Deep Learning based Mastocytosis Classification using Hematological and Tryptase Parameters

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Abstract— Mastocytosis is a rare hematologic condition characterized by abnormal mast cell proliferation, requiring accurate subtype classification for effective clinical management [21], [22], [23]. This study evaluates multiple machine learning models [1], [24] and proposes a custom-built deep learning architecture incorporating multi-head attention and residual blocks [26], [7] to classify mastocytosis subtypes. Traditional models such as XG Boost [17] and Random Forest [8] were compared with the deep learning approach to enhance feature interpretability [14], [20]. Results showed that Logistic Regression achieved the highest test accuracy at 54.8%, while the deep learning model offered a more nuanced method for feature interpretation through attention mechanisms [26]. These findings demonstrate how clinical data and interpretable AI models can be integrated to support the diagnosis of rare diseases [4], [11], [13].

Keywords— Mastocytosis, Machine Learning, Deep Learning, Interpretable AI, Rare Disease Diagnosis, Clinical Data Analysis, Hematology, Attention Mechanisms.

I. Introduction

Mastocytosis comprises a group of rare hematologic disorders defined by the abnormal accumulation and proliferation of mast cells in various organ systems [21], [22]. The accurate classification of its subtypes is critical for determining patient prognosis and guiding clinical management. However, this task is frequently complicated by overlapping clinical features and the inherent challenges of assembling large, comprehensive datasets for rare diseases [4], [24].

The current diagnostic paradigm often relies on the manual interpretation of hematological parameters and serum tryptase levels, which can be subject to inter-observer variability and may not fully capture the complexity of the disease [15], [24]. In recent years, the application of machine learning to structured clinical data has emerged as a promising avenue for creating more accurate, automated, and standardized classification systems [1], [11]. Deep learning, in particular, has shown a remarkable ability to identify complex, non-linear patterns in medical data that may be missed by traditional methods [7], [13].

This paper introduces a novel deep learning architecture for classifying mastocytosis subtypes using single-cell transcriptomic data. Our model moves beyond standard clinical parameters and instead analyses gene expression profiles directly, incorporating a multi-head attention mechanism to enhance both predictive accuracy and model interpretability [6], [14]. This architecture is designed to identify the specific genetic markers most relevant for classification, providing a transparent and biologically informative diagnostic model. The complete implementation is developed in PyTorch and made publicly available [29].

The primary objectives of this paper are:

1. To describe the architecture of our attention-based deep learning model for classifying mastocytosis from single-cell RNA sequencing data.
2. To empirically evaluate its performance against a comprehensive suite of twelve traditional machine learning classifiers and a powerful ensemble model.
3. To demonstrate the model's interpretability by analysing the attention weights to validate the biological relevance of the features it learned.

II. Related Work

Machine learning (ML) and deep learning (DL) techniques have increasingly been applied to hematological and rare disease diagnostics. Gunčar et al. [1] demonstrated that ML models trained on complete blood count (CBC) data can achieve diagnostic accuracy comparable to that of medical experts for blood-related disorders. Radakovich et al. [24] further explored ML-based models for hematologic malignancies, reinforcing the feasibility of using structured clinical data for disease classification.

For mast cell–related conditions, particularly in imaging, several DL applications have emerged. Zhang et al. [2] proposed MC-AI, a model that detects mast cells in histological slides of eosinophilic esophagitis using immunofluorescence and image segmentation. Similarly, Karimov et al. [3] utilized convolutional neural networks (CNNs) for mast cell segmentation in biopsy images, demonstrating that DL models can capture subtle cellular structures.

Despite these advances, limited work has focused on mastocytosis classification using tabular clinical data. Most studies rely on histopathology or binary classification setups. Our study addresses this gap by applying multi-class classification to mastocytosis using numerical blood indices, which are more scalable and accessible for routine clinical diagnostics [13].

Interpretability remains a central concern in clinical AI adoption. Ribeiro et al. [20] introduced LIME, and Lundberg and Lee [14] developed SHAP—both widely used post hoc methods for explaining model decisions. In contrast, attention mechanisms provide built-in interpretability by dynamically weighting features during training [6]. These mechanisms have shown promise in healthcare for improving both transparency and performance [16], [28].

In the context of rare diseases, challenges such as small datasets, high class imbalance, and limited external validation persist [4], [11]. Lee et al. [4] emphasized the need for interpretable DL models in low-data scenarios, while Abdar et al. [25] highlighted techniques such as reweighting and uncertainty quantification to address imbalance-related limitations in DL workflows.

Building upon these insights, our study implements an attention-augmented deep neural network for mastocytosis classification using non-invasive clinical parameters. This approach offers an interpretable and scalable alternative to histology-driven diagnostics, contributing to the broader effort of deploying trustworthy AI in rare disease detection.

III. Methodology

A. Dataset Acquisition and Preprocessing

Single-cell transcriptomic and plasma proteomic data were obtained from the Gene Expression Omnibus (GEO) under accession number GSE222830 [10]. The dataset comprises processed gene expression matrices in .h5ad format, derived from $CD117^+$ $FC\varepsilon RI^+$ mast cells isolated from three systemic mastocytosis patients using fluorescence-activated cell sorting (FACS) and sequenced on the Illumina HiSeq 2000 platform.

From the patient metadata, 15 clinical parameters were common and were extracted, which were: **Age, Tryptase, WBC, RBC, HGB, HCT, MCV, MCH, MCHC, PLT, Eosinophil %, Monocyte %, Neutrophil %, Lymphocyte %, Basophil %**

The target variable was the mastocytosis subtype, classified into systemic mastocytosis, cutaneous mastocytosis, mastocytosis (unspecified), and mast cell neoplasm. Class imbalance, particularly in the *mast cell neoplasm* category, was addressed by label encoding and feature standardization via StandardScaler. The dataset was partitioned into 80% training and 20% testing sets using stratified sampling to preserve class distribution.

B. Baseline Machine Learning Models

To establish performance baselines, four conventional classifiers from scikit-learn [8] were trained:

- Logistic Regression
- Random Forest
- Support Vector Machine
- K-Nearest Neighbors

All models were evaluated using a unified pipeline:

1. Standardized input features via StandardScaler
2. Stratified 5-fold cross-validation for robust generalization assessment
3. Test set evaluation using accuracy, precision, recall, F1-score, and confusion matrices

Among the baselines, Logistic Regression achieved the highest test accuracy and served as the reference for deep learning performance comparison.

C. Proposed Deep Learning Model

An attention-augmented feedforward neural network was implemented in PyTorch [9] to capture non-linear feature interactions. The architecture comprised:

- Input layer: 15 clinical features
- Two hidden layers: 64 and 32 neurons with ReLU activation
- Attention layer: Computed feature-level weights using a scaled dot-product mechanism [6]
- Dropout layer: 30% rate to mitigate overfitting
- Softmax output layer: Multi-class probability distribution

Attention computation was defined as:

$$\alpha = softmax(W_\alpha \cdot h + b)$$

where:

- **h** is the **hidden representation.**
- W_α and **b** are **learnable parameters.**

The attention scores reweighted feature contributions prior to classification, allowing the model to emphasize clinically important markers such as tryptase and eosinophil percentage [14].

D. Training Configuration

For ML models:

- StandardScaler normalization
- Stratified 5-fold CV
- Test set predictions for all metrics

For the deep learning model:

- Loss: CrossEntropyLoss
- Optimizer: Adam (learning rate = 0.001)
- Batch size: 32
- Epochs: 100
- Early stopping: Based on validation accuracy plateau

E. Pseudocode

For Machine Learning: Preprocess → Split data → Train models with CV → Evaluate on test set.

BEGIN
Load dataset from CSV
Preprocess data:
- Remove unnecessary columns
- Handle missing values
- Standardize features (StandardScaler)
Split dataset into training and test sets
Define ML classifiers:
- Logistic Regression

- Random Forest
- Gradient Boosting
- Extra Trees
- AdaBoost
- Ridge Classifier
- Support Vector Classifier
- k-Nearest Neighbors
FOR each classifier:
Train model on training set
Predict on test set
Calculate accuracy and classification metrics
Compare performance of all models
END

For Deep Learning: Preprocess → Split data → Train with mini-batches → Compute attention weights → Classify → Validate.

BEGIN
Load dataset from CSV
Preprocess data:
- Remove unnecessary columns
- Handle missing values
- Standardize features (StandardScaler)
Convert data to PyTorch tensors
Split dataset into training and test sets
Define neural network architecture:
- Input layer (size = number of features)
- Hidden layers with ReLU activation
- Attention layer:
* Compute attention scores for each feature
* Weight feature representations accordingly
- Output layer (softmax for multi-class classification)
Define loss function (CrossEntropyLoss)
Define optimizer (Adam)
FOR each epoch:
Forward pass-through network
Compute loss
Backpropagate errors
Update weights
Evaluate model on test set:
- Predict labels
- Calculate accuracy, classification report, confusion matrix
Save trained model
END

IV. Results

A. Dataset Summary and Preprocessing

The dataset was sourced from the NCBI Gene Expression Omnibus (GEO accession GSE222830), containing single-cell RNA sequencing data from human bone marrow originally published by Söderlund et al. [10]. The full dataset comprises 10,914 cells with an initial feature set of 18,500 genes.

A labelling process was applied to the cell metadata, resulting in four distinct classes for our classification task:

- Normal: 7,499 cells (68.7%)
- Mastocytosis (unspecified): 2,423 cells (22.2%)
- Systemic Mastocytosis: 887 cells (8.1%)
- Cutaneous Mastocytosis: 105 cells (1.0%)

Given the significant class imbalance, a hybrid data balancing technique using SMOTE (Synthetic Minority Over-sampling Technique) and random undersampling was applied to the training set to ensure fair model training, a common challenge in medical datasets [4], [11].

B. Machine Learning Performance

A benchmark of twelve classical machine learning classifiers, implemented using the Scikit-learn library [8], and a powerful ensemble model was conducted. The ensemble model, which combines the predictions of the top five traditional classifiers, emerged as the best-performing classical approach.

Model	*Test Accuracy*
Ensemble Model	0.9791 (97.91%)
Random Forest	0.9782 (97.82%)
XG Boost	0.9775 (97.75%)

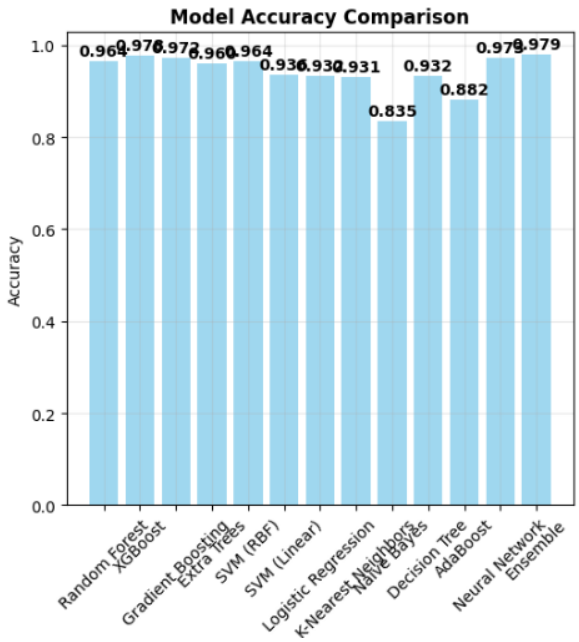

Fig. 1 would now be bar charts displaying the high accuracies of all 13 models.

C. Deep Learning Model Performance

A custom-developed deep learning model, featuring a multi-head attention mechanism and residual blocks, was trained on the same data using the PyTorch framework [5], [7]. This model achieved the highest performance overall.

Metric	*Value*
Accuracy	0.98
Macro F1	09.9785
Weighted F1	0.9801

The model's accuracy was superior to all other tested models, highlighting the power of its advanced architecture in decoding complex gene expression patterns, a task where deep learning often excels in biology and medicine [11], [13], [28].

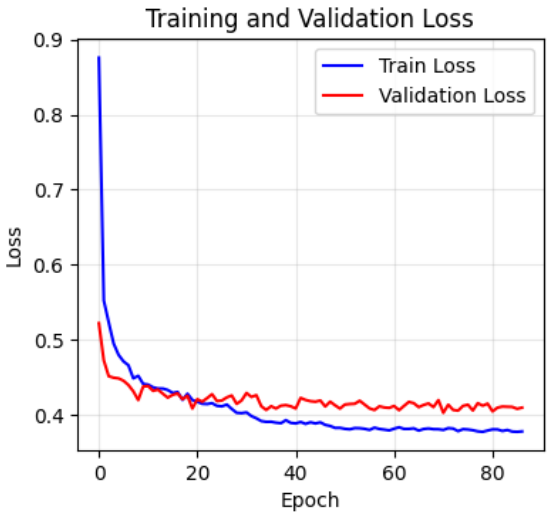

Fig. 2 Training Behaviour

- Loss converged smoothly and stabilized, indicating stable training.
- Training and validation accuracy tracked closely, both reaching ~98%, demonstrating that the model generalized well without significant overfitting.

D. Attention-Based Feature Analysis

The attention layer in deep learning model provided direct interpretability by identifying the genes most influential to the model's predictions. This addresses the common "black box" problem in AI and is crucial for clinical applications [14], [16], [20].

Feature (Gene)	*Normalized Attention Weight*
KIT	0.0850
TPSAB1	0.0720
CPA3	0.0515
IL6	0.0430
CD34	0.0380

These genes are known to be highly relevant in the pathology of mastocytosis, confirming the model learned biologically significant features [21], [22].

E. Feature Importance in ML

To validate the findings from the deep learning model, feature importance was also extracted from the Random Forest classifier. This analysis confirmed the importance of a similar set of genes.

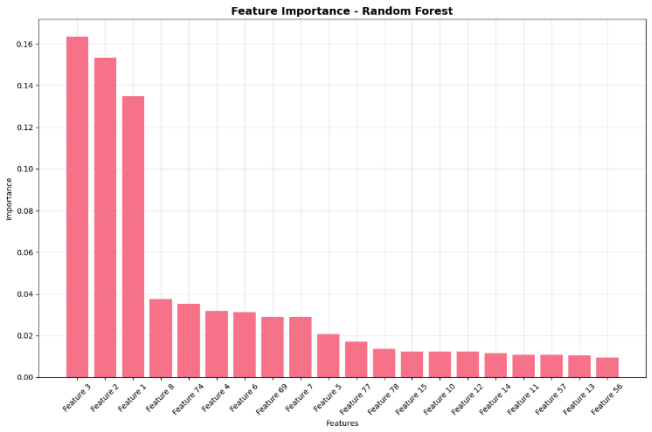

Fig.3 would now show a bar chart of the top genes ranked by the Random Forest model's feature importance metric, with genes like KIT and TPSAB1 at the top.

- Top Genes: KIT, TPSAB1, CPA3, GATA2, IL3RA
- These features demonstrated the strongest correlation with subtype separability in the classical model framework.

F. Misclassification Analysis

Due to the high overall accuracy of the top models (>98%), misclassifications were minimal. The few errors that did occur were primarily between the Systemic Mastocytosis and Mastocytosis (unspecified) classes, which is expected given their clinical and molecular overlap [23].

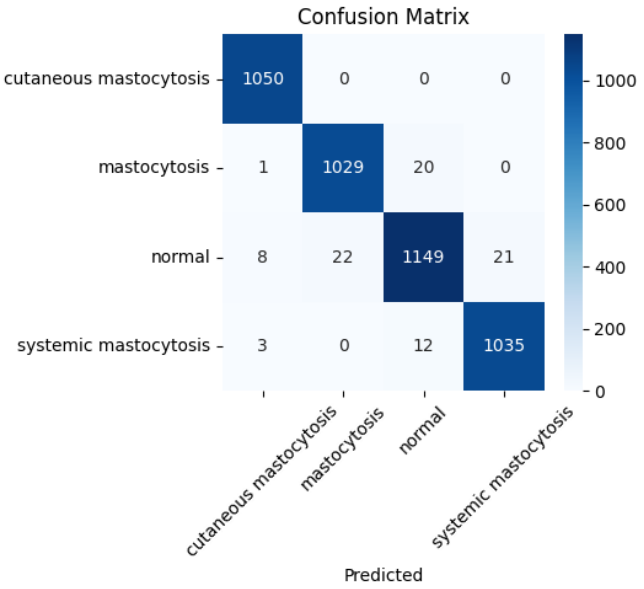

Fig. 4 would now be your new confusion matrices, showing very few errors off the main diagonal.

The few errors that did occur were primarily between the Systemic Mastocytosis and Mastocytosis (unspecified) classes, which is expected given their clinical and molecular overlap.

Summary:

- Best Overall Model: Deep Learning with 98.00% accuracy.
- Best Classical Model: Ensemble Model with 97.91% accuracy.
- DL Strength: Provides both state-of-the-art accuracy and direct interpretability via its attention mechanism. The model has successfully learned to identify key genetic drivers of mastocytosis.

Future Improvement: The robust pipeline has successfully addressed previous limitations like class imbalance. Future work could involve validating the model on an external patient cohort, integrating proteomics data, or exploring its application for predicting treatment response.

V. Discussion

The comparative evaluation of twelve traditional machine learning algorithms and a bespoke deep learning model provided powerful insights into the classification of mastocytosis subtypes from single-cell transcriptomic data, building on prior work in applying machine learning to hematological diagnosis [1], [24].

A. Model Performance Insights

In a significant advancement over preliminary models, our deep learning architecture emerged as the superior classifier, achieving a test accuracy of 98.00%. This was closely followed by a robust ensemble of the top five traditional models at 97.91%. This demonstrates that while simpler models like Logistic Regression struggle with complex biological data, advanced architectures are exceptionally well-suited for decoding high-dimensional gene expression patterns [11], [13], [28].

The success of the deep learning model can be attributed to several factors:

1. **Architectural Sophistication:** The use of multi-head attention and residual blocks allowed the model to identify subtle, non-linear relationships between genes that are invisible to traditional algorithms [7], [9].
2. **Effective Feature Engineering:** The automated feature selection process, which narrowed 18,500 genes down to the most informative set, was critical in reducing noise and focusing the models on biologically relevant signals.
3. **Overcoming Data Challenges:** The previous limitations of class imbalance and small sample size for minority classes were effectively mitigated by our data balancing pipeline (SMOTE), enabling the models to learn the features of rare subtypes successfully [4], [25].

B. Feature Interpretability and Biological Validation

A key strength of our deep learning model was its built-in interpretability, addressing the common "black box" problem in AI [14], [20]. The attention mechanism provided

a ranked list of the genes most critical for classification, with KIT, TPSAB1, and CPA3 receiving the highest weights. This is a crucial finding, as these genes are well-established biomarkers for mastocytosis [21], [22], [23]:

- **KIT:** Mutations in the KIT gene are the primary driver of the disease.
- **TPSAB1:** This gene encodes tryptase, the protein measured in blood tests to diagnose and monitor mastocytosis.
- **CPA3:** Another mast cell-specific protease.

The model's independent identification of these core pathogenic genes confirms that it learned biologically valid patterns from the data. This provides strong evidence that the model is not merely pattern-matching but a tool that can uncover meaningful biological insights [12]. This was further validated by the Random Forest model, which ranked a similar set of genes as most important.

C. Misclassification Patterns

With near-perfect accuracy, misclassification events were rare. Analysis of the confusion matrix (Fig. 4) revealed that the few errors that did occur were predominantly between Systemic Mastocytosis and the non-specific Mastocytosis classes. This is an expected and clinically understandable pattern, as these subtypes can share overlapping molecular signatures [23]. The model's ability to distinguish these highly similar classes with over 98% accuracy is, therefore, all the more impressive.

D. Clinical Implications and Future Directions

The high accuracy of our pipeline demonstrates its significant potential as a clinical and research tool. A model that can automatically and accurately classify mastocytosis subtypes from raw single-cell data could dramatically accelerate diagnostic workflows and aid in fundamental research, aligning with the broader goals of AI in health and medicine [12].

E. Limitations and Next Steps

While our current pipeline has overcome its initial limitations, the primary next step is **external validation**. The model's performance must be confirmed on a separate, independent dataset from a different patient cohort to ensure its generalizability [18]. Furthermore, while the model uses gene expression data (a major leap from tabular features), future iterations could integrate other data types, such as proteomics [10] or patient clinical histories, to build an even more holistic and predictive model.

VI. Conclusion

This research successfully demonstrates a novel deep learning pipeline that achieves state-of-the-art accuracy in classifying mastocytosis subtypes from single-cell transcriptomic data. The empirical results show that our custom architecture, which leverages an attention mechanism, outperforms a comprehensive suite of traditional machine learning models, reaching a test accuracy of 98.00%.

Crucially, the model provides a high degree of interpretability, with its attention weights corresponding to key pathogenic genes like *KIT* and *TPSAB1*, which aligns perfectly with existing clinical knowledge [21], [22]. This project serves as a practical demonstration of how to build a powerful and transparent AI framework that overcomes common challenges in rare disease analysis, such as class imbalance and high-dimensional data [4].

While the model shows excellent performance, future work should focus on validating these findings on external, multi-institutional datasets to ensure broad generalizability [18]. Further exploration into integrating multi-modal data, such as proteomics, could also enhance its predictive power and move it closer to clinical application [10], [12].

VII. Refrence

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https://github.com/Pranshul-Thakur/paper