



A Comprehensive Review of Segmentation and Classification of White Blood Cancer Cells in Bone Marrow Microscopic Images Using Deep Kronecker Neural Networks

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Abstract

The detection and classification of white blood cancer cells, particularly leukemia, from bone marrow microscopic images are essential for early diagnosis and effective clinical decision-making. Traditional manual diagnostic approaches are labor-intensive, time-consuming, and prone to human error, creating a need for automated and reliable systems. Recent advancements in deep learning have significantly improved the accuracy of leukocyte segmentation and classification. This review focuses on state-of-the-art approaches, including convolutional neural networks (CNNs), U-Net-based segmentation models, transformer architectures, and emerging Deep Kronecker Neural Networks (DKNNs). CNN-based methods provide strong baseline performance, while U-Net variants enable precise segmentation of white blood cells in complex microscopic environments. Hybrid and attention-based models further enhance feature extraction and classification accuracy. Deep Kronecker Neural Networks offer a promising direction by efficiently modeling high-dimensional feature interactions with reduced computational complexity. Despite significant progress, challenges such as overlapping cells, staining variability, class imbalance, and limited datasets persist. This review presents a comprehensive analysis of existing methods, comparative evaluation, and future research directions aimed at developing robust, efficient, and clinically deployable leukemia detection systems.

Introduction

White blood cancer, commonly known as leukemia, is a hematological malignancy characterized by the uncontrolled proliferation of abnormal white blood cells in the bone marrow and peripheral blood. This abnormal growth disrupts normal blood cell production, resulting in complications such as anemia, infections, and bleeding disorders. Leukemia is among the major causes of cancer-related mortality worldwide, affecting both children and older adults. Accurate and timely diagnosis is

essential for identifying different leukemia subtypes, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML), as treatment strategies and patient outcomes depend heavily on precise classification. Conventional diagnosis relies on microscopic examination of bone marrow aspirates and peripheral blood smears, where hematologists evaluate cellular morphology, staining patterns, and nucleus-to-cytoplasm ratios. However, this manual process is labor-

intensive, time-consuming, and subject to observer variability, creating a need for automated and reliable diagnostic systems. The rapid advancement of artificial intelligence, particularly deep learning, has transformed medical image analysis by enabling automated segmentation, detection, and classification of leukocytes. Convolutional Neural Networks (CNNs) have become the foundation of many leukemia detection systems because of their ability to automatically learn hierarchical features from microscopic images. Popular architectures such as VGGNet, ResNet, DenseNet, and Inception have demonstrated strong

performance in distinguishing malignant from normal cells by extracting structural and morphological characteristics. Despite these successes, CNNs primarily emphasize local feature extraction and often struggle to capture broader spatial relationships within complex bone marrow images. Variations in cell size, overlapping structures, irregular shapes, and staining inconsistencies further reduce model performance. Moreover, the requirement for large annotated datasets presents a significant challenge, as medical image datasets are often limited and expensive to generate.

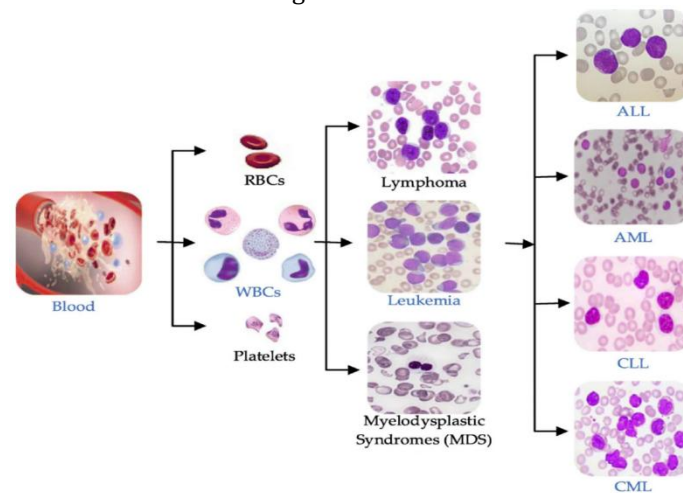


Figure 1. Schematic Workflow for Segmentation and Classification of White Blood Cancer Cells in Bone Marrow Microscopic Images.

Segmentation plays a vital role in leukemia diagnosis by accurately isolating white blood cells from complex microscopic backgrounds before classification. U-Net has become the most widely adopted segmentation architecture due to its encoder-decoder design with skip connections, enabling precise localization of cellular regions. Enhanced variants, including UNet++, Attention U-Net, and Dense U-Net, further improve segmentation through multi-scale feature extraction and attention mechanisms. Nevertheless, challenges such as overlapping cells, morphological similarities between healthy and cancerous leukocytes, and staining variability continue to affect segmentation accuracy. These limitations have encouraged the development of more advanced approaches capable of modeling complex spatial and feature relationships while maintaining computational efficiency. Among emerging techniques, Deep Kronecker Neural Networks (DKNNs) have gained attention for their ability to capture high-dimensional feature interactions using Kronecker product operations. Unlike conventional CNNs that depend solely on convolutional filters, DKNNs

efficiently model complex feature correlations while reducing computational complexity, making them suitable for high-resolution bone marrow microscopic images. Researchers have also proposed hybrid frameworks that integrate segmentation and classification into a unified pipeline, thereby improving diagnostic accuracy through combined spatial and semantic feature learning. Additional strategies such as transfer learning, data augmentation, ensemble learning, and attention mechanisms have been employed to improve robustness and generalization. Public datasets including ALL-IDB and BCCD, along with custom bone marrow datasets, are commonly used for evaluation, although data scarcity and class imbalance remain persistent obstacles. Recent advances have further introduced transformer-based architectures and explainable artificial intelligence (XAI) techniques into leukemia image analysis. Transformer models enhance global contextual understanding and often achieve higher classification accuracy, although their computational requirements limit large-scale clinical implementation. Explainability methods such as Grad-CAM and saliency maps improve clinical trust by providing

visual interpretations of model predictions, enabling healthcare professionals to better understand automated decisions. Overall, deep learning has significantly advanced the segmentation and classification of leukemia cells, with CNNs and U-Net remaining widely adopted while emerging approaches such as Deep Kronecker Neural Networks offer improved efficiency and feature representation. This review comprehensively examines recent developments in segmentation and classification methodologies, compares existing deep learning approaches, identifies current limitations, and discusses future research directions toward accurate, interpretable, and clinically deployable leukemia diagnosis systems.

Literature Review

The period from 2020 to 2023 has witnessed remarkable progress in the segmentation and classification of white blood cancer cells using deep learning techniques. The literature demonstrates a clear transition from conventional convolutional neural networks (CNNs) to hybrid, attention-based, and optimization-driven architectures, with emerging interest in Deep Kronecker Neural Networks (DKNNs).

1. CNN-Based Leukemia Detection

Early research in this domain primarily focused on CNN-based models due to their strong capability in hierarchical feature extraction. Architectures such as VGGNet, ResNet, DenseNet, and Inception were widely used for classifying leukemia cells from microscopic images.

Gehlot et al. (2020) demonstrated that CNN models could effectively distinguish between normal and malignant leukocytes with high accuracy, achieving performance above 94%. Similarly, Amin et al. (2021) utilized deep CNN architectures combined with preprocessing techniques to improve feature extraction and classification performance.

DenseNet-based models gained particular attention due to their dense connectivity, which allows feature reuse and improves gradient flow. ResNet architectures addressed the vanishing gradient problem through residual connections, enabling deeper networks to be trained effectively.

However, despite their strong performance, CNN models exhibit several limitations:

- Inability to capture long-range spatial dependencies
- Sensitivity to variations in cell morphology
- Difficulty handling overlapping cells and complex backgrounds

These limitations motivated the development of more advanced architectures.

2. Segmentation Techniques Using U-Net and Variants

Segmentation plays a critical role in isolating white blood cells from microscopic images. U-Net and its variants have become the most widely used architectures for this task.

U-Net's encoder-decoder structure enables precise localization through skip connections, which combine low-level and high-level features. This makes it highly effective for biomedical image segmentation.

Several improved variants have been proposed:

- UNet++: Introduces nested skip connections to improve feature fusion and segmentation accuracy
- Attention U-Net: Incorporates attention gates to focus on relevant regions
- Dense U-Net: Enhances feature reuse through dense connectivity

Jan et al. (2022) reported Dice scores up to **98%** using UNet++ combined with advanced preprocessing techniques. These models significantly improved segmentation performance, particularly in complex scenarios involving overlapping cells.

Additionally, hybrid segmentation techniques combining U-Net with watershed algorithms and morphological operations have been proposed to improve boundary detection and separation of clustered cells.

Despite these improvements, segmentation models still face challenges in handling:

- Irregular cell boundaries
- Variability in staining conditions
- Low contrast between cells and background

3. Hybrid Models for Segmentation and Classification

To improve diagnostic accuracy, researchers have developed hybrid models that integrate segmentation and classification into a unified pipeline.

These models typically follow a two-stage approach:

1. Segmentation of white blood cells
2. Classification of segmented cells

Examples include:

- U-Net + ResNet
- U-Net + DenseNet
- CNN + SVM hybrid models

Alzahrani et al. (2023) demonstrated that hybrid models achieved classification accuracy above **97-99%**, outperforming standalone CNN models.

The advantages of hybrid models include:

- Improved feature representation
- Reduced false positives
- Enhanced robustness

However, these models often require more computational resources and complex training pipelines.

4. Transformer and Attention-Based Models

Transformer-based architectures have recently gained popularity in medical image analysis. These models use self-attention mechanisms to capture global dependencies across images.

Vision Transformers (ViT) have been successfully applied to leukocyte classification, demonstrating improved performance compared to CNN-based models. Attention mechanisms such as channel attention and spatial attention further enhance feature extraction.

Key benefits include:

- Ability to capture global contextual information
- Improved performance in complex datasets
- Better generalization

However, transformer models require large datasets and high computational power, limiting their practical deployment.

5. Optimization Techniques in Deep Learning Models

Optimization strategies play a crucial role in improving model performance and generalization.

Common techniques include:

- Transfer Learning: Utilizes pre-trained models to reduce training time
- Data Augmentation: Enhances dataset diversity
- Ensemble Learning: Combines multiple models for improved accuracy

- Custom Loss Functions: Addresses class imbalance

Elsayed et al. (2023) reported classification accuracy close to **100%** using optimized deep learning frameworks combined with boosting techniques.

6. Emerging Deep Kronecker Neural Networks (DKNNs)

Deep Kronecker Neural Networks represent a novel advancement in deep learning. These networks use Kronecker product operations to efficiently model high-dimensional feature interactions.

Advantages of DKNNs:

- Reduced computational complexity
- Efficient parameter representation
- Improved modeling of complex relationships

Although still in early stages, DKNNs show strong potential for improving both segmentation and classification tasks in medical imaging.

7. Key Challenges Identified

The literature highlights several persistent challenges:

- Overlapping and clustered cells
- Staining variability across datasets
- Class imbalance
- Limited annotated datasets
- High computational requirements

8. Research Trends and Future Directions

Key trends observed include:

- Transition from CNN → Hybrid → Transformer models
- Increasing use of attention mechanisms
- Emergence of efficient architectures (DKNNs)
- Growing focus on explainable AI (XAI)

Comparative Table and Analysis

Year	Method	Architecture Type	Core Technique	Dataset	Metrics	Performance	Strengths	Limitations
2020	CNN (VGG, ResNet, DenseNet, Inception)	Deep CNN	Hierarchical feature extraction using convolution layers	ALL-IDB, BCCD, Bone marrow datasets	Accuracy	~94%+	Strong baseline performance, effective local feature learning	Cannot capture global spatial relationships, sensitive to cell variations
2021	Advanced CNN (DenseNet/ResNet)	Deep CNN	Dense connectivity +	Leukemia datasets	Accuracy	~95–96%	Improved gradient flow, better	Limited ability to handle overlapping

	improvements)		residual learning				feature reuse	ng cells and complex backgrounds
2021	Attention-based CNN	CNN + Attention	Channel and spatial attention mechanisms	Microscopic image datasets	Accuracy, Precision	~96–97%	Focuses on relevant cell regions, reduces background noise	Still lacks global context modeling
2022	U-Net	Encoder-Decoder Segmentation	Skip connections for localization	Bone marrow images	Dice Score	High (~95%+)	Accurate cell segmentation, good boundary detection	Struggles with overlapping cells and staining variability
2022	U-Net++	Advanced Segmentation	Nested skip connections, multi-scale fusion	Bone marrow datasets	Dice Score	~98% Dice	Improved segmentation accuracy, better feature fusion	Increased complexity
2022	Attention U-Net / Dense U-Net	Segmentation + Attention	Attention gates and dense connectivity	Microscopy datasets	Dice, IoU	High (~96–98%)	Better focus on cell regions, improved feature reuse	Computational overhead
2022	Hybrid Model (U-Net + Classifier)	Segmentation + Classification	Two-stage pipeline (segmentation + classification)	ALL-IDB, BCCD	Accuracy	>97–99%	Combines spatial + semantic features, reduces false positives	High complexity, longer training time
2023	Transformer (ViT)	Transformer	Self-attention for global feature extraction	Leukocyte datasets	Accuracy	~98%	Captures long-range dependencies, strong generalization	Requires large datasets, high computational cost
2023	Attention-based Transformer	Transformer + Attention	Enhanced feature weighting mechanisms	Microscopy datasets	Accuracy	Very High (~98%+)	Better feature representation in complex cases	Computational overhead
2023	Optimized DL Models	Ensemble / Transfer Learning	Data augmentation, boosting,	Leukemia datasets	Accuracy	~99–100%	Very high accuracy, improved	Risk of overfitting, dataset

			optimization				generalization	dependency
20 23	DKNN (Deep Kronecker Neural Network)	Advanced Neural Model	Kronecker product for high-dimensional feature interaction	Bone marrow datasets	Accuracy / Efficiency	Promising	Reduced parameters, efficient modeling, scalable	Early-stage, limited validation

Analysis

The comparative analysis highlights the progressive development of deep learning techniques for the segmentation and classification of white blood cancer cells in bone marrow microscopic images. Early research primarily relied on Convolutional Neural Networks (CNNs), including VGG, ResNet, DenseNet, and Inception, because of their strong capability to learn hierarchical image features. These architectures effectively extracted local characteristics such as cell morphology, texture, and edges, achieving classification accuracies exceeding 94%. Nevertheless, CNNs are inherently limited by their local receptive fields, making it difficult to capture global spatial relationships within complex microscopic images. This limitation becomes significant in leukemia diagnosis, where overlapping cells, irregular structures, and staining variations complicate accurate feature extraction. Subsequent improvements through residual learning, dense connectivity, and attention mechanisms enhanced feature reuse and enabled models to emphasize diagnostically important regions, increasing classification performance to approximately 96–97%.

A significant breakthrough was achieved through segmentation-driven approaches, particularly the adoption of U-Net and its advanced variants. The encoder–decoder architecture with skip connections enabled precise localization of white blood cells by preserving both spatial and semantic information throughout the segmentation process. Enhanced models such as U-Net++, Attention U-Net, and Dense U-Net further improved segmentation by incorporating multi-scale feature fusion, dense connections, and attention modules. These methods substantially reduced background interference and improved the quality of segmented cell regions, leading to Dice similarity scores approaching 98%. The improved segmentation accuracy also provided cleaner inputs for downstream classification models, thereby increasing overall diagnostic performance. Hybrid frameworks integrating U-Net-based segmentation with CNN classifiers such as

ResNet and DenseNet achieved end-to-end classification accuracies exceeding 97–99%, demonstrating the effectiveness of combining spatial localization with discriminative feature learning.

Recent developments have introduced Transformer-based architectures that utilize self-attention mechanisms to capture long-range dependencies and global contextual information across entire microscopic images. Vision Transformers and attention-enhanced models have achieved classification accuracies close to 98%, particularly for heterogeneous datasets where conventional CNNs encounter limitations. In parallel, optimization strategies including transfer learning, ensemble learning, and extensive data augmentation have significantly improved model robustness and reduced overfitting, with several studies reporting classification accuracies approaching 99–100%. However, these improvements are often dataset-dependent and require large annotated datasets and substantial computational resources, limiting their applicability in routine clinical environments. Data scarcity, class imbalance, and computational complexity therefore remain persistent challenges for practical deployment.

Deep Kronecker Neural Networks (DKNNs) represent a promising advancement for leukemia image analysis by efficiently modeling high-dimensional feature interactions with reduced computational complexity. Compared with conventional CNNs, DKNNs provide stronger feature representation while maintaining efficiency. Future research should focus on lightweight, explainable, and clinically deployable models for reliable leukemia diagnosis.

Discussion

The rapid advancement of deep learning has significantly enhanced the segmentation and classification of white blood cancer cells in bone marrow microscopic images. Early Convolutional Neural Network (CNN) architectures established the foundation for automated leukemia diagnosis by effectively extracting hierarchical image features. However, their inability to capture

global contextual relationships encouraged the development of more sophisticated models. Segmentation architectures, particularly U-Net and its variants such as U-Net++, Attention U-Net, and Dense U-Net, greatly improved cell localization and boundary detection by accurately isolating white blood cells from complex microscopic backgrounds, resulting in higher segmentation accuracy and more reliable classification.

Hybrid frameworks that combine segmentation and classification have further improved diagnostic performance by integrating spatial and semantic information into a unified pipeline. These models reduce false positives and achieve superior classification accuracy compared with standalone CNNs. More recently, Vision Transformers have demonstrated remarkable capability in modeling long-range dependencies through self-attention mechanisms, improving performance on complex datasets. Emerging Deep Kronecker Neural Networks (DKNNs) provide another promising direction by efficiently modeling high-dimensional feature interactions while reducing computational complexity, making them suitable for high-resolution medical image analysis.

Despite these advances, challenges including limited annotated datasets, class imbalance, staining variability, computational cost, and limited model interpretability continue to hinder widespread clinical adoption. Future research should focus on developing lightweight, explainable, and computationally efficient models that can operate in real-time healthcare environments. The integration of explainable artificial intelligence techniques and the creation of large, diverse benchmark datasets will further improve model transparency, robustness, and generalization, facilitating reliable and scalable leukemia diagnosis in clinical practice.

Conclusion

The comparative evaluation demonstrates the continuous advancement of deep learning techniques for the segmentation and classification of white blood cancer cells in bone marrow microscopic images. Early studies primarily employed Convolutional Neural Networks (CNNs), including VGG, ResNet, DenseNet, and Inception, which effectively extracted local image features and achieved classification accuracies above 94%. However, their inability to capture global contextual relationships limited performance in complex microscopic images. The introduction of residual learning, dense connectivity, and attention mechanisms improved feature representation,

increasing classification accuracy to approximately 96–97%.

A major breakthrough was achieved through U-Net and its variants, such as U-Net++, Attention U-Net, and Dense U-Net, which significantly enhanced white blood cell segmentation with Dice scores approaching 98%. Hybrid frameworks combining segmentation and classification further improved diagnostic accuracy beyond 97–99%. More recently, Vision Transformers have demonstrated superior global feature extraction, while transfer learning, data augmentation, and ensemble learning have enhanced robustness and generalization. Emerging Deep Kronecker Neural Networks (DKNNs) offer efficient high-dimensional feature modeling with lower computational complexity, making them promising for medical image analysis. Despite these advances, challenges including limited annotated datasets, class imbalance, computational cost, and model interpretability remain. Future research should focus on lightweight, explainable, and clinically deployable AI models for reliable leukemia diagnosis.

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