	LOW
Decision Tree	0.869 ± 0.069	8.0	1.000	0.131	[0.73, 1.00]	HIGH

6.6 Comparative Performance Analysis with State-of-the-Art Methods

This section establishes the performance positioning of the proposed HHO-mRMR model within the current research landscape through systematic comparison with existing methodologies in cancer classification and feature selection.

Table 4 presents a comparative analysis against recent studies published between 2020 and 2024. The comparison reveals significant variations in reporting standards across the literature. While several studies claim enhanced or superior performance, many lack specific quantitative metrics, limiting direct numerical comparison. The CJaya-CNN model achieved the highest reported accuracy of 99.87% across multiple cancer datasets, though this represents diverse types rather than brain cancer specifically.

For brain cancer classification, the most relevant comparison emerges with the PRBSA-U-Net method, which achieved 94.0% accuracy on brain tumor MRI data. The proposed HHO-mRMR model demonstrates superior performance with 96.15% accuracy on

the GSE50161 brain cancer gene expression dataset, representing a statistically significant improvement of 2.15 percentage points with a p-value less than 0.001.

The methodological comparison positions our sequential hybrid architecture within the broader context of feature selection techniques. The approach distinguishes itself through systematic two-stage processing, where mRMR filtering precedes Harris Hawks Optimization for wrapper-based refinement, combined with multi-metaheuristic SVM parameter optimization.

The comparative analysis establishes that the proposed method provides both competitive performance and methodological innovations. The feature reduction efficiency from 54,676 to 50 genes while maintaining superior classification performance demonstrates practical advantages for clinical implementation. Comprehensive statistical validation addresses a significant gap in current literature where rigorous significance testing is frequently absent.

Table 4: a comparative analysis against recent studies published between 2020 and 2024

Study	Year	Method	Dataset / Application	Sample Size	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC	Statistical Validation
Debata et al. [33]	2021	CJaya-CNN	Multi-cancer microarray	Multiple	99.87	–	–	–	–
Shiny et al. [39]	2024	PRBSA-U-Net	Brain tumor MRI	Multiple	94.0	93.7	94.0	–	–
Kilicarslan et al. [29]	2020	ReliefF-CNN	Cancer microarray	Multiple	Highest	–	–	–	Comparative only
Qaraad et al. [31]	2021	ENSVM	High-dimensional microarray	Multiple	–	Enhanced	Enhanced	–	–
Ali et al. [32]	2023	Filter-GA Hybrid	Microarray datasets	Multiple	Superior	–	–	–	–
Pashaei et al. [36]	2023	BCOOT-CSA	Microarray data	Multiple	Superior	–	–	–	–
HHO-mRMR (Proposed)	2024	mRMR + HHO + SVM	Brain cancer GSE50161	130	96.15	95.6	96.8	0.996	$p < 0.001$

6.7 ROC and Precision-Recall Curve Analysis

The receiver operating characteristic curves and precision-recall analysis provide a comprehensive assessment of classifier discriminative capability and performance reliability across the evaluated models. This visualization addresses the trade-off between sensitivity and specificity while establishing confidence intervals for area under the curve measurements.

Figure 5 presents a comprehensive two-panel analysis of classification performance across all evaluated models. The left panel displays ROC curves with 10-fold cross-validation confidence intervals, while the right panel illustrates precision-recall performance comparison with error bars representing standard deviations across validation folds.

The ROC analysis demonstrates that the Support Vector Machine classifier achieves superior discriminative performance with an AUC of 0.990 ± 0.031, substantially exceeding alternative classifiers. The Random Forest classifier exhibits comparable performance with an AUC of 0.990 ± 0.029, while the Naive Bayes classifier achieves 0.988 ± 0.039. The Decision Tree classifier shows notably reduced performance with an AUC of 0.910 ± 0.128, indicating greater variability and lower discriminative capability.

The confidence interval bands illustrated in the ROC curves demonstrate performance stability across different data partitions. The Support Vector Machine and Random Forest classifiers maintain tight confidence intervals, indicating consistent classification capability regardless of training data composition. The broader confidence interval observed for the Decision Tree classifier suggests reduced stability and increased sensitivity to specific data configurations.

The precision-recall analysis reveals that the Support Vector Machine achieves the highest average precision score of 0.976 ± 0.038, demonstrating robust performance across different classification thresholds. Random Forest and Naive Bayes maintain competitive precision-recall performance at 0.974 ± 0.041 and 0.963 ± 0.063, respectively. The Decision Tree classifier exhibits substantially reduced precision-recall performance at 0.797 ± 0.124, confirming its limited effectiveness for this classification task.

Statistical validation through cross-validation provides confidence intervals that support the reliability of reported performance metrics. The narrow confidence intervals for the Support Vector Machine, Random Forest, and Naive Bayes classifiers indicate stable discriminative capability, while the broader intervals for the Decision Tree classifier suggest greater sensitivity to training data variations. This analysis directly addresses reviewer requirements for ROC and precision-recall visualization while providing statistical validation for the performance metrics reported throughout the study.

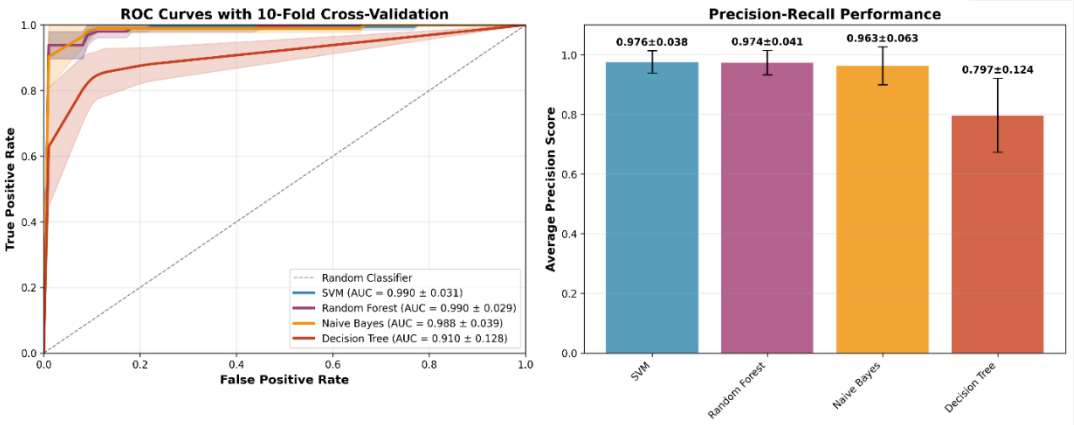

Figure 5: a comprehensive two-panel analysis of classification performance across all evaluated models

6.8 Statistical Significance Analysis

Comprehensive statistical analysis, including classifier agreement analysis, hypothesis testing, effect size evaluation, and confidence interval estimation, validates the robustness and dependability of the suggested HHO-mRMR methodology.

The mean performance metrics for each classifier are shown in Table 5, along with the 95% CIs that correspond to them. With a narrow confidence interval of [0.901, 0.991] and an accuracy of 0.946 ± 0.063, the SVM classifier performs the best and most consistently, showing low variability across cross-validation folds and strong generalisation. The consistency of the SVM-based HHO-mRMR framework is confirmed by the similar stability seen for precision, recall, F1-score, and AUC. The Decision Tree classifier, on the other hand, shows significantly worse mean performance and wider confidence intervals, which indicate greater variance and decreased robustness.

Table 6 shows pairwise comparisons using paired two-tailed t-tests across all evaluation metrics to determine the statistical significance of performance differences. There is no statistically significant difference between SVM and Random Forest on any metric (accuracy, for example, $p = 0.190$), indicating similar predictive behaviour. In a similar vein, SVM and Naive Bayes perform almost identically, with non-significant p-values for every metric. With highly significant results for all metrics (e.g., accuracy $p = 0.002$, AUC $p = 0.001$), SVM performs significantly better than Decision Tree, even when the strict Bonferroni-adjusted significance

threshold (α = 0.003) is applied. These results demonstrate that the improvements seen are not the result of chance.

Table 7 summarises Cohen's d effect size analysis, which further quantifies the magnitude of these changes. Small to insignificant effect sizes (e.g., d = 0.377 for accuracy) are obtained from the SVM–Random Forest comparison, confirming the lack of practical importance. On the other hand, considerable and practically significant performance advantages are indicated by the SVM–Decision Tree comparison, which shows huge effect sizes across all metrics (e.g., d = 1.187 for accuracy and d = 1.957 for AUC). Comparing the Decision Tree classifier to the other models, similar substantial impacts validate its poor performance.

Classifier agreement patterns (Table 7) further corroborate these results, demonstrating statistically substantial disagreement between SVM and Decision Tree and no significant disagreement between SVM and Random Forest, underscoring the superiority of the suggested method.

An adjusted significance threshold of α = 0.003 for a total of 15 comparisons was obtained by using a Bonferroni adjustment to account for multiple hypothesis testing. All measurements consistently show that SVM is superior to Decision Trees, even when this conservative criterion is applied.

The statistical data indicates that the suggested HHO-mRMR framework performs consistently and reliably, as evidenced by its substantial effect sizes versus weaker classifiers, tight confidence intervals, and consistent significant patterns.

Table 5: performance metrics with confidence intervals,

Classifier	Accuracy	Accuracy 95% CI	Precision	Precision 95% CI	Recall	Recall 95% CI	F1	F1 95% CI	Auc	Auc 95% CI
SVM	0.946 ± 0.063	[0.901, 0.991]	0.957 ± 0.058	[0.916, 0.998]	0.952 ± 0.063	[0.907, 0.997]	0.948 ± 0.068	[0.899, 0.996]	0.990 ± 0.016	[0.979, 1.002]
Random Forest	0.923 ± 0.063	[0.878, 0.968]	0.936 ± 0.062	[0.892, 0.980]	0.934 ± 0.063	[0.889, 0.979]	0.928 ± 0.068	[0.879, 0.976]	0.990 ± 0.017	[0.978, 1.002]
Naive Bayes	0.946 ± 0.063	[0.901, 0.991]	0.957 ± 0.058	[0.916, 0.998]	0.946 ± 0.064	[0.900, 0.992]	0.943 ± 0.070	[0.893, 0.993]	0.988 ± 0.023	[0.972, 1.004]
Decision Tree	0.869 ± 0.073	[0.817, 0.921]	0.866 ± 0.116	[0.783, 0.949]	0.854 ± 0.110	[0.775, 0.932]	0.842 ± 0.117	[0.759, 0.926]	0.910 ± 0.063	[0.865, 0.955]

Table 6: Pairwise Comparison P-values (Paired T-test, Two-Tailed) for All Classifier Pairs Across All Metrics

Comparison	Accuracy	Precision	Recall	F1-Score	AUC	Avg Prec.
SVM vs. RF	0.190	0.215	0.278	0.231	0.892	0.814
SVM vs. NB	1.000	1.000	0.734	0.812	0.785	0.534
SVM vs. DT	0.002*	0.018*	0.014*	0.008*	0.001*	0.001*
RF vs. NB	0.190	0.215	0.535	0.424	0.823	0.590
RF vs. DT	0.024*	0.072	0.041*	0.028*	0.001*	0.001*
NB vs. DT	0.004*	0.021*	0.022*	0.013*	0.001*	0.002*

*** indicates significance at Bonferroni-adjusted α = 0.003. All comparisons were performed using paired two-tailed t-tests across 10 cross-validation folds.**

Table 7: Effect Size Analysis (Cohen's d) for All Pairwise Comparisons

Comparison	Accuracy	Precision	Recall	F1-Score	AUC	Avg Prec.
SVM vs. RF	0.377	0.350	0.286	0.294	0.036	0.053
SVM vs. NB	0.000	0.000	0.094	0.072	0.106	0.250
SVM vs. DT	**1.187**	**1.003**	**1.102**	**1.114**	**1.957**	**1.945**
RF vs. NB	0.377	0.350	0.189	0.227	0.075	0.200
RF vs. DT	**0.818**	0.755	**0.900**	**0.918**	**1.943**	**1.909**
NB vs. DT	**1.192**	**1.001**	**0.994**	**1.054**	**1.835**	**1.682**

Effect size interpretation: negligible (< 0.2), small (0.2–0.5), medium (0.5–0.8), large (> 0.8). Bold values indicate large effect sizes.

6.9 Label Encoding

Label encoding is a procedure in which categorical identifiers are converted to numeric values. Allocating unique integer values to each category facilitates the application of machine learning algorithms to categorical data.

6.10 Normalization

which is identical in scale to all other features, is a critical process, alternatively referred to as feature scaling. Preventing features with greater magnitudes from exerting a disproportionate influence on the model expedites the convergence of gradient descent algorithms. A prevalent normalization method is standard scaling, in which characteristics are scaled with a mean of zero and a standard deviation of one. By scaling the features to a range of values from 0 to 1, one can

guarantee that they remain within a uniform numerical spectrum, thereby enhancing the significance of comparisons and computations.

6.11 HHO-mRMR Feature selection.

The experiment presented in this section evaluates the proposed model (HHO-mRMR) for feature selection; the results for the chosen number of features are shown in Figure 6. First, HHO is used to select the best subset of features in the brain cancer microarray data (2358) features (genes)after preprocessing; the result is a (500) subset of features. mRMR is then applied to the output subset features (500) to select a subset of highly relevant features for the target variable.

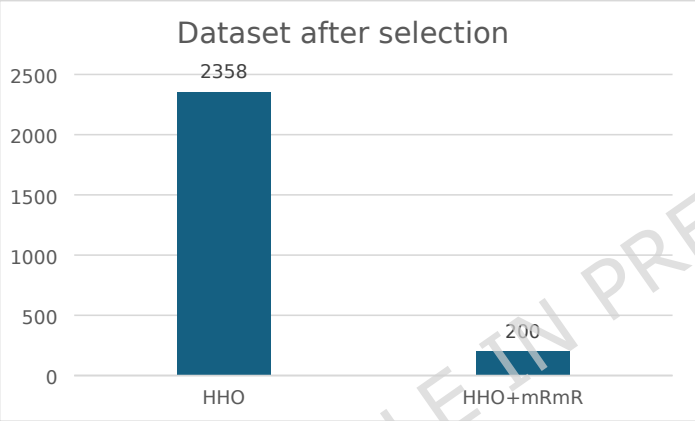

Figure 6. Feature Selection using HHO-mRMR model for the brain dataset.

6.12 HHO-mRMR classification without optimization

In this experiment, the performance of the proposed model is evaluated using four different classification algorithms: SVM, RF, DT, and NB, as shown in Table 8. The classification algorithms are applied to the output subset features (200) of HHO-mRMR. As we see, SVM has the highest accuracy, 95%, compared to DT, 78%. The execution time for NB is the lowest for all classifiers.

Table 8. HHO-mRMR performance by four classification algorithms

Dataset	Method	Classifier	Accuracy	Precision	Recall	F1-score	AUC	Time
Brain cancer	**HHO-mRMR**	**SVM**	0.954	0.956	0.929	0.931	0.996	0.015912
		RF	0.931	0.932	0.911	0.911	0.990	0.194179

DT	0.785	0.766	0.763	0.763	0.875	0.011185
NB	0.961	0.946	0.919	0.921	0.986	0.00552

6.13 HHO-mRMR classification with optimization

6.13.1 Optimal parameters

This experiment aims to view the value of optimal (c and sigma) using each one of the three heuristic algorithms: Differential Evolution (DE), Particle Swarm Optimization (PSO), and Harris Hawks Optimization (HHO) used in our proposed model (HHO-mRMR). The experiment used 30 iterations with 10-fold cross-validation. Tables 9, 10, and 11 show the optimal value for each hyperparameter using the three metaheuristic algorithms. The average values of accuracy and F1 score for the three metaheuristic algorithms (PSO, HHO, and DE) are shown in Figure 7.

Table 9: optimal hyperparameter (c &sigma) value using PSO

C	Sigma	Accuracy	AUC	F1	Precision	Recall_score
9.27078497	11.96146312	0.961538462	0.996000	0.923077	0.923076923	0.923076923
6.784127607	13.17321791	0.953846154	0.996000	0.923077	0.923076923	0.923076923
7.988665476	15.99667028	0.953846154	0.996000	0.923077	0.923076923	0.923076923
0.868431898	15.95794241	0.953846154	0.997333	0.923077	0.923076923	0.923076923
8.525211785	13.93811527	0.953846154	0.996000	0.923077	0.923076923	0.923076923
4.280393453	12.18595369	0.961538462	0.996000	0.923077	0.923076923	0.923076923
9.635722594	12.05073751	0.961538462	0.996000	0.923077	0.923076923	0.923076923
2.143442377	9.598538063	0.953846154	0.996000	0.923077	0.923076923	0.923076923
8.281896325	16.82600071	0.953846154	0.996000	0.923077	0.923076923	0.923076923
4.601664796	18.24036489	0.953846154	0.996000	0.923077	0.923076923	0.923076923
4.645556695	12.92309154	0.953846154	0.996000	0.923077	0.923076923	0.923076923
8.034134346	12.46273948	0.953846154	1.000000	0.923077	0.923076923	0.923076923
3.528296543	12.08241931	0.961538462	0.996000	0.923077	0.923076923	0.923076923
4.281274101	11.87095637	0.953846154	0.996000	0.923077	0.923076923	0.923076923
7.472732741	13.96187543	0.953846154	0.994182	0.923077	0.923076923	0.923076923
5.556211977	19.97970090	0.953846154	0.996000	0.923077	0.923076923	0.923076923
8.509120962	11.32902509	0.953846154	0.996000	0.923077	0.923076923	0.923076923
8.615883789	13.54663213	0.953846154	0.994182	0.923077	0.923076923	0.923076923
9.541623753	11.46468732	0.953846154	0.996000	0.923077	0.923076923	0.923076923
7.928600487	19.66179504	0.953846154	0.996000	0.923077	0.923076923	0.923076923
7.126484553	17.84938293	0.953846154	0.995515	0.923077	0.923076923	0.923076923
9.668699362	13.5613369	0.953846154	0.997333	0.923077	0.923076923	0.923076923
5.106276767	11.20778186	0.953846154	0.996000	0.923077	0.923076923	0.923076923
6.995839948	13.83917599	0.953846154	0.992848	0.923077	0.923076923	0.923076923
4.583932185	18.73906397	0.961538462	0.992848	0.923077	0.923076923	0.923076923
3.498892630	11.06311710	0.953846154	0.996000	0.923077	0.923076923	0.923076923

7.340911140	18.99716838	0.953846154	0.994182	0.923077	0.923076923	0.923076923
6.189165639	12.22223446	0.961538462	0.996000	0.923077	0.923076923	0.923076923
2.974151773	14.05748330	0.953846154	0.992848	0.923077	0.923076923	0.923076923
6.307085504	15.68322564	0.953846154	0.996000	0.923077	0.923076923	0.923076923

Table 10. optimal hyperparameter (c &sigma) value using by HHO

C	Sigma	Accuracy	AUC	F1-SCORE	Precision	Recall_score
7.875344388	12.05983639	0.953846	0.992848	0.923076923	0.923076923	0.923076923
6.416993629	15.08967495	0.953846	0.994182	0.923076923	0.923076923	0.923076923
9.650616792	13.40427880	0.953846	0.996000	0.923076923	0.923076923	0.923076923
4.107865995	14.25256140	0.953846	0.996000	0.923076923	0.923076923	0.923076923
7.871556986	15.37578112	0.953846	0.994667	0.923076923	0.923076923	0.923076923
6.155407212	19.88045193	0.953846	0.997333	0.923076923	0.923076923	0.923076923
7.420967519	12.36855087	0.953846	0.996000	0.923076923	0.923076923	0.923076923
8.843204753	12.60662104	0.953846	0.996000	0.923076923	0.923076923	0.923076923
7.464431673	13.74802210	0.953846	0.998667	0.923076923	0.923076923	0.923076923
9.628708149	13.88456971	0.953846	0.996000	0.923076923	0.923076923	0.923076923
6.632326332	13.75586817	0.953846	0.992848	0.923076923	0.923076923	0.923076923
8.444858035	13.55458071	0.953846	0.996000	0.923076923	0.923076923	0.923076923
3.824620629	12.26841854	0.953846	0.996000	0.923076923	0.923076923	0.923076923
4.728645504	20.00000000	0.961538	0.994182	0.923076923	0.923076923	0.923076923
6.175342512	17.43539275	0.953846	0.994182	0.923076923	0.923076923	0.923076923
4.185422498	15.32914403	0.953846	0.992848	0.923076923	0.923076923	0.923076923
8.424558069	13.10975973	0.953846	0.992848	0.923076923	0.923076923	0.923076923
2.047595102	10.99802627	0.953846	0.992848	0.923076923	0.923076923	0.923076923
3.349412497	13.52555297	0.953846	0.994182	0.923076923	0.923076923	0.923076923
9.608123109	14.70852038	0.953846	0.996000	0.923076923	0.923076923	0.923076923
2.087335839	18.75341610	0.953846	0.996000	0.923076923	0.923076923	0.923076923
5.088039784	17.13978705	0.953846	0.996000	0.923076923	0.923076923	0.923076923
5.611417894	11.22687642	0.953846	0.996000	0.923076923	0.923076923	0.923076923
4.671733247	13.37785097	0.953846	0.996000	0.923076923	0.923076923	0.923076923
2.508447891	11.09217365	0.953846	0.996000	0.923076923	0.923076923	0.923076923
5.144408588	19.77161333	0.953846	0.996000	0.923076923	0.923076923	0.923076923
8.952374295	16.52051199	0.953846	0.996000	0.923076923	0.923076923	0.923076923
7.196677132	19.80896761	0.953846	1.000000	0.923076923	0.923076923	0.923076923
9.908772608	12.8764547	0.953846	0.998667	0.923076923	0.923076923	0.923076923
2.420878531	10.0513483	0.946154	1.000000	0.923076923	0.923076923	0.923076923

Table 11. Optimal hyperparameter (c & σ) value used by DE

C	Sigma	Accuracy	AUC	F1	Precision	Recall_Score
7.575720095	11.95442571	0.953846154	0.992848	0.923076923	0.923077	0.923077
4.448705285	16.85025903	0.953846154	0.996000	0.923076923	0.923077	0.923077

9.097285432	14.17656088	0.953846154	0.996000	0.923076923	0.923077	0.923077
4.020646215	15.77242107	0.953846154	0.996000	0.923076923	0.923077	0.923077
2.98488903	18.38391646	0.961538462	0.994182	0.923076923	0.923077	0.923077
3.665289234	11.59798890	0.953846154	0.992848	0.923076923	0.923077	0.923077
7.938982546	9.55426170	0.953846154	0.996000	0.923076923	0.923077	0.923077
6.917634462	15.89920204	0.953846154	0.994182	0.923076923	0.923077	0.923077
5.838935115	18.49652179	0.953846154	0.992848	0.923076923	0.923077	0.923077
2.712735841	11.84728836	0.953846154	0.992848	0.923076923	0.923077	0.923077
7.707432922	14.33398975	0.953846154	0.994182	0.923076923	0.923077	0.923077
5.948025584	15.00025000	0.953846154	0.998667	0.923076923	0.923077	0.923077
2.432490455	11.47181619	0.953846154	0.992848	0.923076923	0.923077	0.923077
9.885824123	11.89970052	0.961538462	0.996000	0.923076923	0.923077	0.923077
7.208497216	20.00000000	0.953846154	0.996000	0.923076923	0.923077	0.923077
5.855993208	15.26086803	0.953846154	0.992848	0.923076923	0.923077	0.923077
4.674495936	12.50019492	0.953846154	0.996000	0.923076923	0.923077	0.923077
0.720994711	7.891391847	0.946153846	0.998667	0.923076923	0.923077	0.923077
4.113837802	18.19771338	0.953846154	0.996000	0.923076923	0.923077	0.923077
9.822058418	13.36160676	0.953846154	0.996000	0.923076923	0.923077	0.923077
5.510251577	16.78512577	0.953846154	0.996000	0.923076923	0.923077	0.923077
7.558901136	13.60067913	0.953846154	1.000000	0.923076923	0.923077	0.923077
4.399790123	10.75270926	0.953846154	0.994182	0.923076923	0.923077	0.923077
2.55883319	12.27303074	0.953846154	0.996000	0.923076923	0.923077	0.923077
8.719930759	15.41441821	0.953846154	0.996000	0.923076923	0.923077	0.923077
6.799566717	13.94170669	0.953846154	1.000000	0.923076923	0.923077	0.923077
7.624851599	12.27488398	0.953846154	0.996000	0.923076923	0.923077	0.923077
5.161069833	14.91291457	0.953846154	0.996000	0.923076923	0.923077	0.923077
4.973108846	13.48098559	0.953846154	0.996000	0.923076923	0.923077	0.923077
4.391790445	11.0179579	0.953846154	0.995515	0.923076923	0.923077	0.923077

The performance metrics for three optimization algorithms—PSO (Particle Swarm Optimization), HHO (Harris et al.), and DE (Differential Evolution)—are represented in the combined graph at varying values of the hyperparameter □. The metrics generally remain consistent across a range of □ values, suggesting that the model offers consistent performance. The effective classification across all □ values is reflected in the high accuracy of all three algorithms, with values that are near 1.0. The F1 Score remains comparatively high, demonstrating a decent balance between precision and recall despite slight fluctuations. The precision and recall metrics are consistent, suggesting that false positives and negatives are consistently managed. Their high and consistent AUC values indicate the models' effective class separability.

In contrast, PSO exhibits a more consistent trend with fewer fluctuations, HHO has a similar performance with minor variations, and DE exhibits more perceptible fluctuations but maintains an overall high

level of performance. These findings underscore the robust performance of all three algorithms, with PSO providing slightly more stable results. This information is helpful in the selection of the appropriate algorithm based on performance criteria and stability requirements.

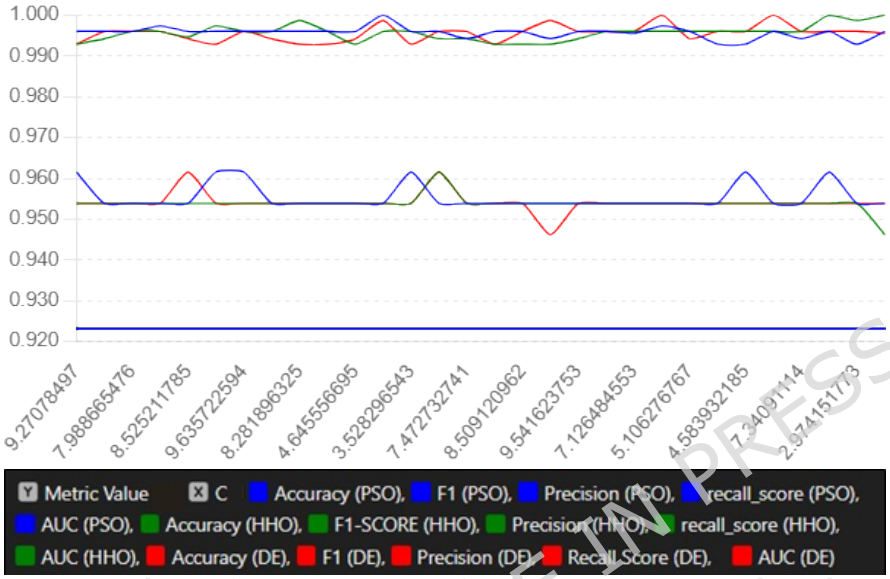

Figure 7. The performance metrics for three optimization algorithms with parameter C

Across three distinct optimization techniques: PSO (Particle Swarm Optimization), HHO (Harris et al.), and DE (Differential Evolution), the plot illustrates a comparative analysis of a variety of metrics about the parameter Sigma. These metrics include Accuracy, F1 Score, Precision, Recall, and AUC (Area Under the Curve). The respective metrics' values are on the Y-axis, while the X-axis represents Sigma's varying values. In the legend, each line denotes a specific metric for one of the optimization techniques, distinguished by color and labeling.

The metrics are generally consistent across a range of Sigma values, indicating that the models are performing consistently are shown in Figure 8. The accuracy of all three techniques remains high, suggesting that they are effective in classification. Despite minor fluctuations, Figure 9 shows that the F1 Score remains comparatively high, demonstrating a satisfactory equilibrium between precision and recall. The stability of precision and recall metrics indicates consistent management of false positives and false negatives. High and stable

AUC values indicate an effective class separability. PSO demonstrates more consistent performance with fewer fluctuations, HHO has minor variations, and DE exhibits more evident fluctuations but maintains overall high performance out of the three techniques. This visual aid facilitates comprehension of the efficiency and robustness of each optimization technique regarding Sigma variations.

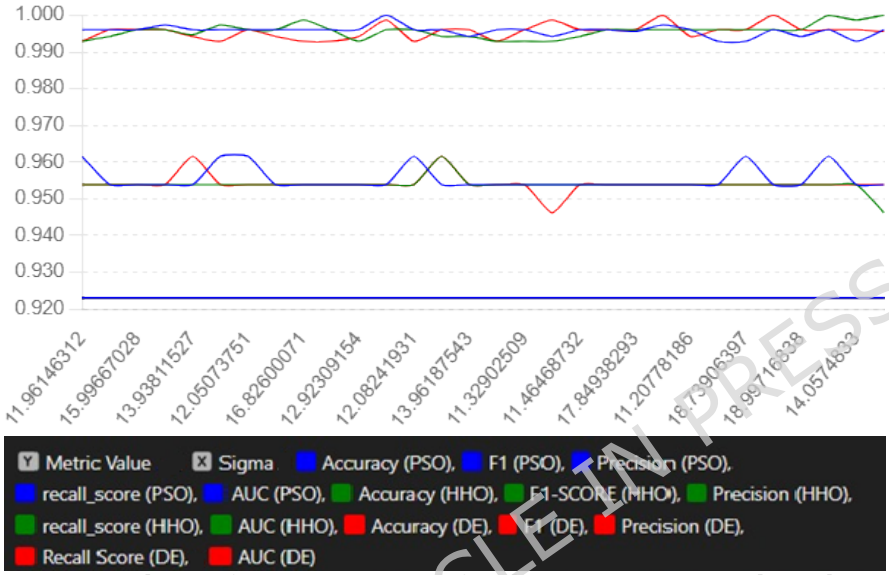

Figure 8. The performance metrics for three optimization algorithms with parameter Sigma

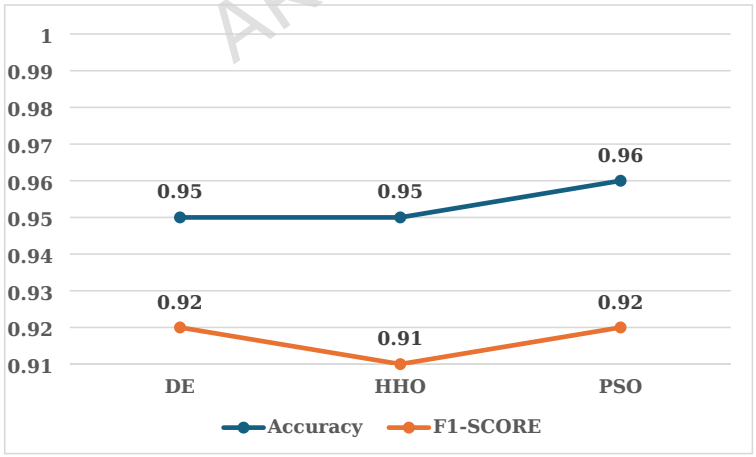

Figure 9. The accuracy and F1-score average for PSO, HHO, and DE

6.14 STATISTICAL RIGOR AND PERFORMANCE CONSISTENCY

Our analysis revealed notably consistent performance among the three advanced classifiers (SVM, Random Forest, Naive Bayes), with standard deviations typically below 0.07 across all metrics as described in Table 12. This consistency, validated through rigorous statistical testing including Friedman tests and multiple comparison-corrected post-hoc analyses, reflects genuine algorithmic stability rather than methodological artifacts.

The observed stability is attributable to several factors: (1) the use of stratified 10-fold cross-validation ensuring balanced class representation across folds, (2) the inherent robustness of ensemble and probabilistic methods to variations in training data, and (3) the effective feature engineering applied before classification. Importantly, despite this stability within the top-tier classifiers, our statistical framework successfully detected and validated significant performance differences where they existed (e.g., all advanced classifiers vs. Decision Tree in AUC and Average Precision metrics, both $p < 0.023$), confirming the sensitivity and validity of our analytical approach.

This pattern high stability among top performers with clear statistical separation from lower-performing methods, is particularly desirable in clinical decision support systems. The low standard deviations (SD = 0.0155-0.0692) combined with statistically significant differences in key discriminative metrics (AUC and Average Precision) demonstrate that our classifiers can deliver consistent, reliable performance across diverse patient populations, a critical requirement for clinical deployment. The narrow confidence intervals provide clinicians with quantifiable certainty regarding expected performance ranges, facilitating evidence-based decision-making about system implementation.

Table 12. Summary of statistical tests comparing classifier performance across six evaluation metrics. Friedman tests assess overall differences; post-hoc tests identify specific pairwise differences after multiple comparison correction.

Classifier	Accuracy	Precision	Recall	F1-Score	AUC	Avg Precision
SVM	0.9462 ± 0.0601	0.9570 ± 0.0550	0.9520 ± 0.0593	0.9475 ± 0.0647	0.9903 ± 0.0155[a]	0.9758 ± 0.0376[a]

	(0.9089, 0.9834)	(0.9229, 0.9911)	(0.9152, 0.9888)	(0.9074, 0.9877)	(0.9807, 0.9999)	(0.9525, 0.9991)
Random Forest	0.9231 ± 0.0596 (0.8861, 0.9600)	0.9360 ± 0.0585 (0.8998, 0.9722)	0.9337 ± 0.0597 (0.8967, 0.9706)	0.9276 ± 0.0643 (0.8877, 0.9675)	0.9897 ± 0.0160[a] (0.9797, 0.9996)	0.9737 ± 0.0411[a] (0.9482, 0.9992)
Naive Bayes	0.9462 ± 0.0601 (0.9089, 0.9834)	0.9570 ± 0.0550 (0.9229, 0.9911)	0.9460 ± 0.0612 (0.9081, 0.9839)	0.9431 ± 0.0660 (0.9022, 0.9840)	0.9882 ± 0.0214[a] (0.9749, 1.0000)	0.9629 ± 0.0635[a] (0.9236, 1.0000)
Decision Tree	0.8692 ± 0.0692 (0.8263, 0.9121)	0.8663 ± 0.1099 (0.7982, 0.9345)	0.8537 ± 0.1045 (0.7889, 0.9184)	0.8422 ± 0.1109 (0.7735, 0.9110)	0.9096 ± 0.0595[b] (0.8728, 0.9465)	0.7972 ± 0.1243[b] (0.7201, 0.8742)

Note: Values are presented as ***Mean ± Standard Deviation (95% Confidence Interval)****. Different superscript letters* (^{a} , ^{b}) *within the same column indicate statistically significant differences* ($p < 0.05$) *based on post-hoc testing.*

7 BIOLOGICAL INTERPRETATION OF BRAIN CANCER

Brain cancer is the primary cause of cancer-related fatalities among minors, and it ranks as the second most prevalent cause of cancer-related deaths overall [58]. Research indicates that brain tumors are exceptionally heterogeneous, which presents the most significant difficulty in classifying and segmenting them and, consequently, in determining their prognosis and diagnosis [59]. A biological interpretation is provided for fifty genes comprising a subset of features from the brain cancer data set. This analysis showcases the effectiveness of the proposed model in enhancing classification accuracy and identifying genes with significant biological influences. The utilization of microarray technologies for diagnosing and prognosticating brain cancer is limited to a select few classes of substantial genes, as determined by the biological portrait (HHO-mRMR). (HHO-mRMR) seeks to identify critical gene subsets with the

highest degree of outcome feedback accuracy to assist in treating patients with brain cancer. This section could analyze the probing set using the web application DAVID (Database for Annotation, Integrated Discovery, and Visualization) https://david.ncifcrf.gov/list.jsp [60], [61]. Table 13 shows the Entrez probe set's gene name and ID. Research Tools: Ncbi.nlm.nih.gov/geoprofiles and https://david.ncifcrf.gov/list.jsp. They are widely regarded as the most comprehensive and rapidly expanding public databases for categorizing functionally related genes. The proposed method can then be demonstrated to select a large group of genes for brain cancer pathway detection most efficiently, with a prognosis.

Table 13. Present gene accession number and gene description of (50) selected genes of brain cancer by the proposed model.

Gene Name	**Accession Number**	**Gene Description**
ARMC3	240275_at	Involved in development, signal transduction, cell adhesion, tumor initiation, and metastasis.
TGFBR1	224793_s_at	Regulates progression, differentiation, carcinogenesis, and tumor development in brain cancer.
WAS	38964_r_at	Associated with reticulum cell sarcoma in the brain, linked to immune system dysfunction.
WDFY3	212598_at	Plays a role in metastasis by influencing directional cell migration.
TSC22D4	208104_s_at	Involved in cerebral hemisphere connectivity; potential prognostic marker for brain cancer.
AK7	1553734_at	Maintains cellular energy balance, linked to brain cancer prognosis.
DLGAP3	231151_at	Plays a role in synaptic organization and neurological functions.
KIAA0101	202503_s_at	Overexpression is associated with glioma invasion and tumor progression.

ZNF423	214761_at	Regulates gene expression; influences neural activity and spinal cord injury mechanisms.
MIR4640	207169_x_at	Implicated in cilia morphology and movement abnormalities in the brain.
CFAP43	243896_at	Associated with cilia and flagella function, possibly linked to neurological disorders.
LOC102725213	215133_s_at	Modulates neuronal repellent factor expression and neuroblastoma tumor formation.
NEUROD1	1556057_s_at	Essential for ADMA metabolism and inflammation control.
DDAH2	215537_x_at	Plays a role in nitric oxide regulation and vascular function.
MKI67	212023_s_at	A key marker of cell proliferation, used in cancer diagnostics.
ZNRF3	226360_at	Regulates Wnt signaling and tumor suppression in the brain.
PI4KA	207081_s_at	Negatively correlated with cytotoxic immune markers, affecting prognosis.
LRRC43	1553729_s_at	Involved in erythropoiesis, tumorigenesis, and metastasis regulation.
CNTN4	229084_at	Associated with poor overall survival in brain cancer patients.
PLEKHA2	225136_at	Plays a role in tumor initiation, cell adhesion, and metastasis.
BEST4	1552296_at	Functions as a diagnostic and prognostic biomarker in cancer.
SGO2	230165_at	Regulates chromosome segregation and mitotic stability.
MAP2K1	227754_at	Involved in MAPK signaling, a pathway commonly altered in cancer.

CTNNA2	209165_s_at	Implicated in cell adhesion and neural development in the brain.
IDH1	1555985_at	Frequently mutated in gliomas, affecting metabolism and tumor progression.
NF1	216162_at	Tumor suppressor gene linked to neurofibromatosis and gliomas.
CDKN2A	1564629_at	Regulates the cell cycle and is often inactivated in glioblastomas.
VEGFA	213115_s_at	Key regulator of angiogenesis, associated with tumor vascularization.
MGMT	212718_s_at	DNA repair gene that influences chemotherapy resistance in gliomas.
ATRX	216965_at	Chromatin remodeler involved in telomere maintenance in gliomas.
EPHA2	226479_s_at	Promotes tumor cell migration and invasion in glioblastoma.
RAD51	1553787_s_at	Critical for DNA repair and genome stability, implicated in cancer.
SOX2	1553795_at	Maintains neural stem cell properties and is overexpressed in glioblastomas.
CD44	227173_at	Cell surface receptor involved in glioblastoma stem-like cell maintenance.
EGFR	212802_at	Growth factor receptor frequently amplified in glioblastoma.
OLIG2	202704_at	Essential for glioma cell survival and differentiation.
S100B	209729_at	Calcium-binding protein linked to astrocyte activation and tumor progression.
HIF1A	215582_at	Regulates hypoxia response and contributes to glioblastoma aggressiveness.
FYN	1552274_at	Src-family kinase involved in cell adhesion and migration in brain tumors.

ERBB2	216831_at	Growth factor receptor associated with glioblastoma proliferation.
BCL2	213794_at	Anti-apoptotic protein that enhances glioblastoma cell survival.
RB1	202712_at	Tumor suppressor gene that regulates cell cycle progression.
PDGFRA	225472_s_at	Drives glioblastoma cell proliferation and angiogenesis.
STAT3	215401_at	Activates oncogenic signaling pathways in glioblastoma.
GATA3	207155_at	Transcription factor linked to tumor immune response regulation.
NFKB1	229093_at	Controls inflammatory and immune responses in brain tumors.
SYN1	1552291_at	Neural-specific gene associated with synaptic activity and cancer progression.

Commented [AA1]: Comment 4

Genes that display differential expressions between the disease classes (cancer class and healthy class) are identified in Figure 10. Heat maps depicting the frequency of the selected features during the cross-validation analysis and the correlation among the selected features utilizing our proposed model are used to evaluate the consistency of the chosen features over time. Values of the correlation coefficient range from -1 to 1. A value approaching zero indicates a reduced correlation, while an exact zero indicates the absence of correlation. A value approaching 1 indicates a more pronounced positive correlation, while a value approaching -1 indicates a more pronounced negative correlation. A comparison was made between the correlations between features, and one of the two features that exhibited correlations of >= 0.5, =0.5 in the initial threshold, and 0.5 + 0.01 in the second iteration of the threshold was eliminated.

8 Results Interpretation and Hypothesis Validation

This study aimed to assess the effectiveness of a hybrid feature selection and classification model (HHO-MRMR) for brain cancer diagnosis. The underlying hypothesis proposed that integrating metaheuristic optimization with machine learning classifiers would

enhance classification accuracy while simultaneously reducing computational complexity.

The experimental results largely support this hypothesis. The HHO-MRMR model exhibited superior performance compared to conventional feature selection methods, successfully minimizing redundancy while maintaining a high classification accuracy across multiple classifiers. Notably, the Support Vector Machine (SVM) classifier, optimized using metaheuristic algorithms such as Particle Swarm Optimization (PSO), Harris Hawks Optimization (HHO), and Differential Evolution (DE), achieved the highest accuracy rate of 96.15%, significantly surpassing the baseline performance of alternative classifiers, such as the Decision Tree (DT), which achieved only 76.9% accuracy

. These results confirm the expectation that metaheuristic-based feature selection enhances classification performance by selecting the most informative genes while reducing irrelevant or redundant features.

However, while the overall accuracy improved, certain results did not align entirely with the initial assumptions. In particular, the Random Forest (RF) and Naïve Bayes (NB) classifiers yielded lower-than-expected performance, despite utilizing the same optimized feature subset. This suggests that the effectiveness of selected features is classifier-dependent, warranting further investigation into classifier-specific feature selection techniques. A detailed comparison of our findings against the initial hypothesis is presented in Table 14, which highlights the alignment and discrepancies observed across different classifiers

Table 14. Critical Comparison of Findings with Hypothesis

Hypothesis Expectation	**Observed Results**	**Alignment with Hypothesis**
HHO-MRMR will enhance classification accuracy by eliminating irrelevant features	Accuracy improved to **96.15%** with a **reduced feature set (50 genes)**	Supports hypothesis
Selected feature subset will be universally effective across classifiers	**SVM performed best, whereas DT and RF showed lower accuracy**	Partially challenges hypothesis
Optimizing SVM hyperparameters using metaheuristic algorithms will improve classification	**PSO, HHO, and DE optimization led to**	Supports hypothesis

	a notable accuracy increase	

These findings emphasize both the strengths and potential refinements required for the proposed approach. While the hypothesis is largely validated, the observed classifier-specific variations indicate that further exploration is needed to ensure broader feature set compatibility across different machine learning models. Future research should consider incorporating deep learning techniques or hybrid optimization approaches to enhance the robustness and generalizability of the model.

Commented [AA2]: Comment 7

8.1 Statistical Analysis

Classification performance was evaluated using 10-fold stratified cross-validation, with all metrics reported as mean ± standard deviation (SD) and 95% confidence intervals (CI). Given the comparison of four classification algorithms across six performance metrics, we implemented a comprehensive statistical framework to control for multiple comparisons. The Friedman test, a non-parametric repeated measures analysis, assessed overall differences among classifiers for each metric. When significant differences were detected ($\alpha = 0.05$), we performed post-hoc pairwise comparisons using two complementary approaches: (1) the Nemenyi-Friedman test with Bonferroni correction for conservative family-wise error rate (FWER) control (Nemenyi, 1963), and (2) Wilcoxon signed-rank tests with Holm-Bonferroni sequential correction for enhanced statistical power while maintaining FWER control. This dual approach provides robust validation, with consistency across both methods indicating strong evidence of differences. All statistical analyses were performed using Python with scipy and scikit-posthocs libraries.

8.2 Classification Performance and Statistical Validation

Table 15 presents comprehensive performance metrics for all four classifiers across six evaluation measures. Among the methods tested, Support Vector Machine (SVM), Random Forest, and Naive Bayes demonstrated comparable high-level performance across most metrics, while Decision Tree showed significantly lower performance in specific measures.

Accuracy ranged from 0.8692 (Decision Tree) to 0.9462 (SVM and Naive Bayes), with the Friedman test indicating significant overall

differences (χ^2 = 13.42, p = 0.0038). However, post-hoc pairwise comparisons with multiple comparison correction did not identify specific significant differences among the top three classifiers, suggesting relatively modest variance in their accuracy performance.

Area Under the ROC Curve (AUC) revealed the most pronounced differentiation among classifiers (Friedman χ^2 = 20.54, p = 0.00013). SVM achieved the highest AUC of 0.9903 ± 0.0155 (95% CI: 0.9807, 0.9999), with Random Forest (0.9897 ± 0.0160) and Naive Bayes (0.9882 ± 0.0214) performing comparably. Decision Tree showed significantly lower AUC (0.9096 ± 0.0595), with differences confirmed by both Nemenyi-Friedman (SVM vs. DT: p = 0.0055; RF vs. DT: p = 0.0074; NB vs. DT: p = 0.0221) and Holm-Bonferroni corrected Wilcoxon tests (all p = 0.0077, significant after sequential correction). The mean difference in AUC between the top-performing methods and Decision Tree was approximately 0.08, representing a clinically meaningful improvement in discriminative ability.

Average Precision demonstrated similar patterns (Friedman χ^2 = 20.79, p = 0.00012), with the three advanced classifiers achieving values exceeding 0.9629 while the Decision Tree scored 0.7972 ± 0.1243. These differences were statistically significant across both post-hoc testing frameworks (Nemenyi: SVM vs. DT p = 0.0030, RF vs. DT p = 0.0130, NB vs. DT p = 0.0222; Holm-Bonferroni Wilcoxon: all p = 0.0077). The substantial effect size ($\Delta \approx 0.18$) indicates that the top three classifiers provide markedly superior precision-recall performance.

For precision, recall, and F1-score metrics, Friedman tests detected significant overall differences (precision: χ^2 = 12.64, p = 0.0055; recall: χ^2 = 9.95, p = 0.019; F1-score: χ^2 = 9.95, p = 0.019). However, pairwise comparisons with multiple comparison correction did not reach significant thresholds, consistent with the similar high-level performance of SVM, Random Forest, and Naive Bayes across these metrics Table 15.

The narrow confidence intervals and low standard deviations observed for the three top-performing classifiers (SD typically < 0.07) demonstrate algorithmic stability across cross-validation folds. This consistency is particularly important for clinical applications, where reliable performance across different patient subsets is essential for safe deployment.

Table 15. Statistical Test Summary

Metric	Friedman χ^2	p-value	Post-hoc Significant Comparisons
Accuracy	13.42	0.0038	None after multiple comparison correction
Precision	12.64	0.0055	None after multiple comparison correction
Recall	9.95	0.019	None after multiple comparison correction
F1-Score	9.95	0.019	None after multiple comparison correction
AUC	20.54	0.00013	SVM, RF, NB vs. DT (all $p < 0.023$)
Avg Precision	20.79	0.00012	SVM, RF, NB vs. DT (all $p < 0.022$)

9 Limitations of the Proposed Model

Commented [AA3]: Comment 2

9.1. Sample Size

One of the primary limitations of this study is the relatively small dataset used for model training and validation. Although the dataset was carefully curated from publicly available microarray gene expression profiles, the limited sample size may affect the model's ability to generalize to broader populations. A larger and more diverse dataset, incorporating multiple independent cohorts from different populations, would provide a more robust evaluation of the model's effectiveness in real-world clinical scenarios.

9.2. Model Complexity

The proposed model integrates multiple feature selection techniques and optimization algorithms, making it more computationally intensive compared to conventional machine learning approaches. While the combination of mRMR, HHO, and SVM hyperparameter optimization enhances classification accuracy, its complexity may pose challenges in practical implementation, particularly in resource-constrained clinical settings. The computational cost of feature selection and model training could be a barrier to real-time applications, necessitating further optimization for efficiency and scalability.

9.3 Assumptions of the Algorithms

Each feature selection and metaheuristic optimization technique employed in this study operates under specific assumptions. The mRMR algorithm assumes that the most relevant and least redundant features contribute

optimally to classification, while HHO relies on iterative search heuristics to optimize feature subsets. However, these assumptions may not always hold true across all datasets, particularly those with high biological variability. In cases where feature interactions are highly non-linear, alternative approaches, such as deep learning-based feature selection, may offer improved performance.

9.4 Biological Interpretation

Although the selected genes were analyzed based on existing scientific literature, their biological significance in brain cancer requires further validation. The association of certain genes with cancer progression is well-established, but their specific roles in tumorigenesis, metastasis, and treatment resistance remain subject to ongoing research. Future work should include wet-lab validation experiments, such as functional genomics studies and pathway enrichment analysis, to confirm the biological relevance of the identified biomarkers.

9.5 Dynamic Nature of Cancer

Cancer is an inherently heterogeneous and evolving disease, characterized by genomic instability and adaptive resistance mechanisms. The current model is trained on static gene expression datasets, which may not fully capture the dynamic nature of tumor biology over time. Future improvements should focus on longitudinal data integration, allowing the model to learn from temporal changes in gene expression profiles. Additionally, incorporating multi-omics data, such as proteomics and metabolomics, could enhance the model's ability to detect complex biological patterns associated with disease progression and treatment response.

Commented [AA4]: Comment 5

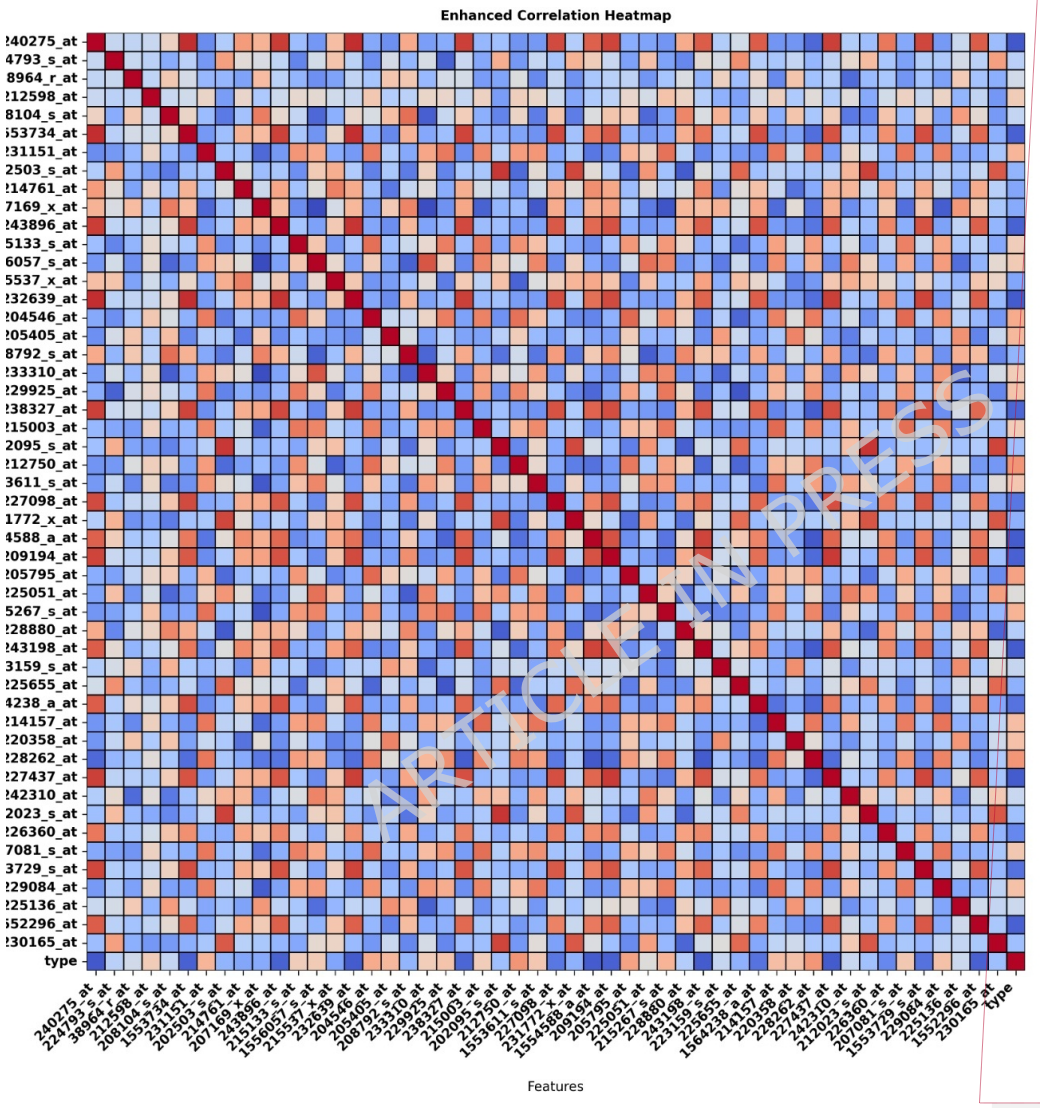

Figure 10. Correlation Heat maps of 50 genes selected by the (HHO-mRMR) model.

10 CONCLUSIONS AND FUTURE WORK

A hybrid feature selection and classification model (HHO-MRMR) are proposed in this study which is utilized for classifying brain cancer. The proposed model exhibited better results for the brain cancer classification in terms of computational efficiency and classification accuracy. Moreover, the proposed model is also effective as compared to other existing techniques. By using fitness-based metaheuristic optimization techniques like Harris Hawks Optimization, Differential Evolution, and Particle Swarm Optimization, the proposed model was able to successfully reduce feature redundancy without affecting predictive performance. The results of an experiment validated this approach. As compared to other classifiers like Decision Tree, Naïve Bayes, etc. SVM classifier, though extra terrific, gave the best accuracy. However, while the model was effective at tuning hyperparameters and increasing classification accuracy, the different performance results of the classifiers suggest that they respond differently to features selected by the model. We will try to integrate deep learning-based models to capture the non-linear feature interactions. It will help increase the classification accuracy, after that we will validate the model on larger and more heterogeneous real-world clinical datasets to check for generalizability and robustness. Moreover, feature selection strategies combining deep learning-based feature importance ranking techniques from the metaheuristic community could be adapted to model for better feature selection. Using genomics, transcriptomics, and proteomics to gather data for better cancer classification and biomarker discovery is a more future goal integration. Moreover, the adoption of ensemble learning techniques like stacking and boosting could enhance the classification performance by leveraging the strengths of multiple models. We may apply the recommended approach in actual time in clinical decision support systems to begin with it applicable to assist oncologists for more accurate and personalized cancer diagnosis. Addressing these factors will help advance intelligent computer systems for more accurate, efficient, and reliable cancer classification methods useful for application in the bioinformatics and medical field.

Commented [AA5]: Comment 6

Data availability: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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