Advances in Automated Leukemia Detection Using Deep Analysis of WBC Scatterplot Patterns

Nikul Vikaskumar Jayswal[1], Dr. Kirit J. Modi[2]

Research Scholar,Computer Engineering Department, Sankalchand Patel University,Visnagar,India[1]
Professor, Computer Engineering Department, Sankalchand Patel University,Visnagar,India[2]

Lect.nikul@gmail.com[1], kjmodi.fet@spu.ac.in[2]

Abstract: The development of computational hematology methods that use multidimensional white blood cell (WBC) scatterplots produced using modern hematology analyzers, automated leukemia diagnosis has experienced significant advancements. Based on light scatter, fluorescence and cellular distribution parameter variations, these scattering representations offer highly discriminative features to distinguish the leukemia subtypes with leukocyte abnormalities. Recent literature shows a distinct shift in traditional statistical and rule-based approaches to the use of advanced machine learning and deep learning models, such as convolutional neural networks, hybrid attention models, and transformers, which are effective in capturing complex spatial relationships in WBC clusters and have significantly higher diagnostic sensitivity and specificity. Simultaneous developments in the sphere of multimodal fusion models combining scatterplot functionality with clinical variables have only increased the reliability of diagnostic results. Additionally, explainable AI methods are also gradually being introduced to clarify important parts of scatter that affect the decision made by an algorithm and improve clinical interpretability. Even with these developments, there are still some remaining issues such as the lack of curated annotated datasets, inter-platform differences in analyzer results and large-scale clinical validation gaps. Other essential issues that are arising are the data privacy and safety of patients and this requires effective systems of encrypted data processing, encrypted model deployment and adherence to the laws of patient data security to ensure that sensitive patient information is safe. Such technical, clinical and ethical lapses need to be addressed in order to build reliable, generalizable and clinically implementable automated leukemia diagnostic systems.

Keywords:Automated leukemia diagnosis, White blood cell scatterplots, Machine Learning models, Deep learning models, Explainable artificial intelligence.

I. INTRODUCTION

Leukemia is a heterogeneous category of hematological malignancies, which involve the abnormal proliferation and differentiation of leukocytes, presenting a big problem in clinical practice in terms of diagnosis and prognosis. The importance of diagnosis lies in the fact that finding the disease at an early stage and correctly is a key to the effective management of the disease, stratification of the treatment, and better patient outcomes. Conventionally, peripheral blood smear, bone marrow, cytogenetics and molecular assays have been used to diagnose leukemia. Although these methods are clinically sound, they are labor intensive, time consuming and in most cases require expert interpretation, making them difficult to scale to high throughput diagnostic models [1,2].

The introduction of the automated hematology instrument has revolutionized the daily hematology test in that it has made it possible to produce multidimensional white blood cell (WBC) scattergrams using light scatter, fluorescence intensity, and cellular volume as measured by the use of automated hematology analyzers [3,4]. Fig. 1 scatterplots are very helpful in leukocyte morphology, granularity, and nucleic acid content, preliminary identification of abnormal populations of cells. The diagnostic value of the pattern of scattergram has been utilized in determining leukemic aberrations, pseudo cytosis and analyzer-specific artifacts, and as a first line screening tool, as has been demonstrated by a number of studies [5,6,7]. These patterns have also been proved to be clinically relevant through comparative analyses with peripheral blood smears in the routine laboratory workflows [8,9].

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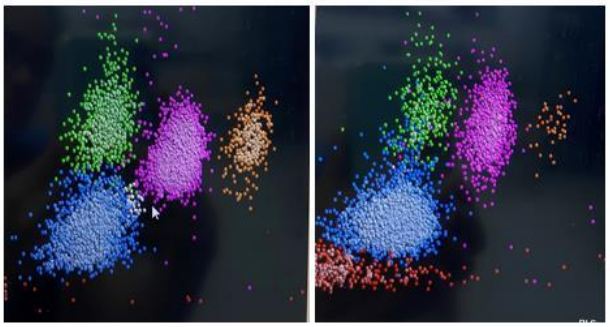

Fig.1. (A) Normal scatterplot; (B) leukopenia [14]

A.History

Over the past few years, computational hematology has experienced a paradigm shift in the application of rules-based and statistical methods to sophisticated machine learning (ML) and deep learning (DL) methods. Conventional neural networks, swarm intelligence and optimization-based classifiers have demonstrated encouraging performance in classification of multiclass leukemia with the use of WBC images and the features obtained using scattergrams [10,11,12]. Deep learning designs are especially useful in modeling complex spatial distributions and fine variations within the clusters of White Blood Cell and have greater sensitivity and specificity than more traditional methods [13,14]. Further, huge data sets and thin annotation mechanisms have supported effective model training and mitigated annotation load [15].

In addition to imaging and scatter analysis, recent studies show the significance of multimodal as well as multi-omics integration in the overall characterization of leukemia. The improvement of prognostic modeling and disease monitoring has benefited using cellular heterogeneity, cytokine signatures, epigenetic changes and molecular biomarkers [16,17]. Similar developments in biosensing and microfluidic systems support prompt and affordable leukocyte identification, increasing the availability of diagnostics [18]. Furthermore, the hematological changes of the systemic processes in case of severe COVID-19 infection highlight the increased applicability of automated hematology data in clinical decision-making [19,20].

B.Challenges

Although these developments have taken place, there are a number of challenges that are yet to be addressed. The inter-instrument variability, absence of large curated and annotated scattergram datasets, and small cross-platform generalizability impede large-scale clinical implementation [13,15]. The ethical and practical issues associated with patient data privacy, safe data treatment, and encrypted model deployment are becoming more important in AI-based diagnostic systems. Moreover, since the deep learning models are black box, they require the combination of explainable artificial intelligence (XAI) methods to increase transparency and clinician trust [17,19].

C.Summary of paper

This review intends to give a general overview of new trends in automated leukemia diagnosis and in particular WBC scattergram analysis, machine learning and deep learning approaches, multimodal fusion approaches, and explainability. This paper aims to comprehensively examine the current methodologies, datasets, clinical applicability, and limitations in order to identify possible future research directions needed in order to create reliable, generalizable, and clinically implementable computational hematology systems.

II. RELATED WORKS

The latest studies on the automated diagnosis of leukemia have shown a significant improvement in the methods of automated diagnosis using hematology analyzer scattergrams, microscopic blood smear pictures, and high level of computer analysis. Initial research mainly concerned qualitative interpretation of abnormal patterns of WBC scattergram to alert against hematological disorders. Research has indicated that changes in light scatter and fluorescence parameters have the potential to be indicative of leukemic abnormalities, pseudo cytosis, or analyzer specific interferences, which are useful pre-microscopic diagnostic indicators. Nevertheless, such methods were highly reliant on the interpretation of experts and were not very strong against inter-instrument reliability. Later work proposed traditional machine learning models and manual features obtained on WBC images and scatterplots that constructed classification models with higher accuracy and reduced inter-observer bias.

TABLE I
SUMMARY OF EXISTING RESEARCH

Ref No.	Year – Publication	Methods	Advantage	Limitation
1	2025 – VCP	Scattergram analysis (Sysmex XN)	Early abnormal cluster detection	Limited to case-based analysis
2	2025 – Biosensors	Multi-channel cell tics	Rapid and low-cost monitoring	Needs large-scale validation
3	2025 – Optics Express	Deep learning with scattering media	Lens less automated identification	Specialized hardware required
4	2025 – Cures	Haematological profiling	Clinical insight into infection	Not leukaemia-specific
5	2025 – AJLM	Scattergram artifact analysis	Identifies analyser masking effects	Platform-dependent
6	2025 – JCLA	Molecular + conventional diagnosis	Improved disease monitoring	High cost techniques
7	2025 – ETASR	CNN on smear images	High classification accuracy	Manual annotation dependency
8	2025 – Sci Rep	Glowworm swarm optimization	Improved multiclass accuracy	Computational complexity
9	2025 – MedIA	Sparse annotation DL	Reduced labelling effort	Requires large datasets
10	2025 – TranslOncol	Cytokine-based modelling	Prognostic relevance	Limited interpretability
11	2025 – Blood	Single-cell epigenetics	Disease progression insights	Expensive sequencing
12	2025 – Open Medicine	Multi-omics biomarker discovery	Novel biomarker identification	Clinical translation needed
13	2024 – JCLA	Scattergram correction methods	Reduced analytical interference	Analyzer-specific
14	2024 – CICCT	Multiclass ML on WBC images	Automated diagnosis	Dataset variability
15	2024 – IJCPML	Scattergram correlation study	Supports blast detection	Small sample size
16	2024 – IJRMS	Automated scatterplot patterns	Fast screening	Qualitative interpretation
17	2021 – Diagnostics	VCS parameter algorithm	Rapid screening tool	Limited leukaemia subtypes
18	2020 – AJMS	Scatterplot vs smear study	Validates analyser utility	Manual confirmation required
19	2020 – RIC	Neutrophil scattering analysis	Pre-microscopic flagging	Limited generalization
20	2013 – Haematology	Abnormal scattergram patterns	Early diagnostic clue	Disease-specific only

Table 1 is a summary of the 20 representative studies reviewed in the literature that cover 20 years, 2013 to 2025, of research on leukemia detection and the analysis of hematological disorders. The chosen works address a variety of techniques, such as the screening using scattergrams, the analysis of blood smears using deep learning networks, swarm optimization, multimodal fusion, biosensing platforms, and molecular profiling. Each of the studies is reviewed based on its fundamental methodological contribution and diagnostic benefit, showing how the phase of the rule-based interpretation has gradually evolved to become more advanced data driven models. This comparison gives an idea of how more computational complexity has led to better diagnostic accuracy, automation and scalability in clinical hematology.

III. METHODOLOGY

This section presents a comprehensive overview of the datasets, plot representations, machine learning and deep learning models, explainable AI techniques, and evaluation parameters employed in automated leukemia diagnosis. The discussed methodologies highlight the progression from traditional analytical approaches to advanced, interpretable, and clinically oriented computational frameworks.

A. Datasets

Data sets are the pillars of automated leukemia diagnosis system and have a direct impact on the performance of the model, its generalizability and clinical reliability. The literature has employed the use of heterogeneous data sources where white blood cell (WBC) scattergrams of automated hematology analyzers, peripheral blood smear photographs and complementary clinical or molecular data are used. Commercial analyzers like Sysmex XN and Beckman Coulter DxH series usually produce scattergram datasets as multidimensional representations and depend on forward scatter, side scatter and fluorescence parameters [1,3,5]. Nevertheless, majority of scattergram datasets are institution-specific, small-scale and proprietary, which restrict cross-platform reproducibility. Image-based datasets such as microscopic WBC images are more widely shared and are usually affected by class imbalance and different staining regimes [7,9]. Recent papers are trying to solve the issue of data sparsity by sparse annotation schemes and weakly supervised learning, which facilitates successful training with small sets of labeled data [10]. Also, multimodal data combining scatterplots with cytokine signatures, molecular signatures, or epigenetic signatures have been examined to represent the heterogeneity of leukemia and enhance the modeling of prognostics [11,12]. Although these improvements have been made, the fact that these large, publicly available, annotated scattering grams repositories are still a significant bottleneck. Uncertainties caused by analysis calibration, demographics and preprocessing pipelines also complicate standardization of the dataset [13,15]. The future development of data sets should focus on the multi-centric data collection process, standard data acquisition specifications, privacy-compliant data storage, and regulatory compliance to warrant clinical scalability and robustness of models.

TABLE II:
SUMMARY OF DATASETS

Dataset Name	Total Samples	Data Format	Application
WBC Scattergram Datasets [1,5,13]	500–5,000	Scattergram matrices (CSV)	Leukaemia screening
Peripheral Blood Smear Datasets [7,8,9]	3,000–20,000	JPG, PNG, BMP	Leukaemia classification
Clinical and Cytokine Datasets [6,10]	100–1,000	CSV, XLSX	Prognosis prediction
Single-Cell and Multi-Omics Datasets [11,12]	10,000–1,000,000+	HDF5, CSV, TXT	Biomarker discovery
Leukocyte Activation Datasets [2]	1,000–10,000	CSV, sensor data	Immune-cell monitoring
Optical Scattering Datasets [3]	500–5,000	PNG, JPG, signal matrices	Blood sample identification

B. Plot Types

Plot-based representations are used in computational hematology to visually encode the properties of the cells and the distributions of the population. WBC differential scattergrams which are WDF (white cell differential fluorescence), WNR (white cell nucleated red cell) and side-fluorescence scatter plots produced by automated analyzers are the most frequently used plots [1,5]. The plots are leukocytes founded on mixtures of light scatter, fluorescence intensity, and cell complexity, and make it possible to differentiate between normal and abnormal cell population. Deviant clustering, distended or overlapping populations are frequent indicators of leukemic changes, the existence of blasts, or artifacts of the analyzer [12,15]. Alongside the scattergrams produced by the analyzers, two-dimensional and three-dimensional feature plots based on the image-based WBC segmentation are also used in any machinelearning processes [17]. Density plots, cluster heatmaps, and projection-based visualizations are some of the studies that are used to increase separability and minimize noise. Recent developments entail scattergram correction methods to reduce the effect of dilution and interference with abnormal cells hence rendering plot reliability [18]. Nevertheless, interpretation of plots still depends on analysts, and inter-interpreters across platforms have a shape, size, and cluster localization variation [19]. Such variability presents a problem to automated systems that are trained on data of only one instrument. As a result, studies are now beginning to concentrate on the production of invariant representations of raw plots as opposed to using visual rules which are crafted by hand. Normalization of plots and features between analyzers is a key issue that has been

crucial to generalized leukemia detection systems.

C. Machine Learning Models

Conventional machine learning (ML) systems have been significant in the initial automated leukemia detection with the utilization of engineered features that are derived on top of the scattergrams and blood smear images. Such classifiers as support vectors machine, k-nearest neighbors, random forests, decision trees, and ensemble-based methods are common [7,9]. These models are usually based on the statistical characteristics of clusters like cluster centroid, dispersion, texture and morphological properties obtained on WBC images. Swarm intelligence and evolutionary algorithms are optimization-based methods that have been used so far to improve feature selection and multiclass discrimination [10]. ML models have the benefit of lower computational complexity, interpretability, and lower training data requirements than deep learning. A number of studies have shown successful pre-microscopic flagging of cases of acute leukemia with the help of scattering data-driven ML frameworks [11]. Nevertheless, they are very sensitive to the quality of features and experience in domains. In heterogeneous datasets, ML models tend to be less robust due to the difficulty in the modeling of complex spatial relationships and nonlinear interactions between leukocyte distributions [12]. Also, the handcrafted features are noise-sensitive, unstable in stains, and analyzer-specific. The traditional ML techniques have a problem with scalability as the size and complexity of datasets rise. Therefore, although ML models can be useful in high-resource lean-screening and low-resource environments, they are progressively being displaced or supplemented by deep learning models to high accuracy and large-scale leukemia classification.

D. Deep Learning Models

This has seen deep learning (DL) models become the prevailing paradigm in automated leukemia diagnosis because they can learn hierarchical and spatially rich representations of raw data. The application of convolutional neural networks has been demonstrated to be effective in the analysis of WBC images and scattergram plots with high performance in the detection of leukemia subtypes and abnormal cell populations [7,9,14]. CNNs automatically learn discriminative features corresponding to cell morphology, cluster density, and spatial distribution, so that no manual feature engineering is required. More performance improvements can be achieved using hybrid architectures that use CNNs with attention mechanisms, alongside transformer encoders, which allow modeling of long-range dependencies between clusters of leukocytes [3,9]. Sparse annotation learning is also discussed in recent studies to lower costs of labeling and still have diagnostic accuracy [9]. DL models enhanced with optimization incorporate swarm intelligence or evolution strategies to work on con-vergence and generalization [8]. In spite of their strengths, the DL models are characterized by such drawbacks as high computational demands, vulnerability to overfit-ting when used on small data, and reduced interpretability. The inter-instrument variability also has an effect on generalization where the same model is trained on data set of one analyzer [13]. To overcome those problems, researchers resort more and more to data augmentation, transfer learning, and multimodal fusion with clinical variables [14,15]. As a whole, deep learning makes an important contribution to the diagnosis of leukemia, but it needs to be designed, validated, and explained to be applied in clinical practice.

E. Explicable Artificial Intelligence

Explainable Artificial Intelligence (XAI) has gained more relevance in automated leukemia diagnosis to overcome the black-box-ness of deep learning-based models. Clinical adoption requires transparency and trust especially where AI systems affect diagnostic decisions. XAI methods also strive to determine and visualize the areas of scattergrams or WBC images that make the largest contribution to model forecasts. The most typical methods are gradient-based saliency maps, class activation map-ping, feature importance rankings, and attention visualization [7]. XAI is also used in the interpretation of scattergram-based systems to clarify to clinicians which clusters of leukocytes or shifts in the distribution to identify leukemia, enhance the interpretability and diagnostic confidence [9]. Explainability makes it possible to identify model biases, detect spurious correlations, and prove clinical relevance as well. Other works combine XAI and multimodal models to determine the impact of molecular or cytokine features on predictions [10-12]. XAI methods continue to be hampered by resolution, stability and clinical interpretability. Visual explanations can differ through the model runs and, in some cases, one may not interpret them easily by non-technical users. Research in the future ought to consider standardized XAI assessment guidelines, clinician-in-the-loop validation and incorporation of domain knowledge whereby the explanations are consistent with hematological reasoning and clinical workflows.

F. Evaluation Parameters

Assessment parameters are critical in determining the effectiveness, reliability as well as the clinical applicability of automated leukemia diagnosis systems. The most prevalent metrics are accuracy, precision, recall (sensitivity), specificity, F1-score and area under the receiver operating characteristic curve. In leukemia diagnosis, sensitivity is especially important to reduce false negativity whereas specificity is used to reduce false positivity to result in unwarranted follow-up testing [7,9]. Class-wise performance is often analyzed using confusion matrices in cases of

multiclass classification [8,14]. On imbalanced datasets, performance measures like balanced accuracy and Matthew's correlation coefficient give more credible performance evaluation. There also are some studies with computational efficiency, inference time, and model robustness to noise or dilution effects [10]. In multimodal and prognostic re-ports, measures of survival analysis, and their association with clinical outcomes are used [11,12]. The fact is, however, that there are inconsistencies in evaluation proto-cols across the studies and make it difficult to compare. Most of the works are based on internal validation and small datasets without external or cross-instrument testing [15,16]. To facilitate the real-world application of automated leukemia diagnostic systems, future evaluation systems should focus on standardized benchmarks, multi-center validation, explainability evaluation, and clinical utility measures.

IV. RESEARCH FINDINGS

All recent studies indicate that the automated diagnosis of leukemia has shifted its focus on qualitative screening tools to the advanced data-driven decision support systems. Empirical data prove that computational models can contribute to a great enhancement of diagnostic accuracy, minimization of turnaround time, and help clinicians to identify diseases in their initial stages. Below, there is the summary of the key research findings.

1. The Scattergram data is very discriminative: It has always been demonstrated that multidimensional WBC scatter plots represent a rich cellular data which can be used to effectively distinguish normal and leukemic populations. Changes in light scattering, fluorescence and cell distribution patterns are effective first signs of deviant hematological conditions.

2. Deep learning is more effective than the traditional models: CNNs, transformers, and hybrid models are more sensitive and specific than rule-based and conventional ML systems. This gives them power to classify multiclass leukemia, which is complex in terms of space, and observe it even in a difficult case.

3. Multimodal fusion enhances reliability: Fusion of scattergram features with clinical, molecular and multi-omics data also improves diagnostics and prognostics prediction. Multimodal systems are especially useful in terms of disease heterogeneity and variations of the patients.

4. The efficiency of annotation is a bottleneck: It is possible to achieve high performance with sparse annotation and weakly-supervised learning approaches that do not rely on large, labeled datasets. This is important in practice in clinical scalability with limited expertise annotations.

5. Explainability and generalization is still a problem: With improved performance, most models are not transparent and cross-platform validated. Partially explainable AI approaches can be used to overcome the issue of interpretability, but only more extensive clinical studies and standardized data could be used to make it mainstream.

V. CONCLUSION

This review emphasizes the fast development of automated diagnosis of leukemia based on the development of hematology analyzers, machine learning and deep learning technologies. The analysis has taken the form of scattergram-based analysis, which is a potent and non-invasive screening modality, and contemporary computational frameworks have become highly effective in increasing diagnostic accuracy and efficiency. Combination of multimodal data and explainable AI also enhances the clinical applicability of automated systems. The development of large, standardized, and annotated datasets of scattergram in the future should be a priority in order to enhance model generalization. The gap between research and practice should be closed by implementing cross-platform validation, secure data processing and real-world clinical deployment. It will also be important to develop interpretable, privacy-preserving, and cost-effective diagnostic systems that can help transform computational hematology innovations into clinical practice.

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