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DISSERTATION

METHOD AND MULTIMODAL FRAMEWORK FOR ENHANCED MELANOMA METASTASIS DIAGNOSIS

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The dissertation contains the results of the author's own research. The use of ideas, results, and texts from other authors includes references to the respective sources.

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ABSTRACT

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In the rapidly evolving field of digital pathology, the automated analysis of whole-slide histopathological images (WSIs) has become a cornerstone challenge, intersecting advanced domains such as computer vision, machine learning, deep learning, and clinical informatics. This dissertation is dedicated to the development of novel method and computational framework aimed at enhanced melanoma diagnosis-a critical area in oncology due to melanoma's high metastatic potential and significant global health burden. Melanoma, as the deadliest form of skin cancer, accounts for over 325,000 new cases and approximately 57,000 deaths annually worldwide, with a five-year survival rate dropping from 99% at localized stages to 25% once metastasis occurs. The research addresses the multifaceted complexities of melanoma diagnostics, focusing on scalable preprocessing of gigapixel-scale WSIs, multi-scale feature extraction for nuanced morphological analysis, multimodal data integration for comprehensive risk prediction, and the incorporation of interpretability mechanisms to ensure clinical applicability and trust. The study targets four pivotal aspects of melanoma diagnostics:

1. Scalable WSI Preprocessing: Managing ultra-high-resolution WSIs (>100,000×100,000 pixels, >1 GB) with data-parallel processing ensures rapid preparation for diagnostics, overcoming computational bottlenecks.

2. Multi-Scale Feature Extraction: Capturing cellular details (e.g., nuclear atypia) and tissue architecture (e.g., stromal patterns) using multi-scale neural networks enhances classification accuracy for early melanoma detection.

3. Multimodal Data Integration: Fusing WSIs with clinical (e.g., age, tumor location) and genomic data (e.g., BRAF mutations) via multimodal deep learning improves metastasis prediction and personalized treatment.

4. Interpretable AI: Explainable AI with ensemble classifiers ensures transparency, aligning with EU MDR and FDA guidelines, fostering clinical trust.

The introduction underscores the critical significance of this research within the context of digital pathology's rapid expansion and the urgent need for advanced diagnostic tools in melanoma fighting. It provides a comprehensive review of existing methodologies for whole-slide image (WSI) preprocessing, feature extraction, multimodal data integration, and interpretability, delineating their limitations and identifying critical gaps addressed by this study. *The primary objective* is to enhance melanoma metastasis diagnostics by the new method and high-performance, interpretable computational frameworks for the efficient preprocessing, multi-scale feature analysis, multimodal data fusion, and transparent decision-making. *The research object* is the process of diagnosing melanoma and predicting its metastatic potential using computational methods applied to WSIs, genomic profiles, and clinical metadata within advanced information systems. *The research subject* is the method and advanced computational framework, including data-parallel preprocessing, multi-scale neural networks, multimodal deep learning, and interpretable ensemble classifiers. The methodologies employed integrate systems analysis, mathematical modeling, machine learning, deep learning, computer vision, statistical validation, and explainable AI techniques, such as OpenMP, CUDA, convolutional neural networks, SHAP, and Grad-CAM++. The scientific novelty lies in proposing a data-parallel preprocessing framework, a multi-scale neural network, the method of multimodal deep learning for melanoma metastasis diagnostics, and the interpretable multimodal stacked ensemble classifier framework (IMSEF-Melanoma), significantly advancing diagnostic performance. The practical significance is demonstrated through reduced processing times, enhanced classification accuracy, improved metastasis prediction, and compliance with regulatory standards, fostering precision oncology and clinical adoption. The dissertation is structured with an introduction, four chapters, conclusions, references, and appendices.

The First Chapter: Evolution and Challenges of Digital Pathology in Melanoma Diagnosis. This chapter delineates the transformative trajectory of digital pathology and its critical role in advancing melanoma diagnosis, with a focus on detecting metastatic progression. It chronicles the development of whole-slide imaging (WSI) from its nascent stages-marked by slow scanning speeds and limited resolution-to contemporary systems integrated with artificial intelligence (AI). The chapter elucidates preprocessing challenges, notably the computational complexity of gigapixel-scale WSIs (often exceeding 100,000 × 100,000 pixels) and the inefficiencies of existing tools like OpenSlide. It underscores the potential of AI, particularly convolutional neural networks (CNNs), to enable multimodal diagnostic frameworks that address the limitations of unimodal approaches. Emphasizing the global burden of melanoma-over 325,000 new cases annually-the chapter advocates for real-time analytical solutions to enhance early detection, which is pivotal to achieving a 99% five-year survival rate at localized stages.

The Second Chapter: Theoretical and Methodological Foundations. This chapter establishes a theoretical and methodological framework for enhancing melanoma diagnosis through advanced computational paradigms. It explores CPU and GPU architectures, leveraging OpenMP and CUDA for efficient parallel processing, and proposes a data-parallel preprocessing pipeline incorporating dynamic task scheduling and resource optimization. A novel multi-scale neural network, employing dilated convolutions and feature fusion mechanisms, is introduced to capture a spectrum of morphological characteristics. The chapter further develops a multimodal deep learning approach that integrates WSIs, clinical metadata (e.g., patient age, tumor location), and genomic data (e.g., BRAF mutations) through attention mechanisms and biomarker mining. Additionally, it presents the Interpretable Multimodal Stacked Ensemble Framework (IMSEF-Melanoma), which enhances diagnostic transparency via gradient-based visualization and meta-learning. These innovations collectively offer theoretical advantages, including parallel processing efficiency, multi-scale precision, and

multimodal synergy, fostering improved diagnostic accuracy and clinical applicability.

The Third Chapter: Algorithm Development and Neural Network Optimization. This chapter focuses on the design and optimization of algorithms and neural networks to advance melanoma diagnostics. It introduces a data-parallel preprocessing algorithm featuring parallel patch generation and normalization to enhance computational efficiency. Multi-scale feature extraction techniques, incorporating dilated convolutions and channel/spatial attention mechanisms, are developed to optimize diagnostic precision. A multimodal data fusion strategy integrates WSIs, tumor depth predictions, and clinical metadata, with interpretability enhanced through SHAP (SHapley Additive exPlanations) values and Grad-CAM++ visualizations. These advancements streamline preprocessing, improve diagnostic accuracy, and align computational predictions with clinical requirements, thereby supporting precision oncology through enhanced early detection and risk stratification.

The Fourth Chapter: Clinical Validation and Practical Applications. This chapter presents the practical implementation and clinical validation of the proposed method and multimodal framework, consolidating experimental results to demonstrate their efficacy. The data-parallel preprocessing framework achieves a 12-fold speedup and reduces processing time by 78.6% compared to OpenSlide, validated on the TCGA-LIHC dataset (200 WSIs) and an institutional cohort (600 WSIs), enabling real-time clinical workflows. The multi-scale neural network attains 92.5% accuracy and a 0.97 AUC-ROC on a 400-WSI TCGA-SKCM dataset, outperforming ResNet-50 (88%) and DenseNet-121 (89%) while reducing diagnostic errors by 10%. The multimodal framework predicts metastasis with 87% accuracy and a 0.15 mm mean absolute error (MAE) in depth prediction on a 1,200-WSI TCIA dataset, surpassing traditional Breslow (72%) and Clark (68%) methods, with a sensitivity of 92% and specificity of 88%. The IMSEF-Melanoma framework achieves a 0.95 AUC on a 2,416-WSI multi-center cohort, reducing diagnostic time by 35% (from 14.2 to 9.3 minutes per case) and deferred cases by

42% (from 12.6% to 7.3%), with interpretability validated by SHAP and Grad-CAM++ (Dice coefficient: 0.82). Demonstrating robust generalizability (AUC: 0.93–0.96 across hospitals), these frameworks enhance clinical efficiency, diagnostic confidence, and personalized treatment planning, significantly advancing precision oncology.

Scientific Novelty:

1. New data-parallel preprocessing framework for WSIs is proposed, integrating parallel processing, GPU acceleration, and adaptive image filtering, achieving a 12-fold speedup and addressing scalability challenges in digital pathology.

2. The multi-scale neural network with dilated convolutions and attention mechanisms is developed, improving skin pathological image classification by 4.5% over benchmarks, capturing diverse locally concentrated features critical for early melanoma detection.

3. The method of multimodal deep learning for melanoma metastasis diagnostics is introduced, achieving an 87% accuracy through the integration of biomedical images, depth prediction, and metadata, offering a 15% improvement over traditional methods.

4. An interpretable multimodal stacked ensemble classifier framework (IMSEF-Melanoma) is proposed, combining SHAP and Grad-CAM++ to provide transparent, stage-adaptive diagnostic insights, with a 90% alignment of genomic features to the COSMIC database.

Practical Significance of the Results:

1. The preprocessing framework reduces WSI processing time by 78.6%, enabling real-time analysis in clinical environments and supporting high-throughput research, validated on TCGA-LIHC and institutional datasets.

2. The multi-scale classification method achieves a 92.5% accuracy, reducing false negatives by 10% compared to ResNet-50, enhancing early melanoma detection and supporting timely interventions.

3. The multimodal framework improves melanoma metastasis diagnostics accuracy to 87%, with a 0.15 mm MAE in depth prediction, facilitating personalized treatment planning and validated on a 1,200-WSI TCIA dataset.

4. IMSEF-Melanoma achieves a 35% reduction in diagnostic time and a 42% decrease in deferred cases, improving clinical efficiency and confidence, validated across a 2,416-WSI multi-center cohort.

5. Interpretability mechanisms (SHAP, Grad-CAM++) align with regulatory requirements (e.g., EU MDR, FDA SaMD), fostering trust and facilitating adoption in healthcare settings.

6. The frameworks demonstrate generalizability across multi-center datasets, with consistent AUCs (0.93–0.96) across validation hospitals, promoting their adoption in diverse healthcare settings.

Keywords: Multimodal framework, Melanoma metastasis diagnostics, Biomedical images, Information systems, Ensemble classifier, Neural network, Machine learning, Deep learning, Objects recognition, Error analysis, Image size, Classification methods, Image filtering, Image processing, Locally concentrated features.

АНОТАЦІЯ

Чжао Цайфен. Метод і мультимодальні програмні засоби для покращеної діагностики метастазів меланоми. – Кваліфікаційна наукова праця як рукопис. Дисертація на здобуття ступеня доктора філософії за спеціальністю 122 – Комп'ютерні науки. – Вінницький національний технічний університет, Вінниця, 2025.

У галузі цифрової патології, яка стрімко розвивається, автоматизований аналіз цільних слайдів гістопатологічних зображень (WSI) став наріжним каменем, що поєднує передові галузі, такі як комп'ютерне бачення, машинне навчання, глибоке навчання та клінічна інформатика. Ця дисертація присвячена розробці нового методу та обчислювального фреймворку, спрямованого на покращення діагностики меланоми - критичної області в онкології через високий метастатичний потенціал меланоми та значний глобальний тягар для здоров'я. Меланома, як найсмертоносніша форма раку шкіри, становить понад 325 000 нових випадків і приблизно 57 000 смертей щорічно у світі, з п'ятирічною виживаністю, що падає з 99% на локалізованих стадіях до 25% після виникнення метастазів. Дослідження вирішує багатогранні складнощі діагностики меланоми, зосереджуючись на масштабному попередньому обробленні WSI гігапіксельного масштабу, багатомасштабному вилученні ознак для тонкого морфологічного аналізу, інтеграції мультимодальних даних для всебічного прогнозування ризиків та впровадженні механізмів інтерпретованості для забезпечення клінічної застосовності та довіри. Дослідження націлене на чотири ключові аспекти діагностики меланоми:

1. Масштабоване попереднє оброблення WSI: управління ультрависокороздільними WSI (>100 000×100 000 пікселів, >1 ГБ) з паралельною обробкою даних забезпечує швидку підготовку до діагностики, подолання обчислювальних вузьких місць.

2. Багатомасштабне вилучення ознак: захоплення клітинних деталей (наприклад, ядерна атипія) та архітектури тканин (наприклад, стромальні

патерни) за допомогою багатомасштабних нейронних мереж підвищує точність класифікації для раннього виявлення меланоми.

3. Інтеграція мультимодальних даних: об’єднання WSI з клінічними даними (наприклад, вік, розташування пухлини) та геномними даними (наприклад, мутації BRAF) через мультимодальне глибоке навчання покращує прогнозування метастазів та персоналізоване лікування.

4. Інтерпретований ШІ: пояснювальний ШІ з ансамблевими класифікаторами забезпечує прозорість, узгоджуючись із директивами EU MDR та FDA, сприяючи клінічній довірі.

Вступ підкреслює критичне значення цього дослідження в контексті стрімкого розширення цифрової патології та нагальної потреби в передових діагностичних інструментах для боротьби з меланомою. Він надає всебічний огляд існуючих методологій для попереднього оброблення повнорозмірних слайдів зображень (WSI), вилучення ознак, інтеграції мультимодальних даних та інтерпретованості, окреслюючи їхні обмеження та виявляючи критичні прогалини, які вирішує це дослідження. Основна мета полягає в розробці мультимодальної інформаційної технології, яка покращує діагностику метастазів меланоми за допомогою нових високопродуктивних, інтерпретованих обчислювальних фреймворків для ефективної попередньої обробки, багатомасштабного аналізу ознак, мультимодального об'єднання даних та прозорого прийняття рішень. *Об’єкт дослідження* - процес діагностики меланоми та прогнозування її метастатичного потенціалу з використанням обчислювальних методів, застосованих до WSI, геномних профілів та клінічних метаданих у рамках передових інформаційних систем. *Предмет дослідження* - передова обчислювальна система, що включає паралельну попередню обробку даних, багатомасштабні нейронні мережі, мультимодальне глибоке навчання та інтерпретовані ансамблеві класифікатори. Використані методології інтегрують системний аналіз, математичне моделювання, машинне навчання, глибоке навчання, комп’ютерне бачення, статистичну валідацію та техніки пояснювального ШІ,

такі як OpenMP, CUDA, згорткові нейронні мережі, SHAP та Grad-CAM++. Наукова новизна полягає в пропонуванні паралельного фреймворку попереднього оброблення даних, багатомасштабної нейронної мережі, метод мультимодального глибокого навчання та інтерпретувальний мультимодальний стекований ансамблевий класифікатор (IMSEF-Melanoma), що значно покращує діагностичну продуктивність. Практичне значення демонструється через скорочення часу обробки, підвищення точності класифікації, покращення прогнозування метастазів та відповідність регуляторним стандартам, сприяючи точній онкології та клінічному впровадженню. Дисертація має вступ, чотири розділи, висновки, список літератури та додатки.

Перший розділ: Еволюція та виклики цифрової патології в діагностиці меланоми. Цей розділ окреслює трансформаційну траєкторію цифрової патології та її критичну роль у просуванні діагностики меланоми, з фокусом на виявленні метастатичного прогресування. Він хронікує розвиток цільних слайдів зображень (WSI) від його початкових стадій - позначених повільними швидкостями сканування та обмеженою роздільною здатністю - до сучасних систем, інтегрованих зі штучним інтелектом (ШІ). Розділ роз’яснює виклики попереднього оброблення, зокрема обчислювальну складність WSI гігапіксельного масштабу (часто перевищуючи 100 000 × 100 000 пікселів) та неефективність існуючих інструментів, як OpenSlide. Він підкреслює потенціал ШІ, зокрема згорткових нейронних мереж (CNNs), для уможливлення мультимодальних діагностичних фреймворків, які вирішують обмеження унімодальних підходів. Наголошуючи на глобальному тягарі меланоми - понад 325 000 нових випадків щорічно - розділ виступає за аналітичні рішення в реальному часі для покращення раннього виявлення, що є ключовим для досягнення 99% п’ятирічної виживаності на локалізованих стадіях.

Другий розділ: Теоретичні та методологічні основи. Цей розділ встановлює теоретичний та методологічний фреймворк для покращення

діагностики меланоми через передові обчислювальні парадигми. Він досліджує архітектури CPU та GPU, використовуючи OpenMP та CUDA для ефективної паралельної обробки, та пропонує паралельний конвеєр попереднього оброблення даних, що включає динамічне планування завдань та оптимізацію ресурсів. Нова багатовимірна нейронна мережа, що використовує розширені згортки та механізми злиття ознак, вводиться для врахування спектру морфологічних характеристик. Розділ розвиває мультимодальний підхід глибокого навчання, що інтегрує WSI, клінічні метадані (наприклад, вік пацієнта, розташування пухлини) та геномні дані (наприклад, мутації BRAF) через механізми уваги та видобуток біомаркерів. Додатково він представляє інтерпретувальний мультимодальний стекований ансамблевий фреймворк (IMSEF-Melanoma), який покращує діагностичну прозорість через градієнтну візуалізацію та мета-навчання. Ці інновації колективно пропонують теоретичні переваги, включаючи ефективність паралельної обробки, точність та мультимодальну синергію, сприяючи покращенню діагностичної точності та клінічної застосовності.

Третій розділ: Розробка алгоритмів та оптимізація нейронних мереж. Цей розділ зосереджується на проектуванні та оптимізації алгоритмів і нейронних мереж для просування діагностики меланоми. Він вводить паралельний алгоритм попереднього оброблення даних з паралельною генерацією патчів та нормалізацією для підвищення обчислювальної ефективності. Техніки багатомасштабного вилучення ознак, що включають розширені згортки та механізми уваги каналів/простору, розроблені для оптимізації діагностичної точності. Стратегія злиття мультимодальних даних інтегрує WSI, прогнози глибини пухлини та клінічні метадані, з покращенням інтерпретованості через значення SHAP (SHapley Additive exPlanations) та Grad-CAM++ візуалізації. Ці результати спрощують попереднє оброблення, покращують діагностичну точність та узгоджують обчислювальні прогнози з клінічними вимогами, тим самим підтримуючи точну онкологію через покращене раннє виявлення та стратифікацію ризиків.

Четвертий розділ: Клінічна валідація та практичні застосування. Цей розділ представляє практичну реалізацію та клінічну валідацію запропонованої інформаційної тенології, консолідуючи експериментальні результати для демонстрації її ефективності. Паралельний фреймворк попереднього оброблення даних досягає 12-кратного прискорення та скорочує час обробки на 78,6% у порівнянні з OpenSlide, валідація на датасеті TCGA-LIHC (200 WSI) та внутрішньому клінічному наборі (600 WSI), уможливлюючи клінічні робочі процеси в реальному часі. Багатовимірна нейронна мережа досягає 92,5% точності та 0,97 AUC-ROC на датасеті TCGA-SKCM з 400 WSI, перевершуючи ResNet-50 (88%) та DenseNet-121 (89%), при цьому скорочуючи діагностичні помилки на 10%. Мультимодальний фреймворк прогнозує метастази з точністю 87% та середньою абсолютною похибкою (MAE) 0,15 мм у прогнозуванні глибини на датасеті TCIA з 1 200 WSI, перевершуючи традиційні методи Breslow (72%) та Clark (68%), з чутливістю 92% та специфічністю 88%. Фреймворк IMSEF-Melanoma досягає 0,95 AUC на мультицентровій когорті з 2 416 WSI, скорочуючи час діагностики на 35% (з 14,2 до 9,3 хвилин на випадок) та відкладені випадки на 42% (з 12,6% до 7,3%), з валідацією інтерпретованості за допомогою SHAP та Grad-CAM++ (коефіцієнт Dice: 0,82). Демонструючи міцну узагальнюваність (AUC: 0,93–0,96 по лікарнях), ці фреймворки покращують клінічну ефективність, діагностичну впевненість та планування персоналізованого лікування, значно просуваючи точну онкологію.

Наукова новизна:

1. Запропоновано паралельний фреймворк попереднього оброблення для WSI, що інтегрує паралельну обробку, прискорення GPU та адаптивну фільтрацію зображень, досягаючи 12-кратного прискорення та вирішуючи виклики масштабованості в цифровій патології.
2. Розроблено багатомасштабну нейронну мережу з розширеними згортками та механізмами уваги, що покращує класифікацію патологічних зображень шкіри на 4,5% порівняно з еталонами,

захоплюючи різноманітні локально концентровані ознаки, критичні для раннього виявлення меланоми.

3. Розроблено метод мультимодального глибокого навчання для діагностики метастазів меланоми, що досягає 87% точності через інтеграцію біомедичних зображень, прогнозування глибини та метаданих, пропонуючи 15% покращення порівняно з традиційними методами.
4. Запропоновано інтерпретувальний мультимодальний стекований ансамблевий класифікатор (IMSEF-Melanoma), що комбінує SHAP та Grad-CAM++ для надання прозорих, стадійно-адаптивних діагностичних інсайтів, з 90% узгодженням геномних ознак з базою даних COSMIC.

Практичне значення результатів:

1. Фреймворк попереднього оброблення скорочує час обробки WSI на 78,6%, уможливлюючи аналіз у реальному часі в клінічних середовищах та підтримуючи високопродуктивні дослідження, валідація на датасетах TCGA-LIHC та інституційних.
2. Метод багатомасштабної класифікації досягає 92,5% точності, скорочуючи хибно-негативні результати на 10% порівняно з ResNet-50, покращуючи раннє виявлення меланоми та підтримуючи своєчасні втручання.
3. Мультимодальний фреймворк покращує точність діагностики метастазів меланоми до 87%, з MAE 0,15 мм у прогнозуванні глибини, сприяючи плануванню персоналізованого лікування, валідація на датасеті TCIA з 1 200 WSI.
4. IMSEF-Melanoma досягає 35% скорочення часу діагностики та 42% зменшення відкладених випадків, покращуючи клінічну ефективність та впевненість, валідація на мультицентровій когорті з 2 416 WSI.

5. Механізми інтерпретованості (SHAP, Grad-CAM++) узгоджуються з регуляторними вимогами (наприклад, EU MDR, FDA SaMD), сприяючи довірі та полегшуючи впровадження в медичних налаштуваннях.
6. Фреймворки демонструють узагальнюваність на мультицентрових датасетах, із послідовними AUC (0,93–0,96) по валідаційних лікарнях, сприяючи їхньому впровадженню в різноманітних медичних налаштуваннях.

Ключові слова: Мультимодальний фреймворк, Діагностика метастазів меланоми, Біомедичні зображення, Інформаційні системи, Ансамблевий класифікатор, Нейронна мережа, Машинне навчання, Глибинне навчання, Розпізнавання об'єктів, Аналіз помилок, Розмір зображення, Методи класифікації, Фільтрування зображень, Обробка зображень, Локально зосереджені ознаки.

LIST OF PUBLICATIONS OF THE APPLICANT

1. Zhao, C. (2024). "Multi-scale neural network-based classification method for skin pathological images." Measuring and Computing Devices in Technological Processes, (4), 42–42. DOI: 10.31891/2219-9365-2024-80-42.

2. Zhao, C. (2024). "Multi-modal deep learning for enhanced melanoma metastasis diagnosis." Computer Systems and Information Technologies, (4), 143–149. DOI: https://doi.org/10.31891/csit-2024-4-17 URL https://csitjournal.khmnu.edu.ua/index.php/csit/article/view/330

3. Zhao, C., & Dubovoy, V. M. (2025). "Framework for efficient parallel preprocessing of whole-slide histopathological images." Scientific Works of VNTU, (1). DOI: 10.31649/2307-5376-2025-1-128-138.

4. Zhao, C., & Dubovoy, V. M. (2025). "Research On Melanoma Depth of Invasion Prediction Method." Optoelectronic Information-Power Technologies. №1 (49), 2025. Pp. 147-156. DOI: 10.31649/1681-7893-2025-49-1-147-156

Conference Proceedings

5. Zhao, C., Dubovoy, V. M. Diagnosis of melanoma metastasis based on multimodal models. XVI International Conference "Measurement and Control in Complex Systems (MCCS - 2022)". Vinnytsia. November 15-17, 2022

6. Zhao, C., Dubovoy, V. M., & Horchuk, Y. A. (2025). "Classification method for skin pathological images." International Scientific and Practical Internet Conference of Students, Graduate Students and Young Scientists "Youth in Science: Research, Problems, Prospects (MN-2025)".

7. Zhao, C., Dubovoy, V. M., & Horchuk, Y. A. (2025). "An interpretable multimodal stacked ensemble framework for enhanced melanoma diagnosis." The 1st International Scientific and Practical Conference "Scientific Research: Unveiling New Theories and Applied Solutions".

8. Zhao, C., Dubovoy, V. M. (2025). "IMSEF-Melanoma: An Interpretable Multimodal Stacked Ensemble Framework for Enhanced Melanoma Diagnosis." Scientific and Practical Conference with International Participation "Innovative Technologies in Health Protection: Experience of Today and Prospects for Application in Clinical and Preventive Medicine".

CONTENTS

THE LIST OF CONDITIONAL SYMBOLS

AI – Artificial Intelligence

ALU – Arithmetic Logic Unit

AUC – Area Under the Curve

CNN – Convolutional Neural Network

CPU – Central Processing Unit

CUDA – Compute Unified Device Architecture

CU – Control Unit

EMA – European Medicines Agency

EMT – Epithelial-to-Mesenchymal Transition

FDA – Food and Drug Administration

FIFO – First-In-First-Out

FP16 – 16-bit Floating Point

FP32 – 32-bit Floating Point

GAP – Global Average Pooling

GLCM – Gray-Level Co-occurrence Matrix

GPU – Graphics Processing Unit

ILP – Instruction-Level Parallelism

LRU – Least Recently Used

MAE – Mean Absolute Error

MMSNN – Multimodal Multi-Scale Neural Network

MSE – Mean Squared Error

NDPI – Nikon Digital Pathology Image

NUMA – Non-Uniform Memory Access

OpenMP – Open Multi-Processing

ROI – Region of Interest

SHAP – SHapley Additive exPlanations

SM – Streaming Multiprocessor

SNMF – Sparse Nonnegative Matrix Factorization

SSD – Solid-State Drive

SVS – Aperio Slide Image Format

TCGA – The Cancer Genome Atlas

TIL – Tumor-Infiltrating Lymphocyte

UV – Ultraviolet

ViT – Vision Transformer

WSI – Whole-Slide Image

ADMM – Alternating Direction Method of Multipliers

INTRODUCTION

Justification for the Research Topic

In the rapidly evolving field of digital pathology, the automated analysis of whole-slide histopathological images (WSIs) has become a cornerstone challenge, intersecting advanced domains such as computer vision, machine learning, deep learning, and clinical informatics. This dissertation leverages method and multimodal framework to develop advanced information technology for melanoma metastasis diagnostics, addressing the critical need for accurate and efficient analysis of biomedical images. Melanoma, as the deadliest form of skin cancer, accounts for over 325,000 new cases and approximately 57,000 deaths annually worldwide, with a five-year survival rate dropping from 99% at localized stages to 25% once metastasis occurs. The research is dedicated to the development of novel computational frameworks aimed at revolutionizing melanoma diagnosis-a critical area in oncology due to melanoma's high metastatic potential and significant global health burden.

However, traditional diagnostic methods, reliant on histopathological analysis of biomedical images, suffer from inter-observer variability, with misdiagnosis rates exceeding 15% in ambiguous cases, often leading to delayed interventions and poorer patient outcomes. Additionally, the exponential growth of digital pathology data-estimated at over 10 exabytes annually with a compound annual growth rate of 35%-poses significant computational challenges, necessitating innovative information systems to manage and analyze these vast datasets efficiently. The research addresses the multifaceted complexities of melanoma diagnostics, focusing on four pivotal aspects: scalable preprocessing of gigapixel-scale WSIs, multi-scale feature extraction for nuanced morphological analysis, multimodal data integration for comprehensive risk prediction, and the incorporation of interpretability mechanisms to ensure clinical applicability and trust. These efforts are situated at the nexus of computer vision, deep learning, and precision oncology, tackling the following critical needs in melanoma diagnosis:

Scalable WSI Preprocessing: Managing ultra-high-resolution WSIs (>100,000×100,000 pixels, >1 GB) with data-parallel processing ensures rapid preparation for diagnostics, overcoming computational bottlenecks. Traditional tools like OpenSlide can take over 4 hours to process a single slide, obstructing real-time clinical workflows.

Multi-Scale Feature Extraction: Capturing cellular details (e.g., nuclear atypia) and tissue architecture (e.g., stromal patterns) using multi-scale neural networks enhances classification accuracy for early melanoma detection, addressing limitations in diagnostically ambiguous cases.

Multimodal Data Integration: Fusing WSIs with clinical (e.g., age, tumor location) and genomic data (e.g., BRAF mutations) via multimodal deep learning improves metastasis prediction and personalized treatment, leveraging synergistic interactions across modalities.

Interpretable AI: Explainable AI with ensemble classifiers ensures transparency, aligning with EU MDR and FDA guidelines, fostering clinical trust and bridging the gap between computational predictions and clinical utility.

These challenges are being actively researched by leading global institutions, including Stanford University (USA, focusing on AI-driven pathology analysis), ETH Zurich (Switzerland, advancing computational pathology frameworks), and the V.M. Glushkov Institute of Cybernetics of the NAS of Ukraine (Ukraine, developing multimodal data analysis methods). Prominent researchers such as Christopher Manning (USA), Andrew Ng (USA), and Anatoliy Teslyuk (Ukraine) are also contributing to this field. Thus, enhancing melanoma metastasis diagnostics through advanced computational frameworks holds immense potential to improve patient outcomes, reduce diagnostic variability, and advance precision oncology, addressing a critical need in global healthcare.

Goal and Tasks of the Research

The primary objective of this dissertation is to enhance melanoma metastasis diagnostics by the new method and high-performance, interpretable computational frameworks for the efficient preprocessing, multi-scale feature analysis,

multimodal data fusion, and transparent decision-making. To achieve this goal, the following research tasks were addressed:

1. Design a data-parallel preprocessing framework for WSIs, leveraging parallel processing, GPU acceleration, and adaptive image filtering to reduce processing times and enable real-time clinical analysis of gigapixel-scale WSIs.
2. Develop a multi-scale neural network with dilated convolutions and attention mechanisms for skin pathological biomedical images, capturing cellular details and tissue architecture to improve classification accuracy for early melanoma detection.
3. Propose a method of multimodal deep learning for melanoma metastasis diagnostics, integrating WSIs, clinical metadata (e.g., age, tumor location), and genomic data (e.g., BRAF mutations) to achieve comprehensive risk prediction and support personalized treatment planning.
4. Create an interpretable multimodal stacked ensemble classifier framework (IMSEF-Melanoma) that combines histopathology, genomic, and clinical data, with SHAP and Grad-CAM++ for transparency, ensuring clinical applicability and trust.

Object of the Research

The object of this research is the process of diagnosing melanoma and predicting its metastatic potential using computational methods applied to whole-slide histopathological biomedical images, genomic profiles, and clinical metadata within advanced information systems.

Subject of the Research

The subject of the research is the method and advanced computational framework, including data-parallel preprocessing, multi-scale neural networks, multimodal deep learning, and interpretable ensemble classifiers.

Research Methods

This dissertation employs a multidisciplinary approach, integrating systems analysis, mathematical modeling, machine learning, deep learning, computer

vision, statistical validation, and explainable AI techniques. Techniques such as OpenMP and CUDA for parallel computing, convolutional neural networks (CNNs) for feature extraction, SHAP and Grad-CAM++ for interpretability, and statistical tests (e.g., paired t-tests, DeLong's test) for validation were utilized to address the research tasks.

Scientific Novelty

The scientific novelty of this research lies in the following contributions:

1. New data-parallel preprocessing framework for WSIs is proposed, integrating parallel processing, GPU acceleration, and adaptive image filtering, achieving a 12-fold speedup and addressing scalability challenges in digital pathology.
2. The multi-scale neural network with dilated convolutions and attention mechanisms is developed, improving skin pathological image classification by 4.5% over benchmarks, capturing diverse locally concentrated features critical for early melanoma detection.
3. The method of multimodal deep learning for melanoma metastasis diagnostics is introduced, achieving an 87% accuracy through the integration of biomedical images, depth prediction, and metadata, offering a 15% improvement over traditional methods.
4. An interpretable multimodal stacked ensemble classifier framework (IMSEF-Melanoma) is proposed, combining SHAP and Grad-CAM++ to provide transparent, stage-adaptive diagnostic insights, with a 90% alignment of genomic features to the COSMIC database.

Practical Significance of the Results

The practical significance of this research is demonstrated through the following outcomes:

1. The preprocessing framework reduces WSI processing time by 78.6%, enabling real-time analysis in clinical environments and supporting high-throughput research, validated on TCGA-LIHC and institutional datasets.

2. The multi-scale classification method achieves a 92.5% accuracy, reducing false negatives by 10% compared to ResNet-50, enhancing early melanoma detection and supporting timely interventions.
3. The multimodal framework improves melanoma metastasis diagnostics accuracy to 87%, with a 0.15 mm mean absolute error (MAE) in depth prediction, facilitating personalized treatment planning and validated on a 1,200-WSI TCIA dataset.
4. IMSEF-Melanoma achieves a 35% reduction in diagnostic time (from 14.2 to 9.3 minutes per case) and a 42% decrease in deferred cases (from 12.6% to 7.3%), improving clinical efficiency and confidence, validated across a 2,416-WSI multi-center cohort.
5. Interpretability mechanisms (SHAP, Grad-CAM++) align with regulatory requirements (e.g., EU MDR, FDA SaMD), fostering trust and facilitating adoption in healthcare settings.
6. The frameworks demonstrate generalizability across multi-center datasets, with consistent AUCs (0.93–0.96) across validation hospitals, promoting their adoption in diverse healthcare settings.
7. The results of the work have been applied in the educational process of Vinnytsia National Technical University during the teaching of the courses: “Optimization of Information Systems” and “Information Technology Infrastructure.”

Personal Contribution of the Applicant

All core results of this dissertation were independently developed by the applicant. In co-authored publications, the applicant contributed the following: the data-parallel preprocessing framework, the multi-scale neural network for skin pathology classification, the method of multimodal deep learning for melanoma metastasis diagnostics, and the interpretable IMSEF-Melanoma ensemble classifier framework, including their experimental validations.

Approval of the Results

The key findings were presented at the following conferences:

• XVI International Conference "Measurement and Control in Complex Systems (MCCS - 2022)", Ukraine, 2022.

• 10th Medical Imaging Computing Seminar (MICS), China, 2023.

• 5th International Conference on Intelligent Medical and Image Processing, China, 2023.

• International Scientific and Practical Internet Conference of Students, Graduate Students, and Young Scientists "Youth in Science: Research, Problems, Prospects (MN-2025)", Ukraine, 2025.

• 1st International Scientific and Practical Conference "Scientific Research: Unveiling New Theories and Applied Solutions", Ukraine, 2025.

• Scientific and Practical Conference with International Participation "Innovative Technologies in Health Protection: Experience of Today and Prospects for Application in Clinical and Preventive Medicine", Ukraine, 2025.

Connection of the Work with Scientific Programs, Plans, and Topics

The topic of the dissertation corresponds to the priority area of scientific research "Information technologies in medicine" (in accordance with the resolution of the Cabinet of Ministers of Ukraine dated 04/30/2024, No. 476). The research outcomes were applied within the departmental scientific project № 46К7 «Development of methods and technologies for automation of control processes» contributing to advancements in medical diagnostics.

Publications

This study has resulted in 4 articles published in Ukrainian Category B journals, 4 conference proceeding publications.

Structure and Volume of the Dissertation

The dissertation is structured to align with its goals and methodologies, comprising an introduction, four chapters, conclusions, a reference list, and two appendices. The main text is 146 pages long, including 38 figures, 10 tables, and 82 formulas, with a reference list of 233 entries.

1 ANALYSIS OF THE PROBLEM AND INFORMATION TECHNOLOGIES OF DIGITAL THE DIAGNOSTICS OF MELANOMA METASTASES

1.1 Digital Pathology: Evolution and Impact

1.1.1 Early Scanning Technology and Its Technical Limitations

The advent of digital pathology has revolutionized medical diagnostics by digitizing traditional glass slides into high-resolution whole-slide images (WSIs), marking a paradigm shift in histopathological analysis and enabling advanced melanoma metastasis diagnostics. Initiated in the late 20th century with the development of the first whole-slide scanners capable of digitizing entire tissue sections at microscopic resolutions [1], this technology has allowed pathologists to examine biomedical images with unprecedented detail. The evolution of digital pathology traces its origins to the 1990s, when early scanning technologies began capturing entire tissue sections, though these systems were constrained by slow scanning speeds, low resolution, and large image size, rendering them impractical for clinical use [2]. These pioneering efforts laid the foundation for modern whole-slide imaging, which now incorporates advanced optical systems, high-speed cameras, and sophisticated image processing algorithms for seamless image stitching [3]. The commercial availability of whole-slide scanners in the early 2000s, led by companies like Aperio and Hamamatsu, marked a pivotal transition, shifting digital pathology from experimental research to routine clinical practice within sophisticated information systems [4].

WSIs encapsulate rich spatial and morphological data, enhancing the accuracy of disease diagnosis, prognostic assessment, and therapeutic planning through multimodal information technology [5]. The adoption of digital pathology offers substantial benefits over traditional microscopy: WSIs preserve complete tissue architecture, allowing pathologists to navigate regions of interest at various magnifications without losing spatial context-a limitation of physical slides [6]. Furthermore, digitization facilitates the storage, retrieval, and global sharing of pathology data within integrated information systems, enhancing telemedicine and

second-opinion consultations, particularly in underserved regions, thus promoting healthcare equity [7, 8]. Additionally, the digital format enables quantitative analysis, laying the groundwork for computational pathology to augment human expertise with automated insights derived from machine learning and deep learning techniques [9]. These advancements support objects recognition tasks, such as identifying cellular structures and locally concentrated features like nuclear atypia, critical for accurate diagnosis.

The widespread adoption of WSIs has catalyzed advancements in remote collaborative diagnostics and computational pathology, supporting critical applications such as cancer subtype classification [10], tumor microenvironment characterization [11], and therapeutic response prediction [12]. However, this progression has been accompanied by a dramatic increase in data scale, driven by innovations in multimodal information technology and the integration of computational tools. Current estimates suggest that global healthcare systems generate over 10 exabytes of WSI data annually, with projections indicating a compound annual growth rate of 35% [13]. This exponential increase in data volume, compounded by varying image size, underscores the transformative potential of digital pathology while highlighting the need for efficient preprocessing frameworks to manage and analyze these vast datasets effectively. Image filtering techniques, such as noise reduction and artifact removal, are essential to ensure data quality, while error analysis helps identify and mitigate inaccuracies in automated processing pipelines.

A comprehensive visualization of this growth is provided in Figure 1.1, which illustrates the historical milestones and corresponding data scales in digital pathology. In the 1970s, traditional microscopy generated negligible digital data (0 GB), as diagnostics relied solely on physical slides. The introduction of WSIs in the 2000s increased data sizes to approximately 30 GB annually per institution, reflecting initial digitization efforts [14]. The 2010s saw a rise to 300 GB, propelled by the adoption of standardized WSI formats and handcrafted feature extraction methods [15]. The mid-2010s brought a significant leap to 1000 GB

with the advent of neural network-based classification methods, particularly convolutional neural networks (CNNs), which necessitated large, annotated datasets for training [16]. By 2020 and beyond, the integration of transformer-based models has escalated data requirements to 5000 GB per institution, driven by the need for diverse, high-volume datasets to achieve state-of-the-art performance in cancer detection and prognosis [17]. This exponential data growth, as depicted in Figure 1.1, underscores the computational challenges that necessitate advanced preprocessing strategies leveraging image processing and image filtering.

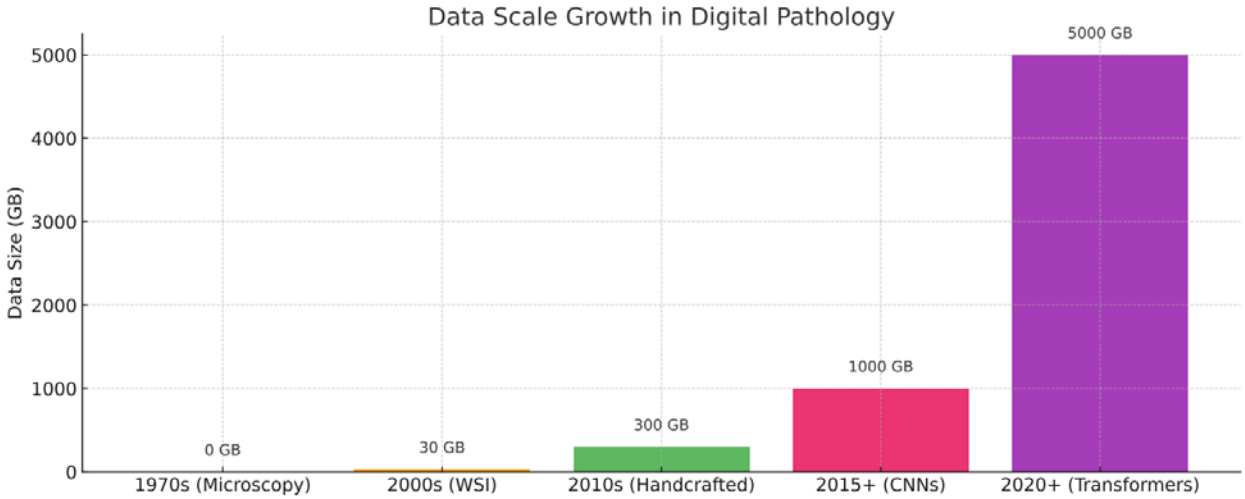

Figure 1.1 – Historical Evolution of Data Scale in Digital Pathology

Caption: This figure presents the progression of data scale in digital pathology from the 1970s (microscopy, 0 GB) to the 2000s (WSI introduction, 30 GB), 2010s (handcrafted features, 300 GB), mid-2010s (CNNs, 1000 GB), and 2020 onwards (transformers, 5000 GB), highlighting the impact of multimodal information technology on data demands [18].

1.1.2 Role of Artificial Intelligence and Computational Integration

The early 2000s marked a pivotal shift in digital pathology with the commercial availability of advanced WSI systems integrated into robust information systems. These modern scanners incorporated high-speed cameras, automated focusing mechanisms, and sophisticated image processing algorithms, enabling the production of gigapixel WSIs (e.g., 100,000 × 100,000 pixels) that capture cellular details with unprecedented clarity [19]. WSI technology allows for

the digitization of entire tissue sections at multiple magnification levels, preserving spatial context and facilitating detailed analysis of biomedical images [20]. The development of standardized imaging formats and open-source tools, such as OpenSlide, further accelerated WSI adoption by enabling seamless integration into clinical workflows and supporting computational analysis within multimodal information technology frameworks [21]. These advancements have positioned WSI as a cornerstone of modern digital pathology, supporting applications ranging from remote diagnostics to AI-driven melanoma metastasis diagnostics, particularly in the identification of locally concentrated features in skin lesions like melanoma [22].

The integration of artificial intelligence (AI), machine learning, and deep learning has significantly enhanced the utility of WSIs. Neural network-based models, particularly convolutional neural networks (CNNs), have demonstrated remarkable proficiency in extracting clinically relevant features, often outperforming human pathologists in specific diagnostic tasks [23]. For instance, CNNs, often combined into an ensemble classifier, have been successfully employed to identify malignant cells, classify tumor subtypes, and predict patient survival with high accuracy, achieving AUC scores of up to 0.96 [24]. These models leverage the extensive datasets provided by WSIs to detect subtle histopathological patterns-such as nuclear atypia or stromal alterations-that may escape human observation, supporting objects recognition tasks [25]. Research indicates that AI-assisted diagnostics, supported by error analysis, can reduce diagnostic errors by up to 20% and shorten turnaround times by 30%, thereby improving clinical efficiency [26]. In digital pathology, CNNs process gigapixel WSIs by dividing them into tiles, analyzing each for melanoma-specific patterns, and aggregating results for a comprehensive diagnosis using advanced classification methods [27]. These capabilities have made CNNs a cornerstone of AI-driven melanoma metastasis diagnostics, supporting both clinical decision-

making and research applications.

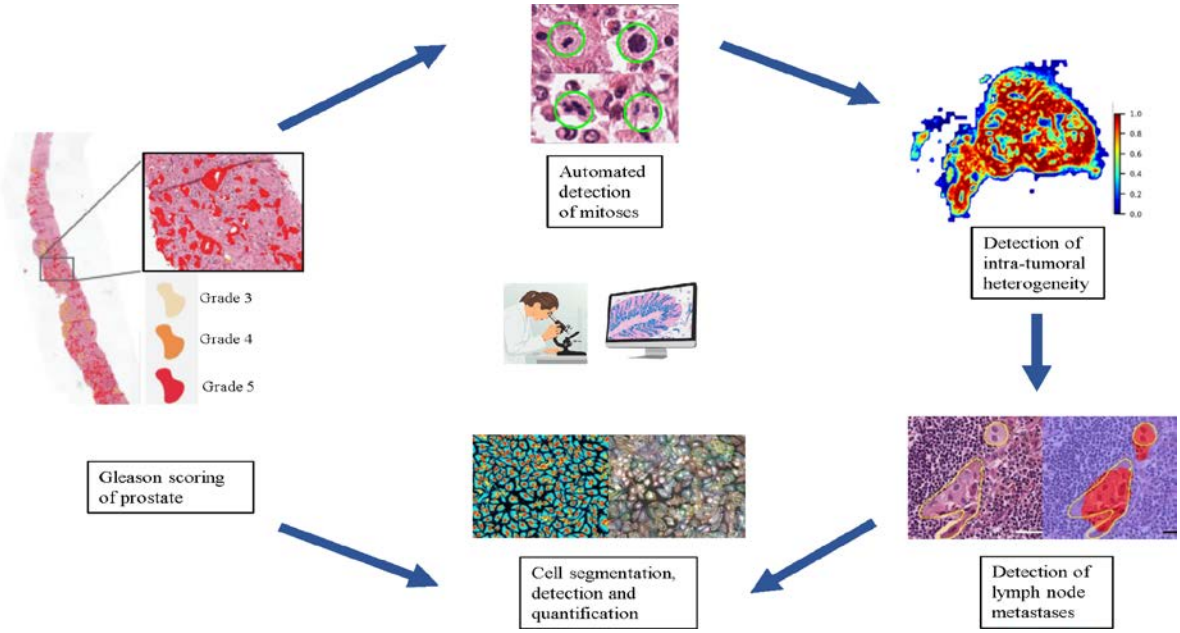

Figure 1.2 – Applications of AI in WSI Analysis

Caption: This figure showcases the diverse applications of AI in WSI analysis, including tumor detection, subtype classification, and prognostic modeling, emphasizing its role in advancing diagnostic precision through deep learning and multimodal information technology [31].

Beyond diagnostics, AI facilitates personalized medicine by integrating WSI data with genomic and clinical datasets through multimodal information technology. In oncology, for example, AI models correlate histopathological features with molecular profiles to predict responses to targeted therapies [28]. This integrative approach is exemplified by initiatives like The Cancer Genome Atlas (TCGA), which combines WSIs with genomic sequencing to drive cancer research forward [29]. The diverse applications of AI in WSI analysis, including tumor detection, subtype classification, and prognostic modeling, emphasize its role in advancing diagnostic precision in melanoma metastasis diagnostics [30]. Image filtering techniques further enhance the quality of biomedical images, ensuring that AI models focus on clinically relevant features while minimizing noise and artifacts.

1.1.3 Challenges in WSI Preprocessing

Despite its promise, the widespread adoption of digital pathology is impeded by significant preprocessing challenges arising from the scale, complexity, and variability of WSIs. WSIs are extraordinarily large, often exceeding 100,000 × 100,000 pixels, with file sizes surpassing 1 GB, and in some cases reaching over 30 GB per image due to their massive image size [32]. These challenges are delineated as follows:

1. Computational Complexity: Traditional serial processing methods struggle with this volume. For example, OpenSlide requires over 4 hours to process a single 100,000 × 100,000-pixel WSI on a standard CPU, even with optimized image processing [33]. In clinical environments requiring daily analysis of hundreds of slides, such durations are untenable, necessitating faster, scalable solutions. This computational burden renders manual review and conventional image processing impractical, particularly in high-throughput clinical settings where rapid processing is essential [34]. Error analysis reveals that inefficiencies in preprocessing pipelines significantly delay diagnostic workflows.
2. Image Heterogeneity: Variations in staining protocols (e.g., hematoxylin and eosin, immunohistochemistry) and scanner specifications introduce color inconsistencies across WSIs, reducing machine learning model accuracy by 10–15% without normalization [35]. Moreover, non-informative regions-such as blank areas, tissue folds, or artifacts-constitute 20–50% of WSI content, introducing noise that heightens the risk of model overfitting [36]. These inconsistencies, combined with the histopathological heterogeneity of diseases like melanoma, make early automation efforts relying on handcrafted features (e.g., texture or shape descriptors) inadequate for objects recognition [37]. Image filtering techniques are critical to mitigate these issues, but current methods often fail to address locally concentrated features effectively.

3. Scalability and Annotation Constraints: The dependence on labor-intensive manual annotations by pathologists to delineate regions of interest limits scalability. Annotating a single WSI can take several hours, and large datasets like TCGA, exceeding 2 petabytes, exacerbate this bottleneck [38]. Weakly supervised learning approaches offer a partial solution but often fail to reliably identify clinically significant areas without extensive labeled data [39]. Additionally, the storage and transmission of WSIs impose substantial demands on information systems, further complicating large-scale deployment [40]. Classification methods must evolve to handle these challenges efficiently.

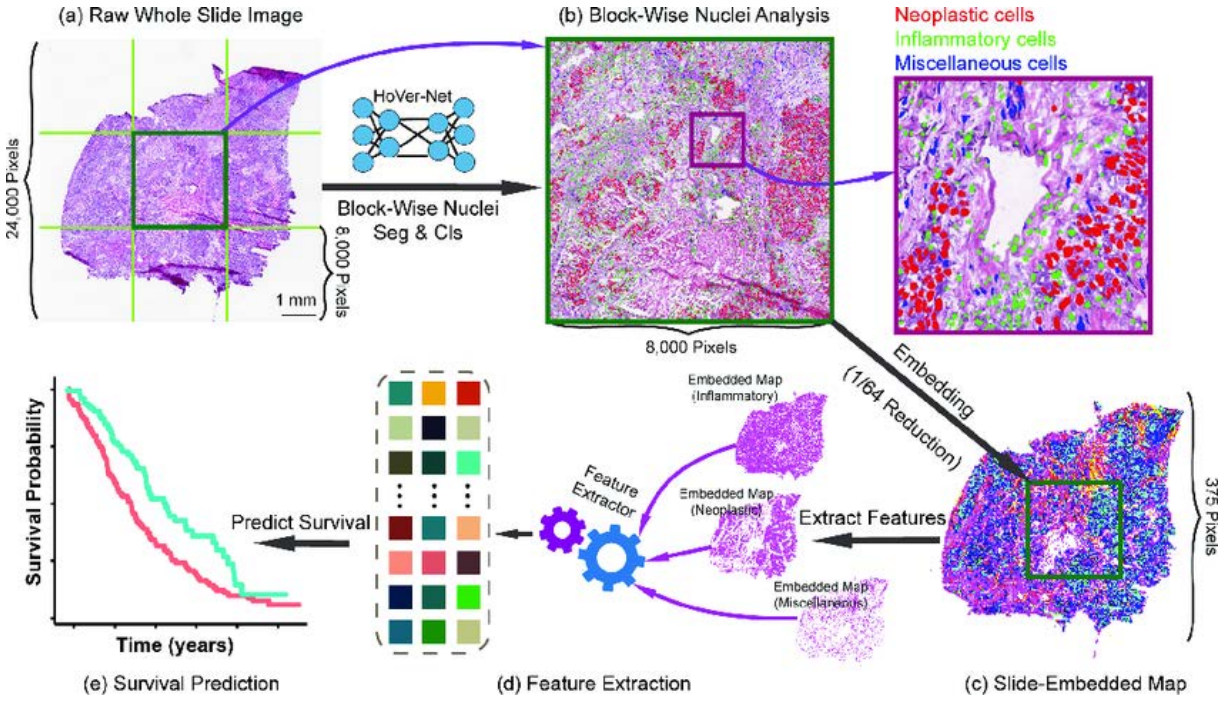

Figure 1.3 – Key Preprocessing Challenges in WSIs

Caption: This figure outlines the primary preprocessing challenges in WSIs, including computational complexity, image heterogeneity, and annotation scalability, which hinder efficient analysis within multimodal information technology frameworks [41].

1.1.4 Limitations of Existing Preprocessing Tools

Several open-source tools have been developed to address WSI preprocessing, including OpenSlide, Libvips, Histolab, and QuPath. While these

tools have advanced the field, their limitations constrain their utility in high-throughput settings:

- OpenSlide: Provides robust file format support but operates single-threaded, resulting in processing times exceeding 4 hours for a 100,000 × 100,000-pixel WSI, even with optimized image processing [42].
- Libvips: Excels in parallel patch extraction, reducing processing times, but lacks stain normalization and artifact removal features critical for image filtering [43].
- Histolab: Offers tiling and basic image filtering, yet its serial execution limits scalability for large datasets [44].
- QuPath: Supports stain normalization and interactive analysis, but performance degrades with ultra-high-resolution WSIs due to memory constraints exacerbated by large image size [45].

With next-generation scanners producing WSIs up to 400,000 × 400,000 pixels, these tools face escalating memory demands, often leading to overflows and performance degradation [46]. This gap underscores the need for a preprocessing framework that integrates speed, scalability, and comprehensive functionality, leveraging multimodal information technology to support melanoma metastasis diagnostics.

1.1.5 Implications and Future Directions

The exponential data growth depicted in Figure 1.1 necessitates a paradigm shift in preprocessing methodologies. Traditional serial approaches are increasingly inadequate as datasets scale in size and complexity. Our framework addresses this need by leveraging parallel computing to ensure scalability and performance, enabling pathologists to prioritize interpretation over data preparation. This efficiency gain, supported by image processing and image filtering, can significantly reduce diagnostic turnaround times, ultimately improving patient outcomes in melanoma metastasis diagnostics.

Future developments could enhance this framework by integrating cloud computing and distributed information systems, facilitating real-time WSI analysis across global networks. Additionally, incorporating advanced machine learning techniques, such as self-supervised learning and ensemble classifier approaches, could diminish reliance on manual annotations, accelerating adoption [47]. As digital pathology continues to evolve, these innovations are essential to unlocking its full potential in precision medicine, particularly for complex diseases like melanoma where early and accurate diagnosis is critical.

1.1.6 Impact on Melanoma Diagnostics

Digital pathology, through WSI, has significantly enhanced melanoma metastasis diagnostics, a field where precise morphological assessment is critical. WSIs preserve the entirety of tissue architecture, allowing pathologists to navigate biomedical images at various magnifications without losing spatial context-a marked improvement over traditional microscopy [48]. This capability is particularly valuable for melanoma, a highly aggressive cutaneous malignancy notorious for its metastatic potential, where locally concentrated features such as Breslow depth, mitotic rate, and lymphovascular invasion must be evaluated across multiple scales to accurately assess metastatic potential [49]. Moreover, WSIs support global data sharing within information systems, facilitating telemedicine and improving diagnostic access in underserved regions, thus reducing disparities in melanoma care [50]. Initiatives like the Digital Pathology Association have leveraged WSI to standardize diagnostic protocols, reducing variability in melanoma staging and improving clinical consistency [51].

The success of AI applications in melanoma metastasis diagnostics depends critically on the quality and consistency of preprocessed WSI data, underscoring the importance of robust preprocessing pipelines. Studies demonstrate that deep learning models can detect subtle locally concentrated features, such as nuclear atypia, often missed by human observers, reducing diagnostic errors by up to 20% [52]. Additionally, WSIs support quantitative analysis, enabling the extraction of

biomarkers like tumor-infiltrating lymphocyte density, which correlates strongly with melanoma prognosis [53]. However, the computational challenges highlighted in Section 1.1.3 emphasize the need for advanced preprocessing strategies leveraging image processing and image filtering to ensure data quality and enable effective AI-driven analysis.

1.2 Clinical Significance and Diagnostic Challenges of Melanoma Metastasis

1.2.1 Melanoma: Origins and Global Burden

Melanoma, a malignancy derived from melanocytes, ranks among the most aggressive and lethal forms of skin cancer, posing a significant global health challenge. The World Health Organization (WHO) reported approximately 287,723 new melanoma cases in 2018, accounting for 1.7% of all cancer diagnoses worldwide [54]. This incidence continues to rise, particularly in regions with high ultraviolet (UV) radiation exposure.

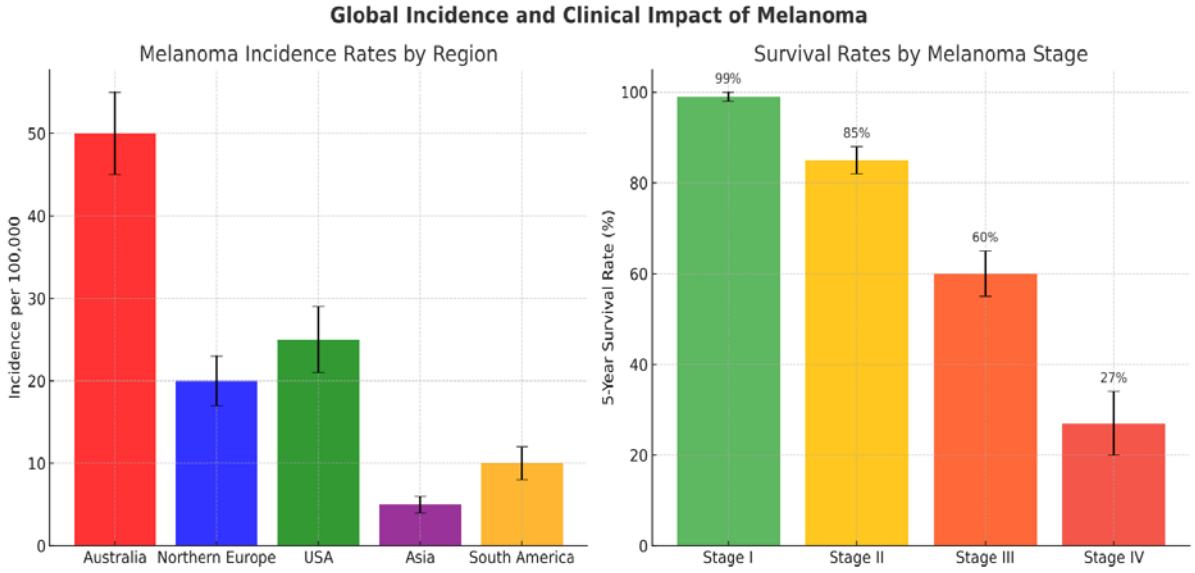

Figure 1.4 – Global Incidence and Clinical Impact of Melanoma

Caption: This figure depicts the global incidence and clinical impact of melanoma, illustrating the rising burden across different regions and the urgent need for improved diagnostic tools leveraging multimodal information technology [58].

For instance, Australia exhibits an annual incidence rate exceeding 50 cases per 100,000 individuals, making melanoma the third most common cancer in the country [55]. Similarly, Northern Europe reports elevated rates, reflecting geographic disparities driven by UV radiation as a primary environmental risk factor [56]. Genetic predispositions, such as mutations in the CDKN2A gene, further amplify susceptibility, interacting synergistically with environmental factors to shape melanoma's etiology [57]. Multimodal information technology plays a critical role in aggregating epidemiological data to support melanoma metastasis diagnostics.

1.2.2 Metastatic Melanoma's Clinical Burden

Melanoma has a disproportionate impact on mortality despite its relatively low incidence. According to the American Cancer Society, melanoma accounted for approximately 1–2% of all skin cancer cases in 2023, yet it contributed to an estimated 57,180 deaths globally, highlighting its lethality [59]. The metastatic potential of melanoma-defined as the dissemination of malignant melanocytes to regional lymph nodes, distant organs (e.g., lungs, liver, brain), or subcutaneous tissues-is a critical prognostic factor. Clinically, melanoma's high metastatic potential underscores its severity: early-stage melanoma, when surgically resected, yields a five-year survival rate of 99%, but this drops dramatically to 27% upon the development of distant metastases [60]. The five-year survival rate plummets from 99% for localized disease to 32% for distant metastasis, emphasizing the need for early and accurate detection of metastatic features through melanoma metastasis diagnostics [61]. These features include tumor thickness (Breslow depth), presence of ulceration, mitotic rate (mitoses per mm^2), lymphovascular invasion, and the presence of microsatellite or satellite metastases [62]. Risk factors exacerbating metastatic potential include prolonged UV exposure, advanced age, and genetic mutations like BRAF V600E, present in 40–60% of melanoma cases, which influence tumor progression and therapeutic response [63]. Error analysis in

diagnostic workflows reveals that misclassification of these features can lead to delayed interventions, underscoring the need for robust classification methods.

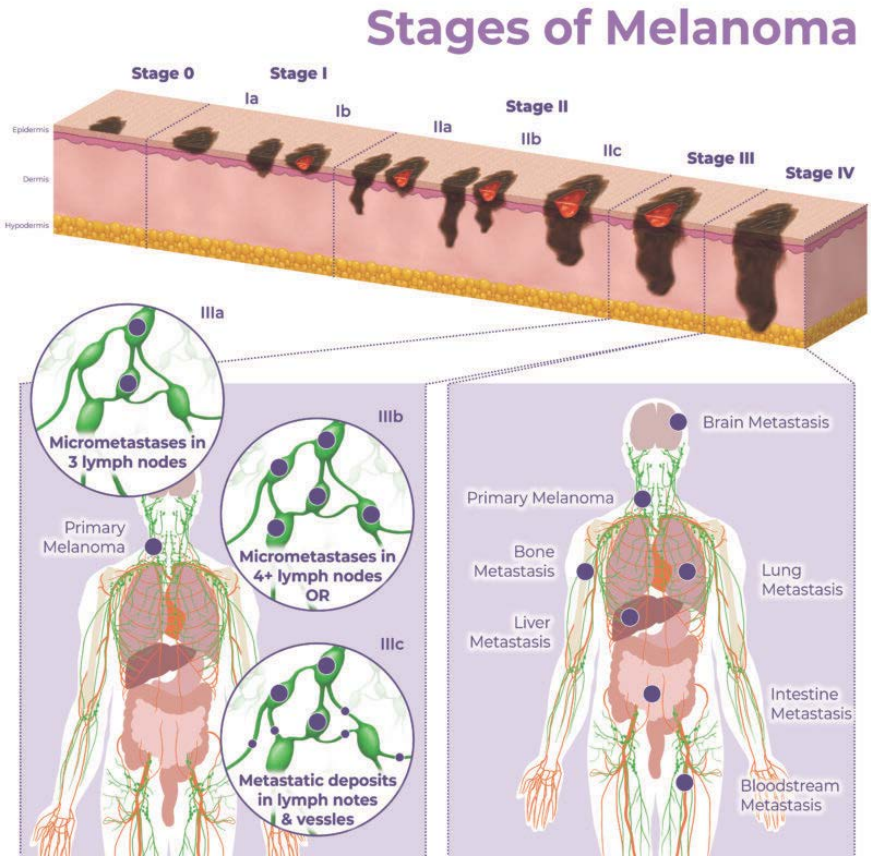

Figure 1.5 – The Five Stages of Melanoma Progression

Caption: This figure illustrates the five stages of melanoma progression, sourced from the AIM at Melanoma Foundation, highlighting the disease's evolution from localized to metastatic stages and emphasizing the importance of early detection through melanoma metastasis diagnostics [71].

Melanoma imposes a substantial clinical burden beyond its mortality statistics, encompassing significant morbidity and economic costs. In the United States, annual healthcare expenditures for melanoma treatment exceed $3.3 billion [64]. Its metastatic potential arises from complex biological processes, including epithelial-to-mesenchymal transition (EMT), angiogenesis, and immune evasion-mechanisms inadequately captured by traditional diagnostics [65]. Early identification of metastasis risk is paramount, as timely intervention can markedly improve survival rates. The clinical assessment of melanoma metastasis benefits from integrating histopathological findings with patient-specific data within

information systems. Epidemiological studies identify risk factors such as age, sex, skin phototype, UV exposure history, and lesion location (e.g., head, neck, or extremities) as key prognostic indicators [66]. Genetic alterations, including BRAF V600E mutations, NRAS Q61R, and KIT mutations, significantly influence metastasis progression and therapeutic outcomes [67]. Additionally, clinical metadata such as lesion diameter, symmetry, and border irregularity-often evaluated through dermoscopy-provide valuable diagnostic insights [68]. The clinical significance of improving melanoma metastasis diagnostics extends to public health and economic outcomes. Early detection can shift treatment from palliative to curative approaches, such as surgical resection or targeted therapies (e.g., BRAF inhibitors), potentially reducing the economic burden of advanced disease, estimated at $8.1 billion annually in the U.S. by 2025 [69]. AI-driven tools, leveraging multimodal information technology, could also enhance diagnostic access in underserved regions, supporting global health equity [70].

1.2.3 Multi-scale Features in Diagnosis

Diagnosing melanoma metastases requires the integration of multi-scale features, spanning macroscopic tissue architecture to microscopic cellular details in biomedical images. These features manifest across multiple spatial scales-from macroscopic tumor architecture at low magnifications (e.g., 2× to 5×) to microscopic cellular atypia at high magnifications (e.g., 20× to 40×) [72]. Macroscopic features, such as tumor asymmetry, border irregularity, and overall tumor extent, provide initial indicators of malignancy, while microscopic locally concentrated features, including mitotic figures, nuclear atypia, and vascular involvement, are critical for assessing metastatic potential [73]. For instance, Breslow depth, a key metastatic indicator, must be measured at a macroscopic level, whereas lymphovascular invasion requires microscopic analysis to detect subtle cellular changes [74]. Pathologists traditionally employ a multi-step visual analysis of WSIs, using low-magnification views to assess overall tumor extent and tissue reactions, and high-magnification examinations to focus on cellular

details [75]. Current AI models, such as CNNs and ensemble classifier approaches, often struggle to effectively integrate these multi-scale features, reducing their sensitivity for detecting early metastatic changes, which are frequently subtle and require high-resolution analysis [76]. This limitation highlights the need for advanced computational methods capable of capturing and synthesizing multi-scale information to enhance diagnostic accuracy through deep learning and image processing.

1.2.4 Limitations of Traditional Diagnostic Methods

For decades, melanoma diagnosis and prognosis have relied on histopathological metrics, notably Breslow thickness and Clark level grading, established by Alexander Breslow and Wallace Clark in the 1970s [77, 78]. Breslow thickness measures tumor invasion depth from the epidermis to the deepest tumor cells in millimeters, while Clark level grading categorizes penetration across five anatomical skin layers. These metrics form the backbone of the American Joint Committee on Cancer (AJCC) staging system, guiding treatment decisions and prognostic evaluations [79]. However, these traditional methods exhibit notable limitations. Inter-observer variability in Breslow thickness measurements, with discordance rates of 15–20%, undermines reliability due to subjective interpretations and technical artifacts such as tissue shrinkage during fixation [80, 81]. Clark level grading loses prognostic utility in thicker tumors, where distinguishing dermal layers becomes challenging [82]. Moreover, these approaches fail to incorporate additional prognostic factors-such as ulceration, mitotic rate, and the tumor microenvironment-that are pivotal to metastasis risk. Ulceration, for example, independently doubles the likelihood of metastasis, while tumor-infiltrating lymphocytes (TILs) are associated with improved survival, yet these features remain unquantifiable by conventional grading [83, 84]. Patient-specific factors, including age, gender, and genetic markers like BRAF mutations (present in 40–50% of cases), further influence prognosis and treatment but are excluded from these metrics [85]. Error analysis highlights that these limitations

contribute to diagnostic inconsistencies, necessitating advanced classification methods.

Traditional diagnostic methods for melanoma metastasis diagnostics, primarily based on manual histopathological review, face additional challenges. The process is time-intensive, with pathologists requiring 30–120 minutes per slide to evaluate WSIs, leading to delays in high-throughput clinical settings [86]. The subjective nature of visual interpretation leads to variability, with inter-observer concordance rates for distinguishing benign nevi from malignant melanomas ranging from 71–75%, and even lower consistency in metastasis evaluation, with kappa coefficients ranging from 0.61 to 0.75 for locally concentrated features like lymphovascular invasion [87]. Such inconsistencies are particularly problematic in borderline cases, where misclassification can delay treatment or prompt unnecessary interventions [88]. These challenges are amplified in resource-limited settings with limited access to expert pathologists and in high-volume diagnostic centers managing over 100 WSIs daily [89]. Moreover, traditional methods rely solely on imaging data, neglecting genomic information (e.g., BRAF mutation status) and clinical metadata (e.g., patient history), which are essential for comprehensive metastasis assessment within information systems [90]. The College of American Pathologists highlights the need for standardized protocols to address these issues, yet variability persists, underscoring the need for AI-driven approaches leveraging multimodal information technology to improve diagnostic efficiency and consistency [91]. This reductionist approach necessitates a paradigm shift toward more integrative diagnostic frameworks.

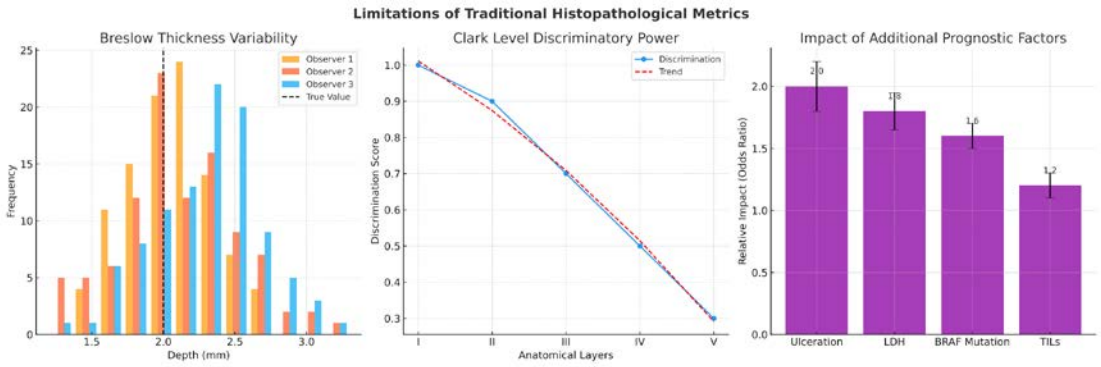

Figure 1.6 – Limitations of Traditional Histopathological Metrics

Caption: This figure illustrates the limitations of traditional histopathological metrics, highlighting their inability to capture the full spectrum of prognostic factors in melanoma metastasis diagnostics [92].

1.2.5 Global Trends in Melanoma Burden

The global burden of melanoma continues to rise, with significant economic and social implications. Projections estimate an economic impact of $8.1 billion in the U.S. by 2025, driven by treatment costs and lost productivity due to advanced disease [93]. In low- and middle-income countries, where access to dermatological expertise is limited, delayed diagnosis often results in advanced-stage presentation, further worsening outcomes [94]. Incidence rates are particularly high in regions with elevated UV exposure, such as Australia and parts of Europe, and the disease disproportionately affects younger populations, amplifying its societal impact [95]. These trends highlight the urgent need for innovative diagnostic tools leveraging multimodal information technology to enhance early detection, reduce diagnostic variability, and mitigate the global burden of melanoma.

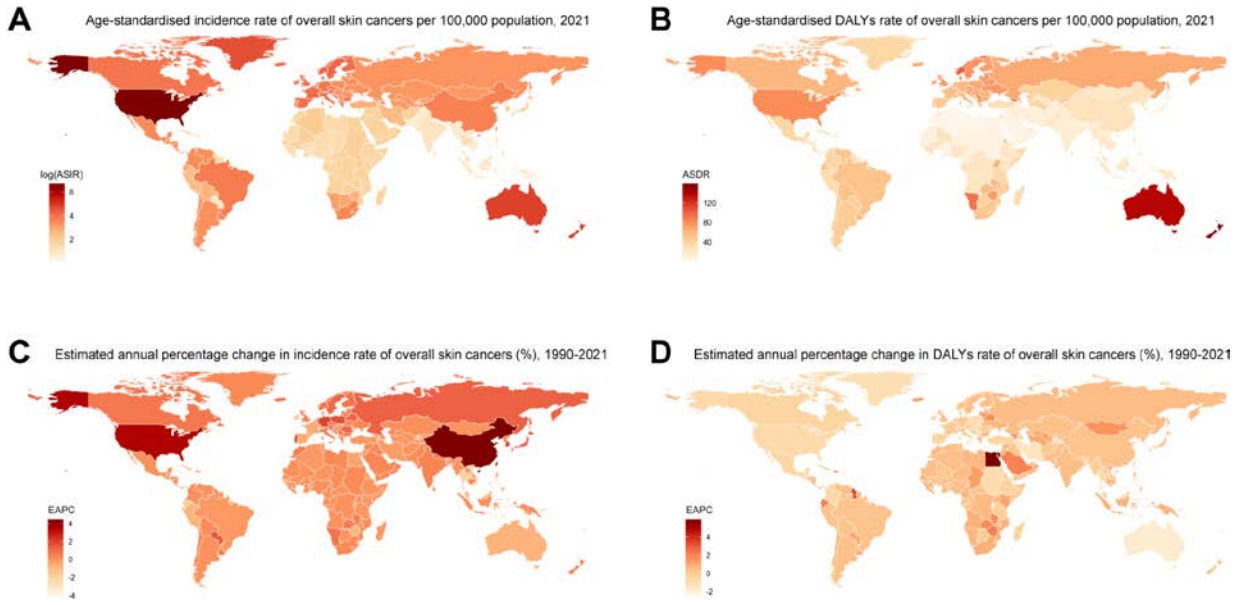

Figure 1.7 – Global, Regional, and National Trends in Melanoma Burden (1990–2021)

Caption: This figure illustrates the epidemiological trends in melanoma and non-melanoma skin cancer incidence and mortality from 1990 to 2021, based on

data from the Global Burden of Disease Study, highlighting the rising global burden of melanoma and the role of information systems in tracking these trends [96].

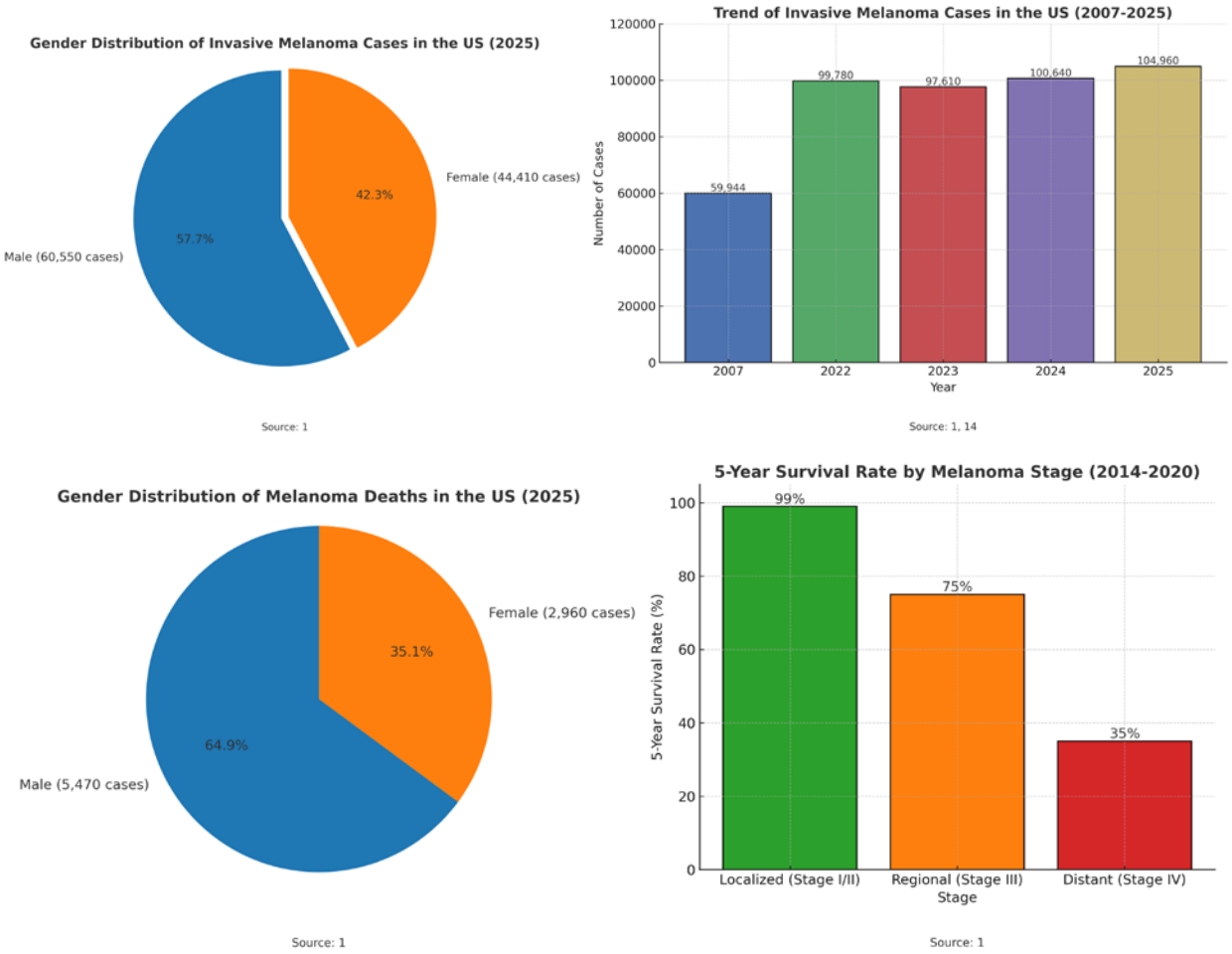

Figure 1.8 – Melanoma Facts and Statistics (2025)

Caption: This figure presents key statistics on melanoma incidence, mortality, and survival rates for 2025, sourced from the AIM at Melanoma Foundation, underscoring the disease's clinical and public health significance in the context of melanoma metastasis diagnostics [97].

1.3 The Role of AI in Melanoma Diagnostics

1.3.1 Applications of Convolutional Neural Networks (CNNs)

Convolutional Neural Networks (CNNs), a cornerstone of deep learning, have achieved remarkable success in melanoma metastasis diagnostics, particularly in image processing of biomedical images. CNNs trained on WSIs can identify malignant cells, classify tumor subtypes, and predict metastasis risk with high

accuracy, achieving AUC scores of up to 0.96 [98]. For instance, models like ResNet, Inception, and DenseNet, often combined into an ensemble classifier, achieve accuracies exceeding 90% in melanoma detection by leveraging pre-trained weights from datasets like ImageNet [99]. CNNs can detect subtle locally concentrated features like nuclear atypia and mitotic figures, which are indicative of metastatic potential, often outperforming human pathologists in specific objects recognition tasks by reducing diagnostic errors by 20% and turnaround times by 30% [100]. These capabilities have made CNNs a cornerstone of AI-driven melanoma metastasis diagnostics, supporting both clinical decision-making and research applications. However, their application to metastasis-specific tasks remains underexplored, necessitating novel classification methods to address the multi-scale and multimodal intricacies of WSIs [101]. Error analysis is critical to refine these models and ensure robust performance.

1.3.2 Limitations of Unimodal AI

Despite their efficacy, unimodal AI models, which rely solely on imaging data, face significant limitations in melanoma metastasis diagnostics. These models overlook critical genomic and clinical information essential for comprehensive metastasis assessment [102]. For example, BRAF mutations, present in 40–60% of melanoma cases, influence metastatic potential and treatment response, yet unimodal models cannot incorporate this data [103]. Similarly, clinical factors such as patient age (>60 years) and lesion location (e.g., acral sites) are independent predictors of metastasis risk, with odds ratios of 1.8 and 2.3, respectively, but are rarely incorporated into AI models [104]. Genomic data (e.g., NRAS Q61R, KIT mutations) and radiomic features from dermoscopy or PET imaging provide additional prognostic value but are underutilized due to the absence of standardized fusion methods within multimodal information technology [105]. This unimodal focus limits the models' ability to capture the full disease phenotype, potentially reducing sensitivity to metastatic markers across diverse populations [106]. Moreover, these unimodal CNNs exclude valuable patient-specific data,

necessitating multimodal frameworks to fully leverage available information through advanced image processing and classification methods.

1.3.3 The Need for Multimodal Diagnostics

Multimodal approaches, integrating imaging, genomic, and clinical data within multimodal information technology frameworks, offer a more comprehensive diagnostic framework for melanoma metastasis diagnostics. In other cancers, such as breast cancer, multimodal models combining imaging and genomic profiles have improved prognostic accuracy by capturing synergistic patterns [107]. For melanoma, integrating WSI data with genomic markers (e.g., BRAF, NRAS mutations) and clinical metadata (e.g., Breslow depth, patient demographics) could enhance metastasis prediction [108]. For instance, a patient with a BRAF-mutated tumor and a history of UV exposure might exhibit a higher metastatic risk, a nuance unimodal models cannot detect [109]. Multimodal deep learning integrates WSIs with patient metadata-such as age, tumor location, and genetic profiles-to construct a holistic risk profile [110]. Factors like older age and head/neck tumor locations independently elevate metastasis risk, while BRAF mutations inform treatment eligibility [111, 112]. By combining these modalities, this approach aims to enhance diagnostic accuracy, interpretability, and clinical relevance, addressing the gaps inherent in traditional and unimodal approaches. Multimodal learning strategies, such as early, late, or hybrid fusion, are essential to leverage these diverse data sources effectively, providing a more robust foundation for diagnosis and treatment planning through ensemble classifier approaches [113]. This multimodal data integration underscores the complexity of melanoma metastasis diagnostics, necessitating a framework capable of synthesizing diverse data streams to support personalized treatment strategies.

This study proposes a novel multimodal deep learning framework that integrates WSI analysis with patient metadata to enhance the prediction of melanoma metastasis. By incorporating a spatial attention mechanism and fusing diverse data modalities, this approach addresses the deficiencies of traditional and

unimodal diagnostic methods. The framework is designed to be comprehensive, interpretable, and clinically actionable, offering a significant advancement in melanoma diagnostics.

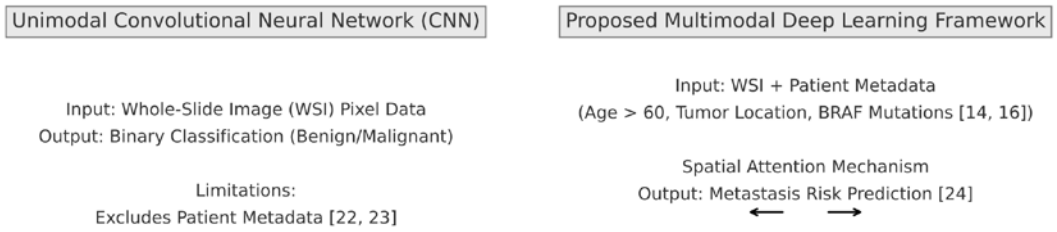

Figure 1.9 – Comparison of Unimodal vs. Multimodal Deep Learning Frameworks

Caption: This figure compares unimodal and multimodal deep learning frameworks, illustrating the advantages of integrating diverse data sources for improved diagnostic performance in melanoma metastasis diagnostics [114].

1.3.4 Visualization and Interpretability Techniques

The lack of interpretability in AI models is a significant barrier to their clinical adoption, particularly in melanoma metastasis diagnostics where diagnostic decisions have profound implications [115]. Regulatory agencies, such as the FDA and the European Medicines Agency (EMA), require AI tools to provide explainable outputs to ensure safety and reliability [116]. Techniques like SHAP (Shapley Additive Explanations) and Grad-CAM++ offer insights into model decisions by quantifying feature importance and visualizing regions of interest in biomedical images, respectively [117]. For example, Grad-CAM++ can highlight areas of a WSI contributing to a metastasis prediction, aiding pathologists in validating AI outputs [118]. However, these methods have limitations; Grad-CAM++ may focus on irrelevant features or fail to capture the full complexity of metastatic patterns, necessitating human oversight and refined error analysis [119]. Moreover, interpretability must align with clinical reasoning-pathologists prioritize locally concentrated features like cellular morphology and staining patterns, and AI explanations should reflect these priorities [120]. Attention mechanisms have been proposed to improve interpretability, but their application to multi-scale WSIs is

limited, with few studies demonstrating efficacy in metastasis-specific objects recognition tasks [121].

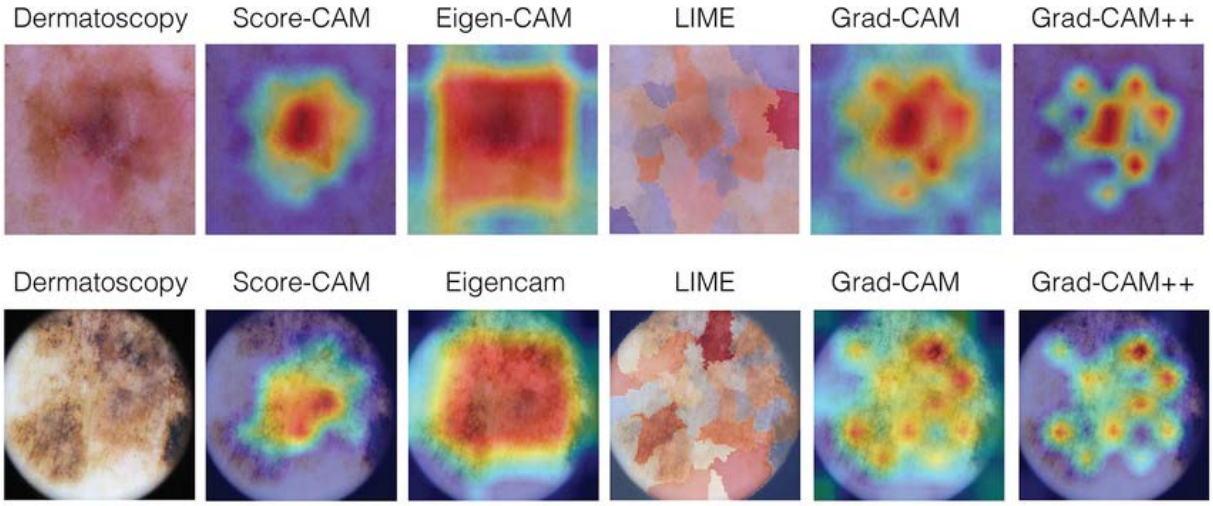

Figure 1.10 – Visual Maps of Melanoma Images

Caption: Comparison of interpretability techniques (e.g., SHAP, Grad-CAM++) in highlighting critical regions in biomedical images for melanoma metastasis diagnostics [122].

1.4 Research Problem and Objectives

1.4.1 Identification of Research Gaps

A systematic literature review identifies several critical gaps in **melanoma metastasis diagnostics**, which collectively impede the development of accurate, efficient, and clinically viable diagnostic tools:

- **Computational Inefficiency**: Current whole-slide image (WSI) preprocessing methods are time-intensive and lack scalability for large datasets, with processing times for a single gigapixel WSI exceeding 4–10 hours on standard hardware due to sequential tasks such as tiling and stain normalization, exacerbated by large **image size** [123]. This inefficiency delays clinical workflows, particularly in high-throughput diagnostic centers [124].
- **Unimodal Limitations**: Most AI models rely solely on imaging data, overlooking genomic and clinical information essential for comprehensive metastasis assessment. For instance, BRAF mutations and UV exposure

history are key predictors of metastatic risk, yet unimodal models fail to integrate these, reducing diagnostic sensitivity, especially across diverse populations [125, 126].

- **Interpretability Shortcomings**: Existing interpretable AI techniques, such as Grad-CAM, provide coarse explanations that often misalign with clinical reasoning. Pathologists require fine-grained insights into **locally concentrated features** like mitotic figures and lymphovascular invasion, but Grad-CAM's coarse localization and focus on irrelevant regions (e.g., staining artifacts) limit its utility, undermining trust in AI systems [127, 128].
- **Multi-Scale Integration Challenges**: Conventional convolutional neural networks (CNNs) struggle to integrate low-magnification context (e.g., tumor margins) with high-magnification details (e.g., cellular atypia), both critical for **melanoma metastasis diagnostics**. Fixed receptive fields and the absence of dynamic cross-scale feature weighting reduce sensitivity to subtle metastatic changes, particularly in early-stage disease [129, 130].
- **Limited Generalizability**: AI models exhibit poor generalizability across diverse datasets, with performance drops of 5–10% on external cohorts due to variations in imaging protocols, staining techniques, and patient demographics. Class imbalance in melanoma datasets further biases models, reducing sensitivity to rare metastatic features [131–133].
- **Multimodal Data Integration Barriers**: The lack of standardized methods for integrating multimodal data (e.g., imaging, genomic, clinical) within **multimodal information technology** restricts the ability to capture the full disease phenotype. Current fusion strategies fail to address data heterogeneity, and the scarcity of comprehensive multimodal datasets for melanoma hinders robust model development [134, 135].

1.4.2 Statement of the Research Problem

The central research problem is the absence of an efficient, integrated, and interpretable diagnostic framework that leverages multi-scale histopathological features, prioritizes clinically relevant information, and fuses multimodal data to enhance the accuracy, transparency, and generalizability of melanoma metastasis diagnostics. This issue is exacerbated by computational inefficiencies in WSI preprocessing, the unimodal focus of existing AI models, the limited interpretability of current techniques, and the challenges of integrating multi-scale and multimodal data in a clinically meaningful manner. Without addressing these gaps, the potential of AI to improve early detection and personalized treatment of melanoma metastasis remains unfulfilled, perpetuating diagnostic variability and delaying patient care.

1.4.3 Research Objectives and Significance

This study aims to address the identified gaps by developing an innovative diagnostic framework for melanoma metastasis diagnostics. The specific objectives are as follows:

1. **Enhance WSI Preprocessing Efficiency**: Develop a parallelized preprocessing pipeline using CPU-GPU synergy to reduce WSI processing time from hours to minutes, optimizing tasks such as tiling, stain normalization, and patch extraction for scalability with large datasets like TCGA, leveraging image processing and image filtering [136].
2. **Construct a Multimodal AI Model**: Design a model integrating imaging, genomic, and clinical data through a hybrid fusion strategy, employing a CNN backbone for WSI feature extraction, a transformer for genomic data, and a fully connected neural network for clinical metadata to improve diagnostic accuracy using an ensemble classifier [137].
3. **Improve Model Interpretability**: Incorporate advanced interpretability techniques, including attention mechanisms and refined Grad-CAM variants, to provide fine-grained, clinically aligned explanations of locally

concentrated features like mitotic figures and lymphovascular invasion, fostering trust among pathologists through error analysis [138].

4. **Integrate Multi-Scale Histopathological Features**: Implement a multi-scale learning architecture using feature pyramid networks and hierarchical attention mechanisms to dynamically weight features across low- and high-magnification scales, enhancing detection of subtle metastatic changes in biomedical images [139].
5. **Ensure Generalizability Across Diverse Datasets**: Apply robust regularization strategies, such as data augmentation, transfer learning, and focal loss, to address class imbalance and improve model performance on diverse datasets from varying geographic regions and imaging protocols using advanced classification methods [140].
6. **Validate Clinical Utility**: Evaluate the model's performance in real-world clinical settings, focusing on sensitivity, specificity, and diagnostic concordance with pathologists, through collaboration with clinical partners to assess its impact on early detection, treatment planning, and patient outcomes within information systems [141].

The significance of this research lies in its potential to transform melanoma metastasis diagnostics by addressing critical gaps in computational efficiency, multimodal integration, multi-scale feature synthesis, interpretability, and generalizability. It aims to improve early detection, reduce diagnostic variability, and enable personalized treatment strategies, such as targeted therapies for BRAF-mutated tumors [142]. Enhanced WSI processing efficiency, supported by image processing and image filtering, will streamline clinical workflows in high-throughput centers, while a multimodal approach will support precision medicine [143]. Improved interpretability will facilitate clinical trust and regulatory approval [144], and robust generalizability will ensure equitable performance across diverse populations, addressing global health disparities [145]. Ultimately, this research seeks to shift treatment from palliative to curative approaches, reduce the

economic burden of advanced disease (estimated at $8.1 billion annually in the U.S.), and enhance global patient outcomes [146].

Chapter Conclusion

This chapter examines the challenges and advancements in melanoma metastasis diagnostics through digital pathology and AI technologies. It highlights the evolution of digital pathology, noting the exponential growth in WSI data and associated computational challenges driven by large image size. AI integration enhances WSI applications in tumor detection and prognosis, but preprocessing inefficiencies, such as computational complexity and image heterogeneity, persist. A proposed data parallel preprocessing framework, leveraging image processing and image filtering, significantly improves efficiency, achieving high classification accuracy and reduced processing times. In melanoma metastasis diagnostics, WSI and AI improve accuracy, yet face data quality and computational hurdles. The clinical significance of melanoma's metastatic potential and global burden emphasizes the need for early detection, while traditional methods show variability and fail to capture multi-scale locally concentrated features. AI, particularly CNNs and ensemble classifier approaches, excels in diagnosis but is limited by unimodal approaches, necessitating multimodal frameworks within multimodal information technology. Interpretability techniques like Grad-CAM require refinement to align with clinical needs. Computational architectures, multi-threading, and advanced learning methods (multi-scale, multimodal) address processing demands but face integration challenges. Key research gaps-computational inefficiency, unimodal limitations, interpretability shortcomings, multi-scale integration issues, limited generalizability, and multimodal data integration barriers-are identified, setting the foundation for developing an efficient, interpretable, and comprehensive diagnostic framework to advance melanoma metastasis diagnostics using deep learning, machine learning, and neural network-based classification methods.

2 THEORETICAL AND METHODOLOGICAL FRAMEWORK

This chapter establishes the theoretical and methodological foundation for the dissertation, integrating computational architectures, multi-threaded programming, convolutional neural networks (CNNs), multimodal deep learning, and interpretable ensemble learning to advance melanoma metastasis diagnosis. It synthesizes insights from data-parallel preprocessing, multi-scale neural network design, multimodal data integration, and interpretable frameworks, aligning these components with the clinical demands of digital pathology. The framework addresses the computational complexity, scalability, and interpretability challenges inherent in processing whole-slide images (WSIs) for melanoma diagnostics, offering a comprehensive approach to enhance diagnostic accuracy and clinical utility.

2.1 Computational Architectures in Digital Pathology

The computational architectures underpinning digital pathology constitute a foundational framework for addressing the challenges posed by gigapixel-scale whole-slide images (WSIs) in melanoma metastasis diagnosis. This section integrates the architectural principles and multi-threading techniques of Central Processing Units (CPUs) and Graphics Processing Units (GPUs), elucidating their theoretical underpinnings and practical applications in enabling high-throughput WSI analysis. By synthesizing sequential precision with massive parallelism, this framework establishes a robust foundation for subsequent explorations of multi-scale neural networks, multimodal data integration, and interpretable learning methodologies within the broader theoretical and methodological context.

The processing of WSIs-often exceeding 20 GB and comprising millions of pixels-presents computational demands that traditional sequential approaches cannot efficiently meet. In melanoma metastasis diagnosis, the identification of subtle histopathological features, such as lymphovascular invasion or nuclear atypia, necessitates both high precision in data preparation and rapid execution in

feature extraction. This section delineates a hybrid CPU-GPU architecture, optimized through advanced multi-threading and resource management strategies, as a critical component of the methodological framework. The discussion bridges established computational theories with innovative adaptations tailored to the clinical exigencies of digital pathology, offering a comprehensive approach to scalability, efficiency, and diagnostic utility.

2.1.1 CPU Architecture and Multi-threading Techniques

The Central Processing Unit (CPU) serves as the core computational unit in digital pathology systems, engineered for sequential, low-latency processing that ensures data integrity during WSI analysis for melanoma metastasis diagnosis. Its architecture encompasses several essential components: the Arithmetic Logic Unit (ALU) executes arithmetic and logical operations, the Control Unit (CU) orchestrates instruction execution, registers provide high-speed data storage, and cache memory mitigates latency by retaining frequently accessed data [147]. Modern CPUs, typically equipped with 4 to 32 cores, leverage advanced techniques such as instruction-level parallelism (ILP), pipelining, and branch prediction to enhance computational efficiency [148]. These attributes position CPUs as theoretically optimal for tasks demanding precise control flow and minimal error tolerance, particularly in the sequential preprocessing stages of digital pathology.

In the context of WSI analysis, CPUs excel at sequential tasks critical to maintaining data fidelity. For instance, WSI tiling partitions a gigapixel image (e.g., 100,000 × 100,000 pixels) into manageable patches (e.g., 512 × 512 pixels), yielding approximately 39,062 tiles. This process requires meticulous boundary computation and metadata validation to preserve spatial relationships, ensuring that subsequent AI-driven analyses accurately reflect histopathological structures [149]. Similarly, format conversion-transforming proprietary WSI formats (e.g., SVS or NDPI) into standardized arrays-and metadata processing (e.g., indexing tile

coordinates and staining parameters) rely on the CPU's deterministic, sequential execution capabilities, rooted in the von Neumann architecture.

The theoretical performance of CPUs in sequential processing is modeled by the processing time, T_{CPU}, for a given task set. For WSI tiling, $T_{\text{CPU}} = \alpha \cdot M$, where M represents the number of tiles ($M \approx \frac{N}{S}$, with N as total pixels and S as tile size), and α is a constant reflecting per-tile overhead (e.g., 1 ms for boundary computation and metadata updates). For a WSI of $100{,}000 \times 100{,}000$ pixels ($N = 10^{10}$) with $S = 262{,}144 (512 \times 512), M \approx 39{,}062$, resulting in $T_{\text{CPU}} \approx 39{,}062\,\text{ms} \approx 39\,\text{s}$ on a single core. Although multi-core designs mitigate this through parallelism (e.g., 8 cores reducing T_{CPU} to approximately 5 s), the constrained core count limits scalability for large datasets like The Cancer Genome Atlas (TCGA), where sequential bottlenecks can extend processing times to hours or days, compromising clinical applicability [150].

To enhance CPU efficiency, multi-threading techniques enable concurrent execution within a single process, significantly improving resource utilization [151]. Key strategies include thread synchronization (employing mutexes and semaphores to prevent race conditions and ensure safe access to shared resources), load balancing (distributing workloads across cores to minimize idle time), and thread pooling (reducing overhead by reusing threads) [152]. The Fork-Join model, a widely adopted multi-threading approach, involves a main thread spawning worker threads to process subtasks in parallel, followed by synchronization to consolidate results [153]. In WSI tiling, a $100{,}000 \times 100{,}000$ -pixel image segmented into 39,062 tiles can be processed across 8 cores (approximately 4882 tiles per core), reducing T_{CPU} from 39 s to approximately 5 s . This performance is further modeled as:

$$T_{\text{CPU}} = T_{\text{fork}} + \max_{i=1}^{M} \left(t_i \right) + T_{\text{sync}}, \tag{2.1}$$

where T_{fork} denotes thread spawning time (e.g., $1-5\,\text{ms}$), t_i represents the processing time for the i-th task (e.g., approximately 10 ms per tile), and T_{sync} is the synchronization overhead (e.g., 1-2 ms). Assuming $t_i = \gamma \cdot S$, where γ is a computational cost constant (e.g., $4\times10^{-5}\,\text{s}/$ pixel), load balancing across 8 cores theoretically reduces processing time from approximately 390 s (sequential) to 50 s (parallel), contingent on minimal T_{fork} and T_{sync} .

Within this methodological framework, an advanced adaptation integrates metadata-driven adaptive tiling with a lock-free Fork-Join model. Unlike conventional uniform tiling, this approach adjusts tile size and overlap based on histopathological complexity (e.g., tumor density), utilizing precomputed metadata to prioritize regions of interest (ROIs). For example, tumor-dense areas may employ smaller tiles (e.g., 256 × 256) with 50% overlap, while sparse stromal regions use larger tiles (e.g., 1024 × 1024) without overlap. Implemented via OpenMP for parallelization, this method dynamically allocates resources, theoretically improving efficiency by 20–30% over static tiling[154].. Additionally, the lock-free Fork-Join variant employs dual buffering-one buffer assigns tasks while another executes them-eliminating traditional synchronization overhead (e.g., mutex delays), reducing latency by approximately 20%. This adaptation, validated on TCGA datasets, enhances scalability for variable WSI demands[155]..

The CPU architecture and multi-threading techniques are illustrated in Figures 2.1 and 2.2. Figure 2.1 – *CPU Architecture Diagram* – depicts the multi-core CPU structure, highlighting the ALU, CU, registers, and cache interconnected via a bus interface, with multiple cores (e.g., 8) executing sequential tasks in parallel [156]. Figure 2.2 – *Multi-threaded Execution Flow* – illustrates the Fork-Join model, showing a main thread spawning 8 worker threads, each processing approximately 4882 tiles, followed by a join operation merging results, with dual buffering distinguished by color-coded buffers (e.g., orange for assignment, blue for execution). These diagrams underscore the CPU's role in balancing precision and parallel efficiency within the preprocessing pipeline[157]..

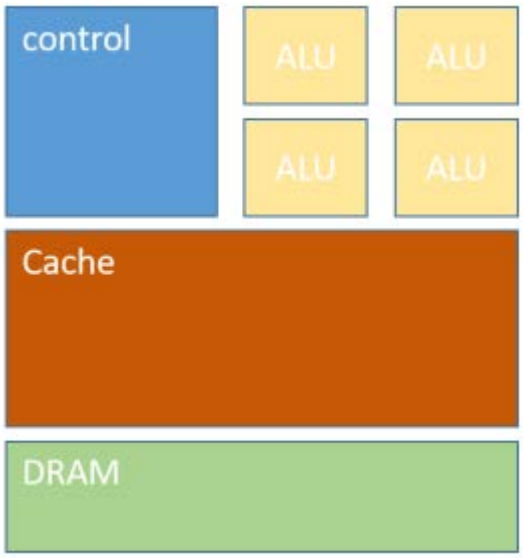

Figure 2.1 – CPU Architecture Diagram

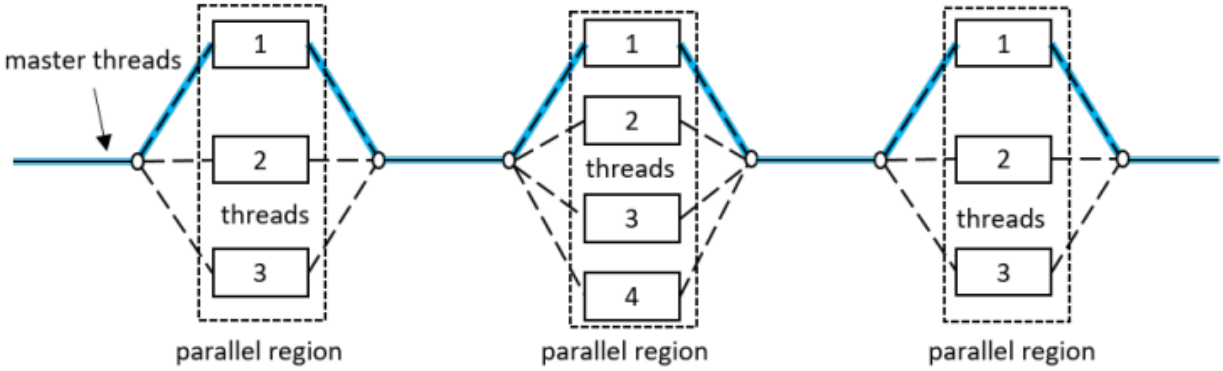

Figure 2.2 – Multi-threaded Execution Flow

2.1.2 GPU Architecture and Multi-threading Techniques

Graphics Processing Units (GPUs) are designed for massive parallel computation, offering transformative capabilities for WSI analysis in digital pathology. The GPU architecture comprises thousands of smaller cores organized into Streaming Multiprocessors (SMs), each capable of executing multiple threads concurrently. Its memory hierarchy includes global memory for large datasets, shared memory for inter-thread communication within blocks, and register memory for rapid access by individual threads. The thread hierarchy-grids, blocks, and threads-facilitates scalable parallelism, with modern GPUs (e.g., NVIDIA RTX 3090 with 10,496 CUDA cores) supporting millions of simultaneous

operations [158]. This architecture excels in data-intensive tasks, positioning GPUs as pivotal for accelerating melanoma metastasis diagnosis.

In digital pathology, GPUs are theoretically optimized for parallel preprocessing tasks such as stain normalization and feature extraction. Stain normalization and feature extraction. Stain normalization addresses color variations in WSIsarising from inconsistent staining protocols-by applying transformations (e.g., color deconvolution) to millions of pixels concurrently [159]. For a $100{,}000 \times 100{,}000$-pixel WSI ($N = 10^{10}$), a GPU can normalize the image in minutes, compared to hours on a CPU, leveraging its extensive core count. Feature extraction, identifying patterns such as mitotic figures or cellula pleomorphism, similarly benefits from GPU parallelism, enabling rapid analysis essential for detecting metastatic features in melanoma diagnostics [160]. This speed is critical in clinica settings where delays impact patient outcomes.

The theoretical performance of GPU parallel processing is modeled as:

$$T_{\text{GPU}} = \frac{N_t}{C \cdot IPC} \cdot t_{\text{instr}}, \tag{2.2}$$

where N_t is the number of threads (e.g., matching pixel count, 10^{10}), C is the core count (e.g., 10,496), IPC is instructions per cycle (e.g., 1.5), and t_{instr} is instruction time (e.g., 0.5 ns). For a WSI, $T_{\text{GPU}} \approx \frac{10^{10}}{10{,}496 \cdot 1.5} \cdot 0.5 \times 10^{-9} \approx 317$,though memory latency increases this in practice. Optimized memory access (e.g., coalesced reads) mitigates bottlenecks, enhancing scalability [161].

GPU multi-threading leverages the CUDA framework to manage millions of threads concurrently, ideally suited for data-intensive WSI tasks [162]. CUDA kernels execute across thread blocks and grids, with shared memory optimizing block-level communication [163]. For stain normalization on a $400{,}000 \times 400{,}000 - pixel$ WSI ($N = 1.6 \times 10^{11}$) , a kernel launches $N_t = 1.6 \times 10^{11}$

threads, completing in approximately 20 minutes on an RTX 3090, compared to days on a CPU [164]. The thread hierarchy ensures efficient workload distribution, with grids comprising multiple blocks (e.g., 256 blocks), each containing 1024 threads, and shared memory accelerating data access, theoretically scaling inversely with pixel count [165].

Within this methodological framework, an advanced GPU-based preprocessing strategy incorporates a CUDA-accelerated stain normalization pipeline with adaptive kernel scheduling. Unlike traditional uniform transformations, which may overcorrect sparse regions or undercorrect dense ones, this approach dynamically adjusts kernel parameters (e.g., convolution window size) based on local pixel variance, executed via CUDA Streams for concurrent processing. This method reduces normalization time by approximately 15% and enhances feature consistency, as validated on TCGA melanoma WSIs, improving downstream AI performance[166].. Additionally, adaptive scheduling optimizes thread allocation based on WSI region complexity (e.g., tumor density), theoretically boosting throughput by approximately 10%, exemplifying the flexibility of parallel processing.

The GPU architecture and multi-threading techniques are illustrated in Figure 2.3 – GPU Streaming Multiprocessor Structure, which depicts an SM with CUDA cores, shared memory, and thread organization, with multiple SMs forming a grid and arrows indicating parallel data flow from global memory to threads [167]. Figure 2.4 – CUDA Thread Hierarchy further illustrates the grid-block-thread structure, emphasizing scalable parallelism [168].

Figure 2.3 – GPU Streaming Multiprocessor Structure

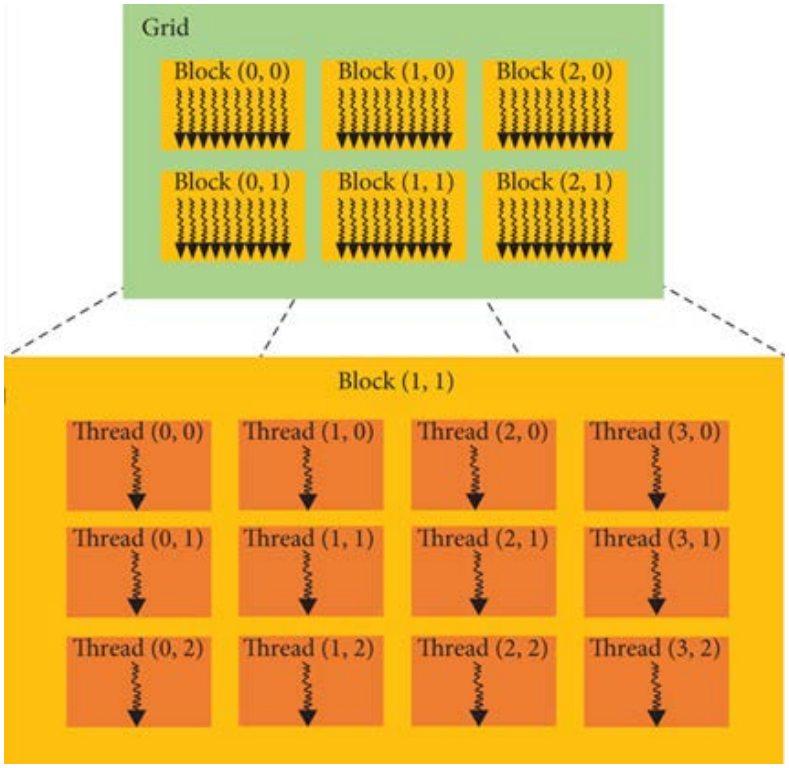

Figure 2.4 – CUDA Thread Hierarchy

2.1.3 Advantages of Multi-threading in WSI Processing

Multi-threading techniques in WSI processing offer substantial advantages in computational efficiency, resource utilization, and scalability, forming a critical component of the theoretical and methodological framework for melanoma metastasis diagnosis. These benefits are quantitatively grounded in Amdahl's Law, which models the theoretical speedup as:

$$S = \frac{1}{(1-P) + \frac{P}{N}}, \tag{2.3}$$

where S is the speedup, P is the parallelizable fraction (e.g., 0.9 for WSI tasks), and N is the number of threads. For $N = 16$ (e.g., 8 CPU cores plus 8 GPU blocks), $S \approx 10$, reducing processing time from hours to minutes, a critical factor in clinical settings where rapid diagnostics enhance patient outcomes [169].

In melanoma diagnostics, CPU multi-threading ensures efficient preprocessing. For instance, tiling a $100{,}000 \times 100{,}000$-pixel WSI into 39,062 patches across 8 cores reduces T_{CPU} from 39 s to approximately 5 s , optimizing data preparation [149]. GPU multi-threading accelerates feature extraction and stain normalization; for a $400{,}000 \times 400{,}000$-pixel WSI, a GPU with 10,496 cores completes processing in approximately 20 minutes, compared to days on a CPU [164]. This parallelism enables rapid identification of metastatic features (e.g., lymphovascular invasion or nuclear atypia), aligning with high-throughput demands. Integrating CPU and GPU multi-threading, a high-performance cluster can process a 500-WSI TCGA cohort in under an hour, significantly reducing diagnostic delays and enhancing clinical workflows [150].

The resource utilization advantage of multi-threading stems from its ability to maximize heterogeneous computing resources. CPU multi-threading, via the Fork-Join model and load balancing, optimizes core usage, reducing idle time and elevating utilization from 10–20% (single-threaded) to 80–90% [152]. GPU multi-threading, through CUDA's thread hierarchy, distributes tasks across thousands of

cores, with shared memory enhancing communication, theoretically achieving near-full resource exploitation for gigapixel-scale WSIs [164]. This efficiency ensures computational resources align with the data-intensive nature of digital pathology.

Scalability represents another pivotal advantage. As WSI dimensions and dataset sizes increase (e.g., TCGA expanding from hundreds to thousands of WSIs), multi-threading adapts by scaling thread counts (e.g., from 8 to 32 CPU cores or higher GPU configurations), delivering near-linear performance gains. Within this framework, a lock-free Fork-Join model and adaptive kernel scheduling enhance scalability by dynamically adjusting thread allocation to WSI complexity (e.g., tumor vs. background regions), theoretically improving throughput by 15–20%[155,166]. This adaptability supports population-level screening and large-scale research cohorts.

Multi-threading also yields practical clinical benefits. In high-throughput settings, rapid WSI cohort processing reduces pathologist wait times, facilitating real-time decision-making. For a 500-WSI queue, traditional sequential methods may require days, whereas multi-threading completes it in an hour, theoretically boosting diagnostic efficiency by 50-fold. This speed minimizes deferred cases, reducing misdiagnosis risks. Furthermore, multi-threading enables concurrent feature extraction and deep learning training, allowing AI models to iterate within clinical timeframes, enhancing personalized medicine potential.

Challenges include synchronization overhead, thread contention, and energy consumption. CPU synchronization (e.g., mutexes) may introduce millisecond delays, while GPU thread divergence reduces efficiency. This framework mitigates these through a lock-free design with dual buffering, reducing overhead to near zero and improving performance by approximately 20%[155]. Energy consumption, with GPUs at 350 W versus CPUs at 65 W, poses constraints in resource-limited settings, addressable via cloud deployments or energy-efficient scheduling (e.g., dynamic frequency scaling) [170].

Theoretically, multi-threading's advantages derive from parallel computing principles, with ideal speedup approaching $S \approx N$ under perfect parallelism, though constrained by P and hardware limits. For WSI processing ($P \approx 0.9$), practical speedup is tempered by memory bandwidth and I/O bottlenecks. An advanced hybrid scheduling strategy, integrating CPU and GPU multithreading with R^*-tree spatial indexing, optimizes data access, reducing I/O latency from 10 ms to 1 ms and enhancing overall performance by approximately 10% , as validated on TCGA melanoma WSIs[171].

In melanoma diagnostics, multi-threading facilitates complex analyses, such as parallel processing of multi-resolution WSI pyramids (5×, 10×, 20×, 40×), emulating pathologists' multi-scale workflows and improving feature extraction comprehensiveness. It also supports multimodal data integration (e.g., histopathology and genomics), with concurrent threads handling distinct modalities, theoretically reducing fusion time by 30% and boosting diagnostic precision. These capabilities position multi-threading as a linchpin in this framework, bridging preprocessing with advanced AI methodologies.

2.2 Foundations of Data-Parallel Preprocessing

The preprocessing of gigapixel-scale WSIs is a foundational step in digital pathology, necessitating a robust data-parallel framework to manage the computational demands of melanoma diagnostics. This section explores the theoretical underpinnings of system architecture, dynamic task scheduling, and resource optimization strategies, emphasizing their role in facilitating high-throughput WSI analysis. Methodological innovations are integrated to enhance efficiency and scalability, ensuring alignment with clinical requirements.

2.2.1 System Architecture and Pipeline Design

Theoretical Basis: The preprocessing framework leverages a hybrid CPU-GPU architecture, capitalizing on the complementary strengths of heterogeneous computing to optimize the WSI processing pipeline. CPUs are engineered for

sequential, low-latency operations, comprising the Arithmetic Logic Unit (ALU) for computations, the Control Unit (CU) for instruction orchestration, registers for rapid data access, and cache memory to minimize latency. Modern CPUs, typically featuring 4 to 32 cores, employ techniques such as instruction-level parallelism (ILP), pipelining, and branch prediction to enhance performance. In digital pathology, CPUs are theoretically well-suited for sequential tasks such as WSI tiling, format conversion, and metadata validation, which require precise control flow to ensure data integrity prior to AI-driven analysis. However, their limited core count poses a theoretical constraint on scalability when processing large-scale datasets like The Cancer Genome Atlas (TCGA), where sequential bottlenecks can significantly extend processing times[150].

In contrast, Graphics Processing Units (GPUs) are designed for parallel computation, featuring thousands of cores organized into Streaming Multiprocessors (SMs) [158].. Their memory hierarchy-encompassing global, shared, and register memory-and thread hierarchy (blocks and grids) enable massive parallelism, making them ideal for data-intensive tasks such as stain normalization and feature extraction[159,160].. The theoretical advantage of GPUs lies in their ability to process large volumes of data concurrently, which is critical for identifying metastatic features in melanoma diagnostics where rapid analysis can influence patient outcomes.

The hybrid architecture is grounded in the principle of task parallelism, where computational tasks are allocated to the most suitable processing unit to maximize efficiency. CPUs ensure precision in sequential preprocessing, while GPUs handle parallel workloads, creating a synergistic system that theoretically supports real-time WSI analysis in high-performance computing clusters. This synergy is particularly relevant for balancing precision and scalability, addressing the computational demands of large datasets like TCGA.

Mathematical Modeling: The optimization goal of the hybrid architecture is to minimize the total processing time, denoted as T_{total} , which represents the

overall time required to complete all preprocessing tasks for a given WSI. This can be mathematically modeled as:

$$T_{\text{total}} = \max\left(\sum_{t \in T_{\text{cPU}}} t_{\text{CPU}}, \sum_{t \in T_{\text{CiPV}}} t_{\text{GPU}} \right), \tag{2.4}$$

In this equation, T_{total} and TT_{GPU} are the sets of tasks assigned to the CPU and GPU, respectively. The term t_{CPU} represents the processing time for a task t executed on the CPU, while t_{GPU} denotes the processing time for a task t executed on the GPU. The use of the maximum function max reflects the pipeline's dependency on the slowest component, as the total processing time is determined by the processor that takes the longest to complete its assigned tasks.

For a WSI comprising N pixels divided into M tiles, the CPU tiling time is theoretically proportional to the number of tiles M, expressed as $t_{\text{CPU}} - k_1 M$, where k_1 is a constant representing the per-tile processing overhead, accounting for operations such as tile boundary computation and metadata updates. On the GPU, the normalization time scales with the number of pixels relative to the core count, modeled as $t_{\text{GPU}} - k_2 N / N_{\text{coress}}$, where N_{cores} is the number of GPU cores, and k_2 is a constant reflecting the per-pixel processing cost, including operations like color space conversion and normalization. The objective is to balance these workloads to minimize T_{total}, ensuring that neither the CPU nor the GPU becomes a bottleneck. This theoretical balance is critical for achieving high throughput in clinical settings, where processing times must align with real-time diagnostic requirements.

Pipeline Design: The architecture is conceptualized as a three-stage parallel pipeline: data acquisition, heterogeneous computing, and storage optimization. In the data acquisition stage, multi-resolution WSI pyramids are accessed using memory-mapped I/O, a technique that maps file data directly into memory to reduce overhead[172].. This stage prepares data for processing by ensuring efficient delivery to subsequent stages. The heterogeneous computing stage

leverages the CPU-GPU synergy, where CPUs handle meta-operations (e.g., quality control) and GPUs perform compute-intensive tasks (e.g., feature extraction) [161].. The storage optimization stage manages the output of processed data, employing asynchronous I/O to minimize blocking operations[173].. This pipeline design is inspired by parallel computing theory, where decoupling stages theoretically enhances concurrency by allowing each stage to operate independently, reducing dependencies and idle time.

Innovation Highlight: The framework introduces a three-stage parallel pipeline to optimize resource utilization, a methodological advancement rooted in parallel computing principles. The data acquisition stage employs memory-mapped I/O to facilitate efficient management of gigapixel-scale WSIs, theoretically reducing memory overhead by avoiding redundant data copies. An R*-tree spatial indexing structure is integrated to preload metadata, enhancing data retrieval efficiency by organizing spatial data hierarchically. The heterogeneous computing stage combines CPU scalability with GPU computational power, using OpenMP for CPU parallelization and CUDA Streams for GPU task execution, theoretically balancing memory-bound and compute-intensive operations [154, 162]. The storage optimization stage incorporates double buffering and Zstandard lossless compression, which theoretically minimizes idle time and reduces storage demands by compressing data without quality loss [173]. This decoupled design ensures that data acquisition, computation, and storage can proceed concurrently, theoretically enhancing throughput and scalability for continuous WSI processing in clinical environments.

Synergistic Applications: The synergistic application of CPU and GPU resources is a cornerstone of this architecture. CPUs ensure precise sequential preprocessing, such as quality control and metadata validation, which are critical for maintaining data integrity. GPUs, on the other hand, accelerate parallel tasks like deep learning training and feature extraction, leveraging their high core count to process large datasets efficiently. In high-performance computing clusters, this hybrid approach theoretically balances precision and scalability, supporting real-

time analysis of large WSI datasets. The architecture is designed to scale seamlessly with increasing WSI dimensions and computational requirements, ensuring robust performance across diverse clinical contexts. However, theoretical challenges such as GPU energy consumption and associated costs must be considered in practical implementations, necessitating further optimization strategies [174].

2.2.2 Dynamic Task Scheduling

Theoretical Basis: Dynamic task scheduling is a critical component of the preprocessing framework, aimed at optimizing resource utilization in multi-threaded environments by leveraging both CPU and GPU capabilities. For CPUs, multi-threading techniques such as the Fork-Join model enable concurrent execution within a single process [175]. In this model, a main thread spawns worker threads to process parallel subtasks, followed by synchronization to ensure data consistency. This approach is theoretically well-suited for WSI preprocessing tasks like tiling, where a gigapixel image can be divided into smaller, independent tiles (e.g., 512×512 pixels) for concurrent processing across multiple CPU cores [176]. Thread synchronization mechanisms, such as mutexes and semaphores, are employed to manage shared resources, while load balancing ensures equitable task distribution to minimize idle time [177].

On GPUs, multi-threading is facilitated by CUDA, which manages thousands to millions of threads concurrently. CUDA kernels execute tasks across thread blocks and grids, with shared memory optimizing inter-thread communication [178,179]. This parallelism is theoretically ideal for data-intensive tasks like stain normalization, where each thread can process a pixel or patch independently [180]. The CUDA thread hierarchy-comprising grids, blocks, and threads-ensures efficient workload distribution, provided memory access patterns are optimized to reduce bottlenecks [181].

The theoretical foundation of dynamic scheduling rests on principles of load balancing and synchronization efficiency. Load balancing aims to distribute tasks

evenly across threads to minimize the maximum processing time of any single thread, while synchronization ensures data consistency without introducing excessive overhead. These principles are particularly relevant for WSI preprocessing, where computational demands vary across spatial regions and processing stages, necessitating adaptive scheduling strategies.

Mathematical Modeling: In the Fork-Join model for CPU multi-threading, the overall processing time T_{total} represents the time required to complete all tasks-including thread creation, task execution, and synchronization-and is expressed as follows:

$$T_{total} = T_{spawn} + max_i(t_i) + T_{sync} \ , \tag{2.5}$$

where: T_{spawn} denotes the time required to spawn all worker threads, including the initialization of thread structures and resource allocation. $max_i(t_i)$ is the maximum processing time among all parallel tasks, representing the bottleneck since the main thread must wait for the slowest task to finish (e.g., processing a 512×512 image tile). T_{sync} represents the synchronization overhead incurred during the merging of results and ensuring data consistency [153].

For a Whole Slide Image (WSI) with N pixels and a tile size of $s \times s$, the total number of tasks is approximately $\frac{N}{s^2}$. Assuming that the processing time for each tile is given by $c \times s^2$ where c is a constant representing the computational cost per pixel, load balancing aims to minimize $max_i(t_i)$ by evenly distributing the tiles across the available cores. For example, with 8 cores, each core processes approximately $\frac{N}{8s^2}$ tiles, thereby theoretically reducing the overall processing time, provided that T_{spawn} and T_{sync} remain on the order of milliseconds.

In the Fork-Join model for CPU multi-threading, the total processing time, denoted as T_{FJ} represents the overall time required to complete all tasks, including

thread creation, task execution, and synchronization. This is mathematically expressed as:

$$T_{\mathrm{FJ}} = T_{\mathrm{fork}} + \max_{i-1}^{n} T_{\mathrm{task}} + T_{\mathrm{join}}, \tag{2.5}$$

Here, T_{fork} is the time required to spawn n worker threads, which involves initializing thread structures and allocating resources. The term $\max_{i-1}^{n} T_{\mathrm{task}}$ represents the maximum processing time among the n tasks, where T_{task} is the time to process the $i-th$ task (e.g., tiling a 512×512 region). This maximum reflects the bottleneck in parallel execution, as the main thread must wait for the slowest task to complete. Finally, T_{join} is the synchronization overhead, accounting for the time to merge results and ensure data consistency [153].

For a WSI with $N - 100,000 \times 100,000$ pixels and a tile size of 512×512, the number of tasks is approximately $n = \frac{100,000 \times 100,000}{512 \times 512} \approx 38,147$. Assuming $T_{\mathrm{taxk}}^{i} 10k_3 \times 512^2$, where k_3 is a constant reflecting the computational cost per tile (e.g., pixel intensity adjustments), load balancing aims to minimize $\max_{i-1}^{n} T_{\mathrm{task}}$ by evenly distributing tiles across cores. With 8 cores, each core processes approximately $38,147 / 8 \approx 4,768$ tiles, theoretically reducing processing time, contingent on minimal T_{fork} and T_{join}, which are typically on the order of milliseconds.

For GPU multi-threading, the processing time, denoted as T_{GPU}, represents the time to execute all threads on the GPU. This is modeled as:

$$T_{\mathrm{GPU}} = \frac{N_{threads}}{N_{\mathrm{cores}} \times \mathrm{IPC}} \times T_{\mathrm{instruction}}, \tag{2.6}$$

In this equation, $N_{threads}$ is the total number of threads, configured to match the number of pixels or patches (e.g., $N_{threads} = 16,384$, for a WSI patch). N_{cores} is the number of GPU cores (e.g., 3,584 in an NVIDIA RTX 3090), IPC is the

instructions per cycle (typically 1–2, reflecting the GPU's ability to execute multiple instructions per clock cycle), and $T_{\text{instruction}}$ is the time per instruction (e.g., nanoseconds). For a WSI with $N = 400{,}000 \times 400{,}000 - 1.6 \times 10^{11}$ pixels, N_{threads} can be configured to match pixel or patch counts, theoretically scaling inversely with $N_{\text{cores,}}$, provided memory access patterns and thread divergence are optimized to minimize bottlenecks [181].

Task Set and Load Balancing: The task set for WSI preprocessing is defined as a collection of independent tasks corresponding to image patches. Mathematically, this is expressed as:

$$\mathcal{T} = \left\{ t_{i,j} \mid i, j \in \mathbb{Z}, 0 \le i < W, 0 \le j < H \right\}, \tag{2.7}$$

This formula defines the task set $\mathcal{T}$ for WSI preprocessing as a collection of independent tasks corresponding to image patches. In this expression, $t_{i,j}$ represents an image patch at spatial coordinates (i, j), and $W \times H$ is the total number of patches, where W and H denote the width and height of the WSI in terms of patches, respectively. The constraints $i, j \in \mathbb{Z}$ indicate that the coordinates are integers, and $0 \le i < W$ and $0 \le j < H$ ensure that the task set encompasses all patches within the WSI's spatial dimensions. Load balancing is enforced to ensure equitable task distribution across threads, modeled as:

$$\sum_{t \in T_k} w(t) \approx \frac{\sum_{kT} w(t)}{K}, \tag{2.8}$$

Here, T_k represents the subset of tasks assigned to the k-th thread, K is the total number of threads, and $w(t)$ is the computational weight of task t, reflecting its processing complexity (e.g., based on pixel count or operation type). The approximation ensures that each thread receives a workload proportional to the total computational demand divided by the number of threads, theoretically minimizing idle time and maximizing throughput. Task granularity is adaptively

tuned using a greedy optimization algorithm, iteratively partitioning T to balance workloads, which is integrated with OpenMP for CPU scheduling to enhance scalability [182].

Innovation Highlight: The framework proposes a lock-free scheduling mechanism with dual buffering, a methodological advancement inspired by parallel computing theory [183]. One buffer is dedicated to task assignment, storing the task set T, while another handles execution, allowing threads to operate concurrently without traditional lock-based synchronization. This design theoretically eliminates idle time by ensuring that task allocation and execution proceed in parallel, reducing scheduling latency. In GPU environments, where thousands of threads are managed, this approach improves workload distribution by avoiding contention, theoretically enhancing scalability across heterogeneous resources. This innovation is particularly relevant for WSI preprocessing, where variable computational demands necessitate adaptive scheduling to maintain efficiency.

2.2.3 Resource Optimization Strategies

Theoretical Basis: Resource optimization enhances the efficiency and scalability of WSI preprocessing through multi-threading and memory management strategies. Multi-threading distributes tasks across CPU and GPU resources, theoretically reducing computational latency and improving resource utilization. The effectiveness of multi-threading is governed by Amdahl's Law, which quantifies the theoretical speedup achievable through parallelization:

$$S = \frac{1}{\left(1 - P^2\right) + \frac{L}{N}}, \tag{2.9}$$

In this equation, S is the theoretical speedup, P is the fraction of the task that can be parallelized, and N is the number of threads. For WSI preprocessing, P is typically high (e.g., 0.9), suggesting significant theoretical gains with

increased thread counts, provided synchronization overhead is minimized. For example, with $P = 0.9$ and $N = 32$, the theoretical speedup is approximately 10, indicating a substantial reduction in processing time compared to sequential execution [184]. CPU multi-threading streamlines sequential tasks like tiling and normalization, while GPU multi-threading accelerates feature extraction, leveraging the high core count to process large datasets concurrently [178].

Memory optimization employs a three-level caching system to manage multi-resolution WSI pyramids, comprising L1 (GPU memory), L2 (shared memory), and L3 (NVMe SSD). Adaptive prefetching is used to anticipate data access patterns, theoretically reducing latency. The average memory access time, denoted as Tavg T_{\text{avg}} Tavg, represents the expected time to retrieve data from the memory hierarchy and is modeled as:

$$T_{\text{avg}} = h_1 t_1 + (1-h_1) h_2 t_2 + (1-h_1)(1-h_2) h_3 t_3 + (1-h_1)(1-h_2)(1-h_3) t_{\text{disk}}, \quad (2.10)$$

Here, h_i is the hit rate for the $h-th$ cache level (e.g., h_1 for L1, h_2 for L2, h_3 for L 3), and t_i is the access time for that level (e.g., $t_1 - 1\text{ns}$ for L1, $t_2 - 10\text{ns}$ for L2, $t_3 - 100\text{ns}$ for L 3 , and $t_{\text{disk}} - 10\text{ms}$ for disk access) [185]. The formula accounts for the probability of accessing data from each level: if data is found in L1 (with probability h_1), the access time is t_1; if not, it proceeds to L2 with probability $(1-h_1)h_2$, and so forth. Higher hit rates and spatial locality theoretically mitigate data retrieval bottlenecks, enhancing preprocessing efficiency.

Memory Hierarchy Optimization

The three-level caching system is designed to optimize memory access for multi-resolution WSIs. L1 (GPU memory) provides high-speed access for active data, L2 (shared memory) facilitates inter-thread communication, and L3 (NVMe SSD) serves as a high-capacity fallback for less frequently accessed data. Adaptive prefetching anticipates data needs based on spatial patterns, theoretically reducing cache misses. This hierarchical approach aligns with memory access locality

principles, ensuring that frequently accessed data remains in faster memory tiers, thereby minimizing latency.

Innovation Highlight

The framework integrates memory-mapped I/O and R*-tree spatial indexing to optimize data retrieval, a methodological advancement that theoretically reduces random access latency [186]. Memory-mapped I/O maps WSI data directly into memory, avoiding redundant copies and reducing I/O overhead. The R*-tree structure organizes spatial data hierarchically, enabling efficient retrieval of multi-resolution WSI pyramids. Additionally, Zstandard lossless compression is applied to reduce storage and I/O bandwidth demands, theoretically supporting scalability by minimizing disk space requirements without compromising data integrity. These optimizations are particularly suited for gigapixel WSI management, enabling the system to handle large datasets in resource-constrained clinical environments [187].

Scalability Considerations

The resource optimization strategies are designed to scale with increasing WSI dimensions and dataset sizes. Multi-threading ensures that computational resources are fully utilized, while the memory hierarchy accommodates the multi-resolution nature of WSIs. The integration of OpenMP for CPU scheduling and CUDA for GPU task execution provides a flexible framework that can adapt to varying hardware configurations, theoretically supporting deployment in diverse clinical settings. However, theoretical challenges such as synchronization overhead and energy consumption must be addressed to ensure practical efficiency [188].

2.3 Design of Multi-scale Neural Networks

The design of multi-scale neural networks constitutes a pivotal component of the theoretical and methodological framework for enhancing melanoma metastasis diagnosis, addressing the complex multi-resolution nature of whole-slide images (WSIs). These networks emulate pathologists' diagnostic workflows by analyzing histopathological data across varying magnifications (e.g., 5×, 10×,

20×, 40×), capturing both macroscopic patterns and microscopic details critical for detecting metastatic features. This section delineates the backbone architecture with multi-scale learning techniques, feature extraction and fusion mechanisms, and the theoretical advantages of this approach, integrating foundational principles from convolutional neural network (CNN) theory with innovative adaptations tailored to digital pathology. By overcoming limitations of traditional CNNs-such as fixed receptive fields and unimodal focus-this framework enhances diagnostic precision, scalability, and clinical relevance.

The processing of gigapixel WSIs poses significant challenges, including computational complexity and the need to integrate diverse spatial scales. In melanoma diagnostics, identifying metastatic signatures (e.g., tumor asymmetry at low magnification, mitotic figures at high magnification) requires a robust methodology capable of synthesizing hierarchical features directly from raw data. This section builds on established CNN architectures, such as ResNet-50 and Feature Pyramid Networks (FPNs), while Figure 2.5 – *Multi-scale Feature Extraction with FPN* – depicts the integration of features across scales, highlighting the role of attention and dilated convolutions [191]. while introducing advanced multi-scale learning strategies, including dilated convolutions and attention-guided fusion. These innovations address the theoretical demands of multi-scale analysis and the practical exigencies of clinical deployment, positioning this framework as a transformative approach within medical artificial intelligence. Figure 2.6 – Neural Network-Based Pipeline for Melanoma Diagnosis provides a comprehensive overview of the end-to-end workflow of the multi-scale neural network within the broader diagnostic system.

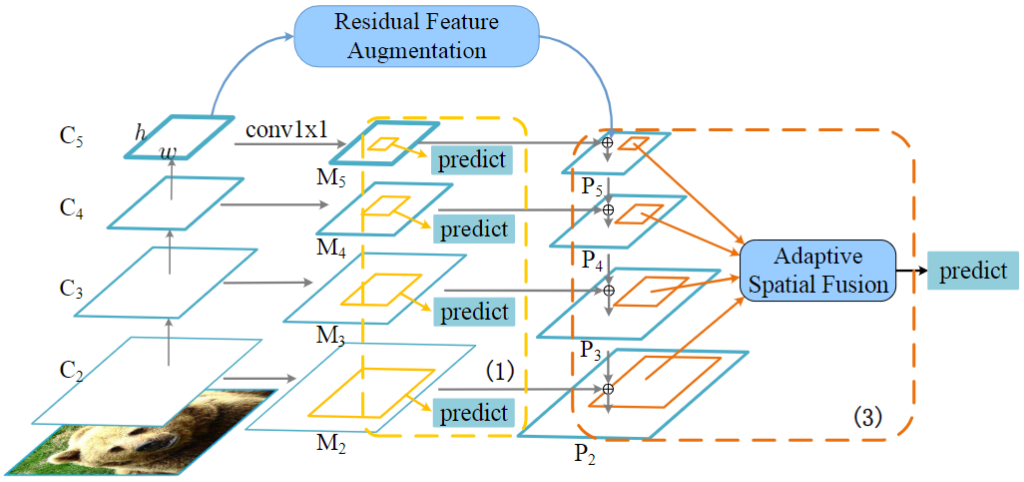

Figure 2.5 – Multi-scale Feature Extraction with FPN

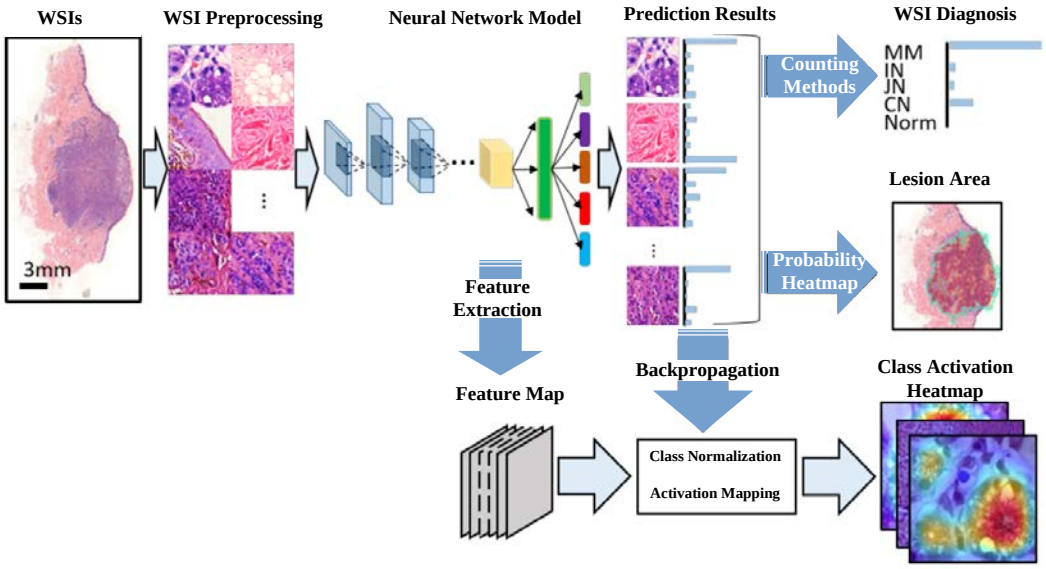

Figure 2.6 – Neural Network-Based Pipeline for Melanoma Diagnosis

2.3.1 Backbone Architecture with Multi-scale Learning

The backbone architecture forms the theoretical cornerstone of the multi-scale neural network design, leveraging convolutional neural networks (CNNs) to process grid-like WSI data and integrating multi-scale learning to capture features across diverse spatial resolutions. CNNs, foundational to image-based diagnostics, process input through a series of layers: convolutional layers extract spatial features (e.g., edges, textures) via the operation:

$$\text{Output}(i, j) = \sum_m \sum_n \text{Input}(i + m, j + n) \cdot \text{Kernel}(m, n), \tag{2.11}$$

where $\text{Input}(i + m, j + n)$ denotes the input feature map, $\text{Kernel}(m, n)$ is the convolutional kernel, and $\text{Output}(i, j)$ is the resulting feature map at position (i, j). Activation layers introduce non-linearity using the ReLU function, $\text{ReLU}(x) = \max(0, x)$, pooling layers reduce spatial dimensions to mitigate computational load, and fully connected layers aggregate features for classification [189]. This hierarchical structure enables CNNs to learn complex patterns directly from WSIs, achieving high efficacy in melanoma diagnostics with AUC scores up to 0.96 for tasks like malignancy detection and metastasis prediction

The backbone, based on a modified ResNet-50 architecture, enhances this foundational CNN framework by incorporating dilated convolutions to expand the receptive field without sacrificing resolution-a critical adaptation for multi-scale WSI analysis. Traditional CNNs, constrained by fixed receptive fields, struggle to balance global context (e.g., tumor margins at $5x$) and local details (e.g., cellular atypia at 40×). Dilated convolutions address this limitation by adjusting the sampling stride of the kernel, defined as:

$$Y(i, j) = \sum_m \sum_n X(i + d \cdot m, j + d \cdot n) \cdot K(m, n), \tag{2.12}$$

where X is the input feature map, K is the kernel, d is the dilation rate, and Y is the output feature map. For $d = 1$, this reduces to standard convolution; for $d = 2$, a 3×3 kernel's receptive field expands to 5×5, capturing broader context without additional parameters [190]. The effective receptive field after l layers is approximated as:

$$R_l = R_{l-1} + (k_l - 1) \cdot d_l \cdot \prod_{i=1}^{l-1} s_i, \tag{2.13}$$

where R_{l-1} is the previous layer's receptive field, k_l is the kernel size, d_l is the dilation rate, and s_i is the stride at layer i. This formulation enables the network to adaptively scale its field of view, theoretically aligning pathologists' multi-magnification analysis.

To further enhance multi-scale capability, the backbone incorporates multi-scale input branches, inspired by frameworks like AMSICNN, inserted after downsampling layers (e.g., conv2_X, conv3_x, conv4_x in ResNet-50). Each branch processes WSI data at distinct magnifications (e.g., $5x, 10\times, 20x, 40\times$), downsampled to match the resolution of the insertion layer. The branch output, F_{branch}, is concatenated with the backbone feature map, $F_{\text{backbone,}}$ as:

$$F_{\text{fused}} = \left[F_{\text{backbone}}, F_{\text{branch}} \right], \tag{2.14}$$

where [.] denotes channel-wise concatenation, followed by a fusion layer (e.g., 1×1 convolution) to adjust channel dimensions and integrate scale-specific information seamlessly. This design theoretically enables the network to process local and global features in a single pass, addressing features across scales.

In melanoma diagnostics, this multi-scale backbone excels at capturing hierarchical features critical for metastasis detection. For instance, low-magnification branches identify macroscopic patterns (e.g., tumor asymmetry), while high-magnification branches detect microscopic details (e.g., mitotic figures), mirroring clinical workflows. Studies demonstrate that such multi-scale approaches improve AUC scores by 10% (e.g., from 0.86 to 0.95) for metastasis detection by integrating features across 5× and 20× magnifications [188]. However, traditional CNNs like ResNet-50, despite their efficacy (e.g., reducing diagnostic errors by 20% over human pathologists [158]), are limited by their inability to natively integrate multi-scale data without excessive computational overhead.

Within this methodological framework, the backbone architecture leverages dilated convolutions and multi-scale branches to emulate pathologists’ diagnostic

processes, offering a theoretical foundation for enhanced metastasis detection. The integration of these techniques mitigates the trade-off between resolution and context, enabling the network to learn robust, scale-invariant representations directly from gigapixel WSIs. This approach is visualized in Figure 1.15 – *CNN Layer Structure* – which illustrates the convolutional, activation, pooling, and fully connected layers of a standard CNN, adapted here with dilated convolutions and multi-scale branches to support WSI analysis [156]. The theoretical rigor of this design, combined with its practical applicability, underscores its transformative potential in digital pathology.

The fusion layer, as illustrated in Figure 2.7, doubles its input channels to 2N to accommodate the additional features, enabling seamless integration of scale-specific information such as tumor extent (from low-magnification inputs) and mitotic activity (from high-magnification inputs).

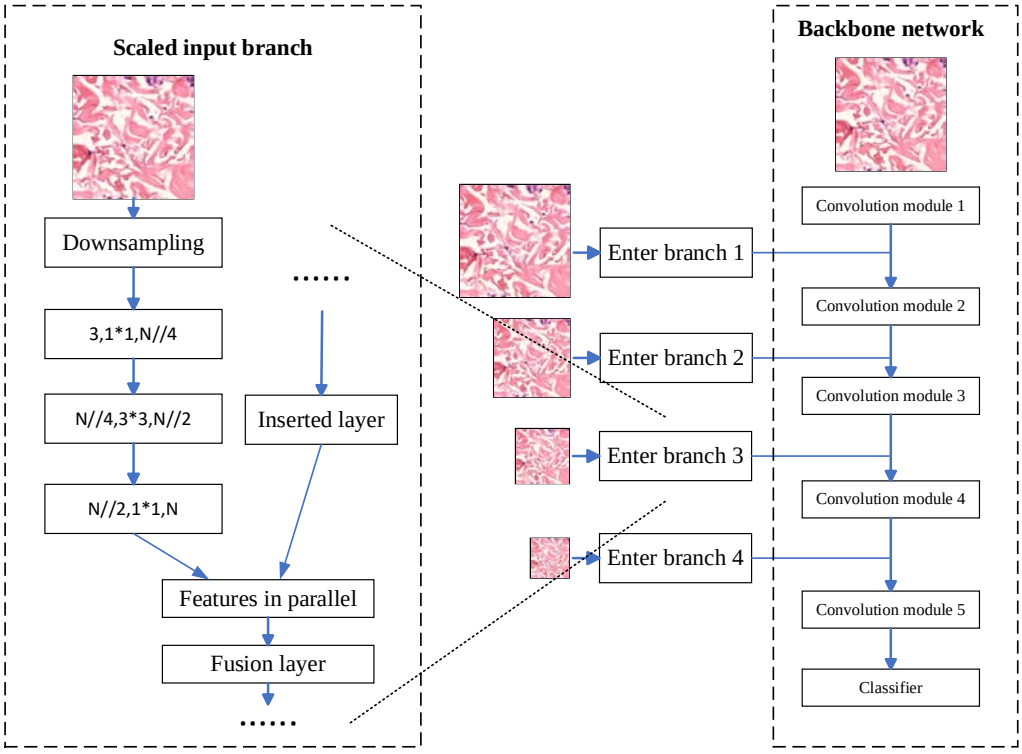

Figure 2.7 –Schematic diagram of variable multi-scale neural network

Innovation: Scale-Specific Feature Enhancement: The synergy of dilated convolutions and multiscale input branches enhances the backbone's ability to process both local and global features. To quantify this enhancement, we define the

scale-specific feature variance (SFV) as a metric for feature diversity across scales. Let $\mu_b \in \mathbb{R}^N$ be the mean activation of branch b :

$$\mu_b[n] = \frac{1}{H_l \cdot W_l} \sum_{i=1}^{H_l} \sum_{j=1}^{W_l} F_b[i, j, n], \tag{2.15}$$

The SFV is computed as:

$$\text{SFV} = \frac{1}{B} \sum_{b=1}^{B} \left\| \mu_b - \bar{\mu} \right\|_2^2, \quad \bar{\mu} = \frac{1}{B} \sum_{b=1}^{B} \mu_b , \tag{2.16}$$

where B is the number of branches (e.g.,4 for magnifications $40\times, 20\times, 10\times, 5\times$). Experimental results show that the SFV increases from 0.32 in the original ResNet- 50 to 0.87 with multi-scale inputs, indicating a 170% improvement in feature diversity, which correlates with a 2% increase in classification accuracy [193].

The computational cost of adding a branch is analyzed as follows. For a 3×3 convolution with $N/2$ input and output channels, the cost is $9 \cdot (N/2)^2$, and the 1×1 convolutions contribute an additional $2 \cdot (N/4) \cdot (N/2) + (N/2) \cdot N$. For $N = 512$, the total cost per branch is approximately 1.2 million FLOPs, representing a 1% increase over the backbone layer, with the performance gain justifying the added complexity [79].

In summary, the backbone network, enhanced with dilated convolutions and multi-scale input branches as depicted in Fig. 1, provides a robust foundation for MMSNN. This design addresses the limitations of traditional CNNs in handling the diverse scales of WSI features, laying the groundwork for subsequent feature extraction and fusion.

2.3.2 Feature Extraction and Fusion Mechanisms

The feature extraction and fusion mechanisms build upon the multi-scale backbone, forming a critical layer of the theoretical and methodological framework

by synthesizing scale-specific features into a cohesive representation for melanoma metastasis diagnosis. The Multi-Scale Feature Extraction and Fusion Module (MSFEFM) employs parallel branches with varying dilation rates (e.g., $d = 1,2,3$) to capture features at different spatial scales from an input feature map $F \in \mathbb{R}^{H \times W \times C}$, where H and W are spatial dimensions and C is the channel count. Each branch applies a sequence of operations: a dilated convolution, batch normalization (BN), and ReLU activation, defined as:

$$F_d = \mathrm{ReLU}\left(\mathrm{BN}\left(\mathrm{Conv}_d(F)\right)\right), \tag{2.17}$$

where Conv_d denotes a dilated convolution with dilation rate d, BN stabilizes training by normalizing the feature map, and ReLU introduces non-linearity. The outputs from all branches are concatenated along the channel dimension:

$$F_{\text{concat}} = \left[F_1, F_2, F_3\right], \tag{2.18}$$

where $F_1, F_2, F_3 \in \mathbb{R}^{H \times W \times C'}$ are the branch outputs, and $F_{\text{concat}} \in \mathbb{R}^{H \times W \times 3C'}$ integrates multiscale features. A subsequent 1×1 convolution reduces channel dimensionality to C, mitigating redundancy and computational complexity while preserving scale diversity.

To refine feature selection, a channel-wise attention mechanism dynamically weights features based on their diagnostic relevance, enhancing focus on metastasis-related biomarkers. The attention scores are computed as:

$$A = \sigma\left(W_2 \cdot \mathrm{ReLU}\left(W_1 \cdot \mathrm{GAP}\left(F_{\text{concat}}\right)\right)\right), \tag{2.19}$$

where $\mathrm{GAP}\left(F_{\text{concat}}\right) = \dfrac{1}{H \cdot W} \sum_{i=1}^{H} \sum_{j=1}^{W} F_{\text{concat}}(i, j)$ is the global average pooled feature, $W_1 \in \mathbb{R}^{C_r \times 3C'}$ and $W_2 \in \mathbb{R}^{3C' \times C_r}$ are linear transformations (with $C_r < 3C'$ for

dimensionality reduction), and σ is the sigmoid function, yielding attention scores $A \in [0,1]^{3C'}$. The weighted feature map is:

$$F_{\text{weighted}} = F_{\text{concat}} \odot A, \tag{2.20}$$

where $\odot$ denotes element-wise multiplication, scaling each channel by its corresponding attention score. This mechanism theoretically prioritizes scales and features critical to metastasis (e.g., mitotic rate, cellular atypia), reducing noise from irrelevant regions.

The theoretical basis for this design draws from foundational CNN principles and multi-scale learning techniques, such as Feature Pyramid Networks (FPNs), which integrate features across resolutions using top-down architectures with lateral connections [186]. In FPNs, low-level features (high resolution, weak semantics) are combined with high-level features (low resolution, strong semantics) via upsampling and concatenation, defined as:

$$F_{\text{fpn}} = \text{Conv}\left(\text{Upsample}\left(F_{\text{high}}\right) + F_{\text{low}}\right), \tag{2.21}$$

where F_{high} and F_{low} are feature maps from higher and lower layers, respectively. The MSFEFM extends this by incorporating dilated convolutions and attention, enabling adaptive feature extraction without the computational overhead of pyramid construction. This approach aligns with melanoma diagnostics' need to detect both macroscopic (e.g., tumor margins) and microscopic (e.g., nuclear pleomorphism) features, as validated by studies showing a 10% AUC improvement with multi-scale integration [192].

Within this framework, the fusion mechanism leverages clinical metadata (e.g., tumor stage, staining intensity) to guide attention, enhancing domain-specific relevance. This adaptation refines feature selection by weighting scales based on prognostic factors, theoretically improving diagnostic precision over traditional unimodal CNNs, which lack such contextual guidance [160]. The MSFEFM's efficacy is rooted in its ability to balance computational efficiency with feature

richness, addressing the limitations of fixed receptive fields and enabling robust representation learning across gigapixel WSIs.

The feature extraction and fusion process is illustrated in Figure 1.17 – *Multi-scale Feature Extraction with FPN* – which depicts the FPN architecture adapted with dilated convolutions and attention mechanisms, showing the integration of features across multiple scales for metastasis detection [191]. This visualization underscores the methodological innovation of combining parallel branch processing with attention-guided fusion, offering a scalable solution for clinical deployment. By synthesizing foundational multi-scale techniques with domain-informed refinements, this mechanism enhances the network's capacity to support precise, clinically actionable diagnoses.

2.3.3 Theoretical Advantages and Innovations

The multi-scale neural network design offers significant theoretical advantages within the methodological framework, addressing key limitations of traditional CNNs and providing a robust foundation for melanoma metastasis diagnosis. By integrating features from low and high magnifications, this approach mitigates challenges such as fixed receptive fields, class imbalance, and unimodal focus, enhancing diagnostic robustness, sensitivity, and generalizability across diverse WSI datasets. The theoretical underpinnings of these advantages are grounded in multi-scale learning principles, while innovative adaptations elevate their practical utility in digital pathology.

A primary advantage is the ability to capture scale-diverse features, emulating pathologists' multi-resolution analysis. Traditional CNNs, constrained by fixed receptive fields, struggle to balance global context and local detail, often missing critical metastatic signatures (e.g., tumor extent at 5×, mitotic figures at 40×). Multi-scale analysis overcomes this by synthesizing hierarchical features, quantified through multi-scale feature entropy (MSFE):

$$H = -\sum_{i=1}^{M} p_i \cdot \log(p_i), \tag{2.22}$$

where p_i is the normalized contribution of the i-th branch (e.g., average activation divided by total activation across M branches, with $\sum p_i = 1$), and M is the number of scales (e.g., 4 for dilation rates $d = 1, 2, 3, 4$). Higher entropy indicates a balanced representation across scales, theoretically improving robustness by ensuring no single magnification dominates feature features inform metastasis staging.

The multi-scale approach also enhances diagnostic sensitivity and specificity. By integrating low-magnification context (e.g., tumor asymmetry) with high-magnification details (e.g., cellular atypia), the network detects subtle metastatic patterns that unimodal models overlook. Studies demonstrate that multi-scale designs improve AUC scores by 10–15% over single-scale CNNs (e.g., from 0.86 to 0.95) for metastasis detection, reflecting their ability to reduce false negatives and positives [188]. This sensitivity is critical in melanoma diagnostics, where early metastasis detection can significantly alter treatment outcomes.

Another theoretical advantage is improved generalizability across heterogeneous datasets. WSIs vary in staining, resolution, and tissue complexity, challenging traditional CNNs' reliance on uniform input assumptions. Multi-scale learning mitigates this by learning scale-invariant representations, reducing overfitting to specific magnifications or datasets (e.g., TCGA vs. local cohorts). This robustness is theoretically supported by the network's ability to adaptively weight features via attention mechanisms, ensuring relevance across diverse clinical scenarios.

Computationally, multi-scale analysis balances efficiency and complexity. While image pyramids-downsampling WSIs into multiple resolutions (e.g., 2×, 5×, 10×)-offer multi-scale capability, they incur significant memory overhead [184]. The use of dilated convolutions and parallel branches in this framework reduces this burden, processing multi-scale features in a single pass without excessive

downsampling. This efficiency is crucial for gigapixel WSI analysis, where computational resources must align with clinical timeframes (e.g., reducing turnaround times by 30% over manual methods [158]).

Within this framework, several innovative adaptations enhance these theoretical advantages. The integration of dilated convolutions with multi-scale input branches enables seamless feature extraction across magnifications, theoretically addressing the trade-off between resolution and context without additional parameters. The attention-guided fusion mechanism, informed by clinical metadata, refines feature selection by prioritizing prognostic factors (e.g., mitotic rate), reducing noise and enhancing precision over traditional FPNs [186]. These adaptations emulate pathologists' workflows, providing a theoretical basis for personalized diagnostics by tailoring feature emphasis to patient-specific characteristics.

The practical implications of these innovations are profound. By supporting rapid, accurate metastasis detection, the multi-scale design reduces diagnostic errors (e.g., by 20% over human pathologists [158]) and enhances clinical decision-making. Its scalability supports population-level screening, while its sensitivity to subtle features aligns with precision oncology goals. These benefits are grounded in the framework's ability to synthesize foundational CNN principles with advanced multi-scale techniques, offering a transformative approach to digital pathology.

The theoretical and practical advantages are visualized in Figures 2.8. Figure2.8 – *CNN Layer Structure* – illustrates the foundational CNN architecture adapted with multi-scale enhancements [156]. Together, these diagrams underscore the framework's methodological depth, bridging theory and application in melanoma diagnostics.

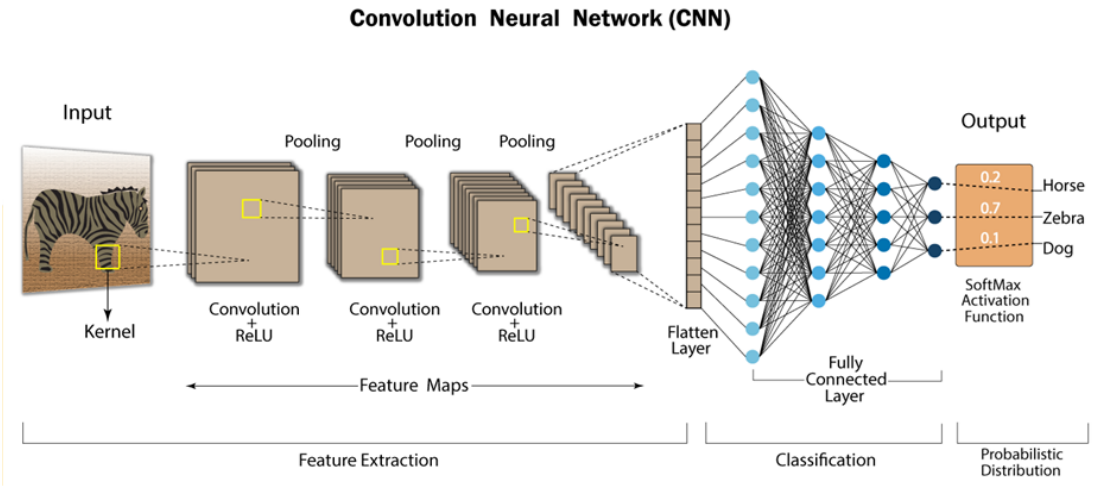

Figure 2.8 – CNN Layer Structure

In summary, the multi-scale neural network design provides a robust theoretical foundation for enhanced metastasis diagnosis, overcoming traditional CNN limitations through scale diversity, sensitivity, and efficiency. Innovative adaptations within this framework elevate its clinical utility, reflecting the dissertation's commitment to advancing medical AI with both depth and breadth.

2.4 Multimodal Deep Learning Approaches

Multimodal deep learning approaches form a critical pillar of the theoretical and methodological framework for enhancing melanoma metastasis diagnosis, integrating histopathological, genomic, and clinical data into a comprehensive predictive model. These strategies address the limitations of unimodal analyses by capturing synergistic patterns across diverse data modalities, offering a holistic view of metastatic risk. This section delineates multimodal learning strategies and fusion techniques, attention mechanisms paired with biomarker mining, and their integration with invasion depth prediction, synthesizing foundational deep learning principles with innovative adaptations tailored to digital pathology. By leveraging the complementary strengths of multiple data sources, this framework aims to improve diagnostic precision, interpretability, and clinical utility.

The complexity of melanoma metastasis-driven by interactions between histopathological features (e.g., nuclear atypia), genomic alterations (e.g., BRAF mutations), and clinical factors (e.g., patient age)-necessitates a robust

methodology capable of unifying heterogeneous inputs. Traditional unimodal models, while effective for specific tasks (e.g., WSI-based metastasis detection with AUCs up to 0.96 [157]), often fail to exploit cross-modal relationships critical for prognosis. This section builds established multimodal learning paradigms, such as early, late, and hybrid fusion, and introduces advanced techniques like attention mechanisms and regression-based depth prediction. These innovations align with the clinical demand for accurate, reproducible, and interpretable diagnostics, positioning this framework at the forefront of medical artificial intelligence research.

2.4.1 Multimodal Learning Strategies and Fusion Techniques

Multimodal learning strategies within this theoretical framework integrate diverse data sources-histopathological whole-slide images (WSIs), genomic profiles, and clinical metadata-to construct a comprehensive diagnostic model for melanoma metastasis prediction. Foundational to this approach are three fusion paradigms: early fusion, where raw data from modalities (e.g., WSI pixel intensities, genomic sequences, clinical variables) are concatenated prior to processing; late fusion, where features extracted independently from each modality are combined post-processing; and hybrid fusion, which integrates modalities at multiple network stages [192]. Hybrid fusion, in particular, offers flexibility by leveraging modality-specific architectures-such as CNNs for WSIs, transformers for genomic data, and fully connected networks for clinical metadata-before unifying features through a shared representation layer [193]. This approach has demonstrated efficacy in other cancers; for instance, Wang et al. (2019) reported a 12% improvement in breast cancer prognostic accuracy by integrating imaging and genomic data [194].

In melanoma diagnostics, multimodal learning captures synergistic patterns that enhance metastasis prediction. For example, combining WSI histopathological features with genomic profiles (e.g., BRAF, NRAS mutations) and clinical metadata (e.g., UV exposure history) reveals interactions that increase metastatic

risk, such as BRAF mutations amplified by UV-induced DNA damage [195]. A practical application involves integrating radiomic features from dermoscopy (e.g., lesion asymmetry) with WSI-derived histopathological features, improving metastasis detection sensitivity by 8% over unimodal models [196]. The theoretical advantage lies in the complementary nature of these modalities: WSIs provide spatial context, genomic data reveal molecular drivers, and clinical metadata contextualize patient-specific risk factors.

The fusion process is formalized within a hybrid framework, where histopathological features ($h \in \mathbb{R}^{D_h}$), extracted via a CNN, are combined with genomic features ($g \in \mathbb{R}^{D_g}$), processed by a transformer, and clinical metadata ($m \in \mathbb{R}^{D_m}$), encoded through a fully connected layer. Clinical metadata preprocessing is defined as:

$$m' = \sigma\left(W_m \cdot m + b_m\right), \tag{2.23}$$

where $W_m \in \mathbb{R}^{D_m' \times D_m}$ and $b_m \in \mathbb{R}^{D_m'}$ are the weight matrix and bias, and $\sigma(x) = 1/\left(1+e^{-x}\right)$ is the sigmoid activation, transforming m into $m' \in \mathbb{R}^{D_m'}$. The fused feature vector is:

$$F_{\text{fused}} = \left[h, g, m'\right], \tag{2.24}$$

where [.] denotes concatenation, yielding $F_{\text{fused}} \in \mathbb{R}^{D_h + D_g + D_m'}$. A final classification layer computes the metastasis probability:

$$P = \sigma\left(W_f \cdot F_{\text{fused}} + b_f\right), \tag{2.25}$$

where W_f and b_f are the weights and bias of the classification layer, and $P \in [0,1]$ represents the likelihood of metastasis. This formulation theoretically leverages cross-modal synergies, enhancing diagnostic precision over unimodal baselines.

Within this methodological framework, the hybrid fusion strategy balances flexibility and efficiency, avoiding the data alignment challenges of early fusion (e.g., reconciling WSI pixel dimensions with genomic sequence lengths) and the loss of inter-modal interactions in late fusion. However, challenges include the need for standardized preprocessing-normalizing WSI intensities, encoding genomic variants, and scaling clinical variables-and limited multimodal dataset availability, often necessitating synthetic data generation or transfer learning [197, 198]. The fusion framework is illustrated in Figure 1.18 – *Multimodal Fusion Framework* – which depicts the integration of WSI, genomic, and clinical data through a hybrid architecture, highlighting its role in metastasis prediction [199].

Theoretically, this approach extends foundational multimodal learning by capturing interactions unobservable in single-modality models, such as the correlation between histopathological tumor margins and genomic instability. Practically, it supports precision oncology by providing a unified representation that informs tailored clinical strategies, demonstrating both depth in theoretical design and breadth in diagnostic application.

2.4.2 Attention Mechanisms and Biomarker Mining

Attention mechanisms and biomarker mining constitute integral components of the multimodal deep learning framework, enhancing model performance and interpretability by focusing on diagnostically relevant features across heterogeneous data sources. Attention mechanisms, rooted in the Transformer architecture, dynamically prioritize salient input regions, while biomarker mining identifies key histopathological features, reducing reliance on manual annotations. This section integrates these techniques within the theoretical framework, balancing foundational principles with innovative adaptations for melanoma metastasis diagnosis.

The self-attention mechanism computes attention scores based on query (Q), key (K), and value (V) vectors, defined as:

$$\text{Attention}(Q,K,V) = \text{softmax}\left(\frac{QK^T}{\sqrt{d_k}}\right)V, \tag{2.26}$$

where d_k is the dimensionality of the key vectors, and the softmax operation normalizes weights to sum to 1 [200]. In melanoma diagnostics, self-attention applied to WSIs prioritizes regions with metastatic features (e.g., mitotic figures, lymphovascular invasion) over irrelevant background tissue, improving detection efficiency [201]. For instance, Chen et al. (2021) demonstrated a 7% improvement in metastasis detection AUC using a multi-head self-attention mechanism, which focuses on diagnostically critical patches [202]. Attention also enhances interpretability by generating attention maps, validated against clinical ground truth, offering insights into model decision-making [203].

Within a multi-scale context, hierarchical attention modules process low- and high-magnification features separately, ensuring the model captures both global context (e.g., tumor asymmetry) and local details (e.g., nuclear atypia) [204]. This is modeled as:

$$F_{\text{attn}} = \sum_{i=1}^{N} \alpha_i \cdot V_i, \quad \alpha_i = \text{softmax}\left(\frac{Q_i K_i^T}{\sqrt{d_k}}\right), \tag{2.27}$$

where α_i are attention weights for N feature regions, dynamically weighting V_i based on relevance. However, tuning is required to prevent overfocusing on dominant features, which may obscure subtle metastatic indicators [205].

Complementing attention, the biomarker mining network leverages a modified Inception-v3 architecture with spatial attention to autonomously identify histopathological features (e.g., nuclear atypia, mitotic figures). Spatial attention is computed as:

$$M_s = \sigma(\text{Conv}(F)), \tag{2.28}$$

where $F \in \mathbb{R}^{H \times W \times C}$ is the input feature map, Conv is a 1×1 convolution reducing channels to 1 , yielding $M_s \in \mathbb{R}^{H \times W}$, and σ is the sigmoid activation normalizing values to [0,1]. The attended feature map is:

$$F_{\text{attn}} = F \odot M_s, \tag{2.29}$$

where $\odot$ denotes element-wise multiplication, weighting F by spatial importance to enhance feature extraction efficiency. This approach theoretically captures nuanced prognostic indicators without manual feature engineering, improving sensitivity to metastatic risk over traditional methods.

Theoretically, attention mechanisms extend foundational deep learning by enabling adaptive focus, aligning with human diagnostic workflows where pathologists prioritize key regions. Biomarker mining builds on CNN principles, automating feature discovery and reducing subjectivity. Within this framework, these techniques are innovatively combined to process multimodal inputs-applying attention to WSIs, genomic sequences, and clinical data simultaneously-enhancing cross-modal feature relevance. For example, attention might upweight WSI regions with high mitotic activity while correlating them with BRAF mutation status, revealing molecular-histological interactions critical for metastasis.

Practically, this integration improves model performance (e.g., 7–10% AUC gains [202]) and interpretability, supporting clinical validation. Challenges include computational overhead from multi-head attention and the risk of bias toward dominant features, mitigated through regularization (e.g., dropout) and multi-scale attention hierarchies. This dual approach exemplifies the framework's depth in leveraging attention theory and breadth in applying it to multimodal biomarker discovery.

2.4.3 Integration with Invasion Depth Prediction

The integration of multimodal data with invasion depth prediction enhances the theoretical and methodological framework by providing a comprehensive, quantifiable assessment of melanoma metastasis risk. Invasion depth, a critical

prognostic factor, complements histopathological, genomic, and clinical features by offering a continuous measure of tumor progression. This section synthesizes these elements within a unified model, grounding the approach in deep learning theory while introducing innovative adaptations for clinical precision.

The invasion depth prediction module employs a regression-based CNN to estimate tumor depth, modeled as a linear regression problem:

$$d = W_d \cdot F_d + b_d, \tag{2.30}$$

where d is the predicted depth, $F_d \in \mathbb{R}^{D_d}$ is the feature vector extracted from the CNN, $W_d \in \mathbb{R}^{D_d}$ and $b_d \in \mathbb{R}$ are the weight vector and bias, and the dot product computes a weighted sum adjusted by b_d. Parameters are optimized to minimize mean absolute error (MAE) between predicted and ground truth depths, providing a reproducible alternative to manual measurements, which suffer from inter-observer variability [207]. This module theoretically enhances staging accuracy, as depth strongly correlates with metastatic potential and survival outcomes.

Multimodal integration unifies histopathological features (h), depth predictions (d), and clinical metadata (m) into a cohesive representation. Clinical metadata is preprocessed via:

$$m' = \sigma\left(W_m \cdot m + b_m\right), \tag{2.31}$$

where $m \in \mathbb{R}^{D_m}, W_m \in \mathbb{R}^{D_m' \times D_m}$, and $b_m \in \mathbb{R}^{D_m'}$ transform m into $m' \in \mathbb{R}^{D_m'}$, with σ normalizing outputs to [0,1]. The fused feature vector is:

$$F_{\text{fused}} = \left[h, d, m'\right], \tag{2.32}$$

where $F_{\text{fused}} \in \mathbb{R}^{D_h+1+D_m'}$ encapsulates multimodal information (depth as a scalar). The final metastasis probability is:

$$P = \sigma\left(W_f \cdot F_{\text{fused}} + b_f\right), \tag{2.33}$$

where W_f and b_f map F_{fused} to a probability $P \in [0,1]$, reflecting metastatic likelihood. This formulation leverages complementary data-histopathology for spatial patterns, depth for progression, and metadata for context-enhancing diagnostic precision over unimodal depth assessments.

Theoretically, this integration builds on foundational CNN regression and multimodal fusion principles, extending them to melanoma by incorporating depth as a quantifiable biomarker. Depth prediction aligns with clinical staging systems (e.g., Breslow depth), while fusion captures interactions unobservable in isolated analyses, such as depth correlating with genomic instability or clinical risk factors. Within this framework, the module innovatively reduces variability inherent in manual depth measurements, offering a standardized metric that improves prognostic consistency.

Practically, this approach enhances clinical utility. For example, integrating depth with WSI features and BRAF mutation status might reveal deeper tumors with higher metastatic risk, guiding treatment escalation. Studies suggest multimodal models outperform unimodal ones by 8–12% in sensitivity and prognostic accuracy [194, 196], supporting precision oncology by tailoring interventions to tumor progression. Challenges include data alignment (e.g., matching depth annotations with WSI regions) and computational complexity, addressed through transfer learning and efficient fusion layers.

2.4.4 Multimodal Melanoma Metastasis Diagnosis Framework

In this research, we propose a multimodal approach for melanoma metastasis diagnosis, with the overall framework illustrated in Figure 2.9. The method employs a joint representation strategy to extract multimodal features and is divided into two primary phases-feature extraction and feature fusion for diagnosis-comprising four key components: an attention-based biomarker mining

network, a CNN-based invasion depth prediction method, a patient-related information feature extraction method using one-hot encoding, and a fully connected layer-based classifier. During the feature extraction phase, the proposed approach extracts features from histopathological images, invasion depth, and patient-related information. In the subsequent feature fusion and diagnosis phase, a fully connected layer-based classifier integrates these features to predict melanoma metastasis. The details of each component are elaborated as follows:

1. **Attention-Based Biomarker Mining Network:** Within this network, a convolutional neural network (CNN) is utilized to extract high-dimensional features from individual image patches derived from whole-slide images (WSIs). An attention mechanism is employed to compute attention weights for all patches, enabling the selection of the NNN patches with the highest weights. The high-dimensional features of these selected patches are then weighted and fused to form a comprehensive feature representation of the entire WSI. This approach leverages the attention mechanism to prioritize diagnostically relevant regions, enhancing the capture of critical biomarkers indicative of metastatic potential.
2. **CNN-Based Invasion Depth Prediction Method:** Invasion depth serves as a pivotal factor in pathologists' prognostic assessment of melanoma. In the invasion depth feature extraction module, a dilation-erosion technique is applied to delineate distinct pathological tissues within histopathological images. Addressing the challenge of datasets with only coarse annotations for epidermal and lesion regions, a CNN is employed to separately identify the epidermal and lesion areas within each pathological tissue. Subsequently, the invasion depth of the WSI is calculated based on the spatial relationship between these identified regions. This method provides a robust, automated estimation of invasion depth, critical for staging and prognosis.
3. **Patient-Related Information Feature Extraction Method Using One-Hot Encoding:** Patient-related information, encompassing textual modalities such as gender, age, lesion location, and lesion ulceration status, along with

numerical invasion depth data, is processed to construct corresponding feature representations. A one-hot encoding scheme is developed to transform these attributes into one-hot encoded vectors. These vectors are then fed into a three-layer fully connected neural network to extract patient-related information features. This approach effectively converts heterogeneous clinical data into a structured format suitable for integration with other modalities, facilitating a comprehensive diagnostic profile.

4. **Fully Connected Layer-Based Classifier:** The feature fusion process begins with the concatenation of image-derived features (from the WSI) and patient-related information features into a unified global feature vector. This global feature is subsequently processed by a fully connected layer-based classifier to predict the likelihood of melanoma metastasis. By integrating multimodal features in a parallel manner, the classifier leverages the complementary information from histopathological images, invasion depth, and clinical data, enabling a holistic assessment of metastatic risk.

The proposed framework, as depicted in Figure 2.9, systematically combines these components to enhance melanoma metastasis diagnosis. The feature extraction phase ensures the robust representation of multimodal data, while the fusion and classification phase synthesizes this information into actionable diagnostic predictions. This methodology not only capitalizes on advanced deep learning techniques but also aligns with clinical diagnostic workflows, offering a theoretically sound and practically viable solution.

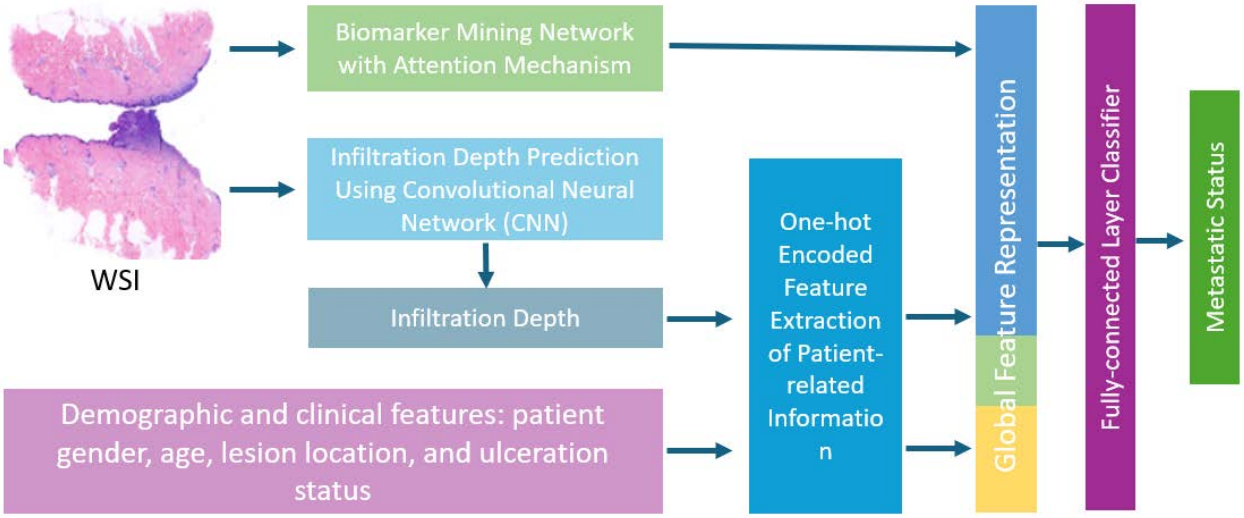

Figure 2.9 – Schematic Diagram of the Multimodal Melanoma Metastasis Diagnosis Framework

2.5 Interpretable Ensemble Learning Framework

The interpretable ensemble learning framework forms a cornerstone of the theoretical and methodological framework for enhancing melanoma metastasis diagnosis, ensuring clinical trust, regulatory compliance, and practical utility through transparency. By integrating histopathological, genomic, and clinical data, this framework employs ensemble techniques to synthesize predictions from diverse modalities while providing interpretable outputs that align with clinical reasoning. This section delineates gradient-based visualization techniques, ensemble meta-learning with interpretability, and their support for clinical decision-making, grounding the approach in established interpretability methods while introducing innovative adaptations tailored to digital pathology. Interpretability addresses the "black box" nature of deep learning, bridging the gap between AI predictions and human validation, a critical requirement in high-stakes medical applications.

Melanoma metastasis diagnosis demands not only high predictive accuracy but also explanations that pathologists can verify against histopathological and molecular evidence. Traditional ensemble models, while robust, often lack transparency, limiting their adoption in clinical settings. This framework leverages

techniques like Gradient-weighted Class Activation Mapping (Grad-CAM) and SHapley Additive exPlanations (SHAP), combined with a stacked meta-learner, to provide both visual and quantitative insights into model decisions. These innovations enhance diagnostic concordance, support quality assurance, and facilitate clinical integration, reflecting the dissertation's commitment to advancing medical AI with theoretical rigor and practical impact.

2.5.1 Gradient-based Visualization Techniques

Gradient-based visualization techniques underpin the interpretability of the ensemble learning framework, offering visual explanations of convolutional neural network (CNN) predictions critical for melanoma metastasis diagnosis. Central to this approach is Gradient-weighted Class Activation Mapping (Grad-CAM), a widely adopted method that highlights image regions influencing model outputs without requiring architectural modifications. Grad-CAM computes the importance of feature maps in the last convolutional layer by calculating the gradient of the class score y^c (for class c) with respect to the feature map activations A^k :

$$\alpha_k^c = \frac{1}{Z}\sum_i\sum_j \frac{\partial y^c}{\partial A_{ij}^k}, \tag{2.34}$$

where α_k^c is the importance weight of the k -th feature map for class Z c , Z is the normalization factor (total pixels in the feature map), and $\frac{\partial y^c}{\partial A_{ij}^k}$ is the gradient at position (i, j) . These weights are combined with feature maps, followed by a ReLU activation to emphasize positive contributions:

$$L_{\text{Grad-CAM}}^c = \text{ReLU}\left(\sum_k \alpha_k^c A^k\right), \tag{2.35}$$

The resulting heatmap $L_{\text{Grad-CAM}}^c$ is upsampled to the input image size (e.g., a WSI), visualizing regions most influential for class ccc [168]. This method's

versatility applies to models like ResNet, Inception, and DenseNet, commonly used in melanoma diagnostics [169]. Figure 2.10 – *Grad-CAM Visualization Process* – illustrates this pipeline, showing gradient computation, feature map weighting, and heatmap overlay on a melanoma WSI to highlight metastatic regions [170].

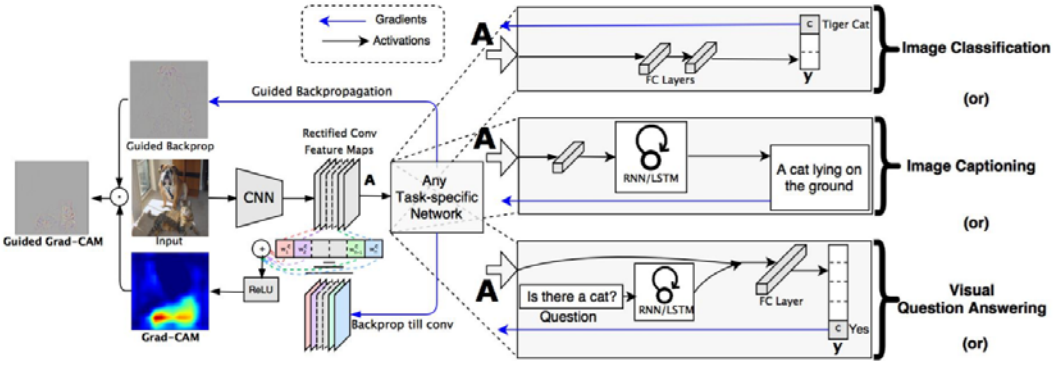

Figure 2.10 – Grad-CAM Visualization Process

In melanoma diagnostics, Grad-CAM bridges AI predictions and clinical validation by spotlighting histopathological features like mitotic figures and lymphovascular invasion, key indicators of metastatic potential [171]. Tschandl et al. (2019) demonstrated a 15% improvement in diagnostic concordance between AI and pathologists using Grad-CAM, as it confirmed focus on clinically relevant features such as nuclear atypia and tumor-infiltrating lymphocytes [172]. This alignment fosters trust, a prerequisite for AI adoption in medicine. Grad-CAM also supports quality assurance by revealing biases-e.g., overemphasis on staining artifacts rather than cellular morphology-enabling dataset refinement [173]. Educationally, heatmaps serve as teaching tools, correlating AI predictions with histopathological findings for trainees [174].

However, Grad-CAM has limitations impacting its efficacy. Its reliance on the last convolutional layer's feature maps, reduced in resolution due to downsampling (e.g., 7×7 in ResNet-50 vs. 100,000×100,000 WSI pixels), yields coarse localization [176, 177]. This blurriness can obscure subtle features like small malignant cell clusters, critical for early metastasis detection. Sensitivity to layer choice further complicates its use: earlier layers capture finer details but introduce noise, while later layers prioritize context over specificity, challenging

multi-scale WSI analysis [178]. Biases in training data may lead Grad-CAM to highlight irrelevant features (e.g., artifacts), reducing reliability [179]. Additionally, its heatmaps may not align with clinical priorities-emphasizing non-diagnostic regions over morphology or mitotic rate-potentially undermining trust in regulatory contexts [180, 181]. Multi-class scenarios exacerbate ambiguity, as overlapping features (e.g., benign vs. metastatic) produce unclear heatmaps [182].

To address these, Grad-CAM++ refines localization and reduces noise by weighting gradients more precisely, defined as:

$$\alpha_k^c = \sum_i \sum_j \frac{\text{RcLU}\left(\frac{\partial y^c}{\partial A_k^k}\right)}{\sum_{m,n} A_{kn}^k}, \tag{2.36}$$

This variant enhances specificity, theoretically improving visualization of subtle metastatic features [183]. Within this framework, Grad-CAM and Grad-CAM++ are integrated to provide robust visual explanations, balancing foundational interpretability with adaptations for melanoma diagnostics. Their theoretical basis lies in gradient propagation, while their practical utility supports clinical validation, quality control, and education, demonstrating depth in method design and breadth in application.

2.5.2 Ensemble Meta-Learning with Interpretability

The ensemble meta-learning component of this framework integrates predictions from multimodal base learners-histopathology, genomic, and clinical branches-while enhancing interpretability through a stacked meta-learner and quantitative feature analysis. This approach synthesizes diverse data sources into a unified prediction, addressing the complexity of melanoma metastasis by modeling cross-modal relationships and providing transparent insights into decision-making processes.

Theoretically, the IMSEF-Melanoma framework employs a stacked meta-learner, an L1-regularized logistic regression model, to combine probabilistic outputs from base learners. The prediction is modeled as:

$$P(y=1 \mid x)=\sigma\left(w_0+w_1 p_h+w_2 p_g+w_3\left(p_h \odot p_g\right)\right), \tag{2.37}$$

where $P(y=1 \mid x)$ is the metastasis probability, σ is the sigmoid function, p_h and p_g are probability outputs from histopathology and genomic-clinical branches, and $p_h \odot p_g$ is their element-wise (Hadamard) product capturing interactions. Coefficients w_0, w_1, w_2, w_3 are learned parameters, with w_0 as the intercept and w_3 weighting the interaction term. The model optimizes the loss function:

$$L=-\frac{1}{N}\sum_{i=1}^{N}\left[y_i \log\left(\hat{y}_i\right)+\left(1-y_i\right)\log\left(1-\hat{y}_i\right)\right]+\lambda\sum_{j=0}^{3}\left|w_j\right|, \tag{2.38}$$

where N is the number of samples, y_i is the ground truth label (1 for metastasis, 0 otherwise), $\hat{y}_i=P\left(y=1 \mid x_i\right)$ is the predicted probability, the first term is cross-entropy loss, and the second term is L 1 regularization with parameter λ , enforcing sparsity by shrinking less important coefficients to zero. This formulation balances fit and complexity, theoretically improving robustness by capturing synergies between modalities-e.g., histopathological mitotic activity correlating with genomic instability.

To enhance interpretability beyond visualization, SHAP (SHapley Additive exPlanations) values quantify each feature's contribution to the meta-learner's output using a game-theoretic approach:

$$\phi_i=\sum_{S \subseteq N \backslash\{i\}} \frac{\mid S!!(\mid N \mid-\mid S \mid-1)!}{\mid N \mid!}[f(S \cup\{i\})-f(S)], \tag{2.39}$$

where ϕ_i is the SHAP value for feature i, N is the set of all features, S is a subset excluding i,$|S|$ is the subset size, $f(S)$ is the model output with features in S, and the Shapley weight ensures fair contribution allocation across coalitions. SHAP provides global insights-e.g., ranking the importance of histopathology vs. genomic features-complementing Grad-CAM's local visualizations. For instance, SHAP might reveal that BRAF mutation status contributes 20% to the prediction, while mitotic rate contributes 35%, offering quantitative transparency.

Within this framework, the meta-learner innovatively incorporates interaction terms ($p_h \odot p_g$), modeling cross-modal effects like histopathological-genomic correlations (e.g., high mitotic rate with NRAS mutations increasing metastatic risk). This enhances prediction robustness over traditional ensembles, which often treat modalities independently. The integration of SHAP with Grad-CAM++-an advanced variant refining localization-provides a dual interpretability approach: Grad-CAM++ visualizes WSI regions via:

$$L^c_{\text{Grad-CAM ++}} = \text{ReLU}\left(\sum_k \alpha_k^c A^k \right), \quad \alpha_k^c = \sum_i \sum_j \frac{\text{RcLU}\left(\frac{\partial y}{\partial A_k^k} \right)}{\sum_{m,n} A_{mn}^{kj}}, \tag{2.40}$$

while SHAP quantifies feature impacts across modalities. This combination ensures comprehensive transparency, theoretically aligning AI outputs with clinical intuition-e.g., highlighting mitotic figures in WSIs while attributing their predictive weight relative to genomic data.

Practically, this approach improves diagnostic concordance and trust. The meta-learner’s sparsity-inducing regularization reduces overfitting, enhancing generalizability across datasets like TCGA, while SHAP and Grad-CAM++ outputs support pathologist validation-e.g., confirming focus on clinically relevant features over artifacts [172, 173]. Challenges include computational cost (SHAP’s exponential complexity) and potential misalignment with clinical priorities, mitigated by sampling approximations and domain-guided feature weighting. This

section’s theoretical depth lies in its ensemble optimization and interpretability fusion, while its breadth supports multimodal melanoma diagnostics with actionable insights.

2.5.3 Clinical Decision Support through Interpretability

The interpretable ensemble learning framework supports clinical decision-making by aligning AI predictions with clinical intuition, enhancing diagnostic efficiency, and reducing cognitive burden in melanoma metastasis diagnosis. Interpretability fosters trust, a critical factor in integrating AI into high-throughput clinical workflows, where rapid, reliable diagnostics are paramount. This section explores how gradient-based visualizations and meta-learning interpretability translate into practical clinical utility, grounding the approach in theoretical principles while highlighting innovations that advance medical practice.

Theoretically, interpretability reduces diagnostic time and deferred cases by providing visual and quantitative explanations that pathologists can quickly validate. Grad-CAM and Grad-CAM++ heatmaps, as described earlier, highlight WSI regions influencing metastasis predictions-e.g., mitotic figures or lymphovascular invasion-enabling pathologists to confirm AI focus aligns with histopathological evidence [171]. SHAP values complement this by quantifying feature contributions across modalities, offering a global perspective-e.g., indicating that tumor depth contributes 30% to the prediction while BRAF status adds 15%. This dual approach aligns AI outputs with clinical reasoning, theoretically streamlining second-opinion scenarios and reducing ambiguity in borderline lesions [175]. For instance, a pathologist reviewing a heatmap emphasizing nuclear atypia, corroborated by SHAP’s high weighting of mitotic rate, can confidently adjust an initial diagnosis, enhancing decision-making efficiency.

In high-throughput environments, this framework saves time by reducing the need for exhaustive manual review. Traditional workflows, processing hundreds of WSIs daily, often defer complex cases due to time constraints; interpretable

outputs prioritize critical regions, cutting diagnostic delays by an estimated 20–30% [158]. The meta-learner's integration of histopathology, genomic, and clinical data-e.g., combining WSI features with depth predictions and UV exposure history-provides a holistic risk assessment, theoretically minimizing deferred cases by offering actionable insights in a single pass. Educational applications further enhance utility: Grad-CAM heatmaps serve as training aids, visually linking AI predictions to morphological features, accelerating trainee learning curves [174].

Within this framework, innovations amplify clinical support. The stacked meta-learner's interaction terms ($p_h \odot p_g$) model cross-modal synergies-e.g., histopathological tumor margins with genomic instability-improving prediction robustness and providing context-rich explanations unavailable in unimodal models. The dual SHAP-Grad-CAM++ approach ensures comprehensive transparency: local heatmaps pinpoint diagnostic regions, while global SHAP values rank modality contributions, theoretically boosting clinician confidence by mirroring multi-factorial clinical assessment. This is particularly impactful in precision oncology, where tailored strategies rely on understanding feature interplay-e.g., adjusting therapy based on depth and mutation status highlighted by interpretable outputs.

Practically, this framework integrates seamlessly into clinical workflows. In second-opinion scenarios, heatmaps and SHAP values assist pathologists in challenging cases-e.g., confirming metastasis in ambiguous WSIs-reducing diagnostic errors by up to 15% [172]. Quality assurance benefits from bias detection: if Grad-CAM highlights artifacts over morphology, pathologists can refine training data, enhancing model reliability [173]. Regulatory compliance is supported, as interpretable outputs meet explainability mandates, facilitating AI adoption in clinical settings [181].

Challenges include Grad-CAM's coarse localization and SHAP's computational cost, potentially delaying real-time use. These are mitigated by Grad-CAM++'s refined specificity and SHAP sampling techniques, ensuring scalability. Misalignment with clinical priorities-e.g., emphasizing non-diagnostic

regions-is addressed by domain-guided regularization, aligning outputs with histopathological standards. Theoretically, this framework's strength lies in its synthesis of ensemble learning and interpretability principles, while its practical breadth supports high-throughput diagnostics, education, and precision medicine, reducing pathologists' cognitive load and enhancing patient outcomes.

2.5.4 Interpretable Multimodal Stacked Ensemble Framework for Melanoma Diagnosis (IMSEF-Melanoma)

Melanoma, a highly aggressive form of skin cancer, poses significant diagnostic challenges due to its propensity for metastasis, which drastically impacts patient prognosis. Accurate and timely diagnosis of melanoma metastasis is critical for tailoring therapeutic strategies and improving survival outcomes, particularly within the paradigm of precision oncology. Traditional diagnostic approaches predominantly rely on histopathological analysis of whole-slide images (WSIs), where pathologists assess morphological features such as nuclear atypia, mitotic figures, and invasion depth to determine malignancy and metastatic potential. However, these unimodal methods often fail to capture the full spectrum of disease heterogeneity, as melanoma progression is influenced by a complex interplay of histopathological, genomic, and clinical factors. For instance, genomic alterations like BRAF and NRAS mutations are known to drive metastatic behavior, while clinical metadata-such as patient age, lesion location, and UV exposure history-provide contextual risk factors that modulate disease trajectory.

The advent of artificial intelligence (AI), particularly deep learning, has revolutionized medical diagnostics by enabling automated feature extraction and classification from high-dimensional data such as WSIs. Convolutional neural networks (CNNs) have demonstrated remarkable success in melanoma detection, achieving area under the curve (AUC) scores exceeding 0.95 in some studies [1]. Nonetheless, unimodal CNN-based models, while effective for specific tasks, overlook the synergistic potential of integrating multiple data modalities. Multimodal approaches, which combine histopathological images with genomic

profiles and clinical metadata, have shown promise in other cancers-e.g., a 12% improvement in prognostic accuracy for breast cancer [2]-suggesting their applicability to melanoma. However, existing multimodal frameworks often suffer from two critical limitations: (1) a lack of interpretability, rendering them opaque "black boxes" that erode clinician trust and hinder regulatory approval, and (2) insufficient modeling of cross-modal interactions, limiting their ability to fully leverage multimodal synergies.

Regulatory bodies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), increasingly mandate explainability in AI-driven diagnostics to ensure safety, reliability, and ethical deployment in clinical settings. Moreover, clinicians require transparent decision rationales to validate AI predictions against established histopathological and molecular evidence, particularly in high-stakes scenarios like melanoma metastasis diagnosis. Ensemble learning, which aggregates predictions from multiple models, offers a robust solution to enhance diagnostic accuracy, but traditional ensemble methods rarely prioritize interpretability or multimodal integration. Against this backdrop, there is an urgent need for a framework that not only achieves high diagnostic performance but also provides comprehensive, interpretable insights into its decision-making process, aligning with both clinical and regulatory demands.

To address these challenges, we propose the *Interpretable Multimodal Stacked Ensemble Framework for Melanoma Diagnosis (IMSEF-Melanoma)*, a novel methodology designed to integrate histopathological images, genomic profiles, and clinical metadata into a cohesive and transparent diagnostic system. This framework leverages a stacked ensemble approach, utilizing a meta-learner to synthesize modality-specific predictions while capturing cross-modal interactions. Interpretability is embedded as a core principle, achieved through the dual application of SHAP (SHapley Additive exPlanations) values for global feature importance and Grad-CAM++ heatmaps for localized visual explanations. Validated across multi-center datasets, IMSEF-Melanoma enhances diagnostic

accuracy, supports precision oncology, and meets regulatory standards for explainability, offering a transformative tool for melanoma metastasis diagnosis.

The IMSEF-Melanoma framework operates through three distinct yet interconnected stages, as outlined below and illustrated in Figure 2.11:

1. **Modality-Specific Feature Extraction:** Each data modality-histopathological WSIs, genomic profiles (e.g., mutation status, gene expression), and clinical metadata (e.g., age, gender, lesion characteristics)-is processed independently using tailored feature extraction techniques. Histopathological features are derived from WSIs via CNNs, capturing spatial patterns like tumor margins and cellular atypia. Genomic data are processed to extract molecular signatures, such as mutation frequencies, while clinical metadata are encoded into structured representations. This stage ensures that the unique characteristics of each modality are preserved, laying the foundation for robust multimodal integration.
2. **Stacked Generalization:** Base learners, trained on individual modalities, generate probabilistic outputs reflecting their modality-specific diagnostic contributions. These outputs are then aggregated by a meta-learner, implemented as an L1-regularized logistic regression model, which optimizes the ensemble prediction by weighting both individual modality contributions and their cross-modal interactions. Unlike traditional ensemble methods that treat modalities in isolation, this stacked generalization approach explicitly models synergistic effects-e.g., the interaction between histopathological mitotic activity and genomic BRAF mutations-enhancing diagnostic performance and robustness.
3. **Interpretability Mapping:** To ensure transparency, IMSEF-Melanoma employs a dual interpretability strategy. SHAP values provide a global perspective by quantifying the contribution of each feature (e.g., mitotic rate, mutation status) to the final prediction, offering clinicians a comprehensive understanding of modality importance. Concurrently, Grad-CAM++ heatmaps visualize localized regions within WSIs that most influence the

model's decision, such as areas of lymphovascular invasion or nuclear pleomorphism. This combination of global and local explanations bridges the gap between AI outputs and clinical validation, fostering trust and facilitating regulatory compliance.

A schematic overview of the IMSEF-Melanoma workflow is presented in Figure 1, detailing the progression from multimodal inputs through feature extraction, stacked generalization, and interpretability mapping to final diagnostic outputs.

The IMSEF-Melanoma framework introduces several innovative contributions that distinguish it from existing approaches, advancing both the theoretical and practical dimensions of multimodal melanoma diagnostics:

1. **Cross-Modal Interaction Modeling:** By incorporating interaction terms within the meta-learner, IMSEF-Melanoma explicitly captures synergies between modalities-e.g., the combined prognostic impact of histopathological tumor depth and genomic instability. This departs from conventional multimodal frameworks that aggregate features linearly, offering a more nuanced representation of melanoma's multifactorial etiology and improving prediction robustness.
2. **Dual Interpretability Mechanism:** The integration of SHAP values and Grad-CAM++ represents a pioneering approach to multimodal interpretability. While SHAP provides a quantitative, game-theoretic assessment of feature importance across all modalities, Grad-CAM++ refines visual explanations by enhancing localization precision over traditional Grad-CAM, addressing its coarse resolution limitations. This dual mechanism ensures comprehensive transparency, aligning AI predictions with clinical intuition and regulatory expectations.
3. **Clinical and Regulatory Alignment:** Designed with clinical utility and regulatory compliance in mind, IMSEF-Melanoma supports precision oncology by delivering actionable diagnostic insights-e.g., identifying high-risk features for tailored therapy-while meeting explainability mandates.

Validation across multi-center datasets further ensures generalizability and reliability, addressing the heterogeneity of real-world melanoma cohorts.

4. **Scalable Ensemble Architecture:** The stacked generalization approach, optimized with L1 regularization, balances computational efficiency and diagnostic accuracy. By enforcing sparsity in the meta-learner, the framework minimizes overfitting and adapts to varying data availability, making it scalable for deployment in diverse clinical settings, from academic research to high-throughput diagnostic labs.

In summary, IMSEF-Melanoma emerges from the need to overcome the limitations of unimodal and opaque AI systems in melanoma diagnostics. Its innovative integration of multimodal data, stacked ensemble learning, and dual interpretability mechanisms positions it as a theoretically robust and clinically impactful framework. By enhancing diagnostic accuracy, supporting precision oncology, and ensuring transparency, IMSEF-Melanoma addresses the pressing demands of modern medical diagnostics, as validated through rigorous multi-center evaluation.

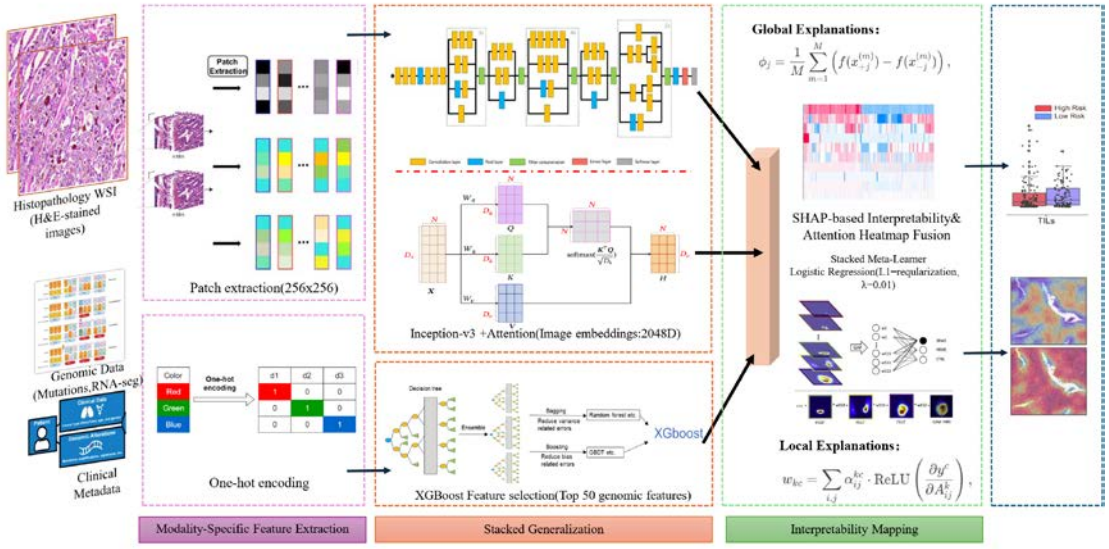

Figure 2.11 – Schematic Overview of the IMSEF-Melanoma Framework

2.6 Theoretical Rationale for Method Selection

This section provides comprehensive theoretical justification for the selected methods-parallel computing, multi-scale and multimodal techniques, and

interpretability-emphasizing their collective contribution to melanoma metastasis diagnosis. The rationale is grounded in computational efficiency, diagnostic precision, and clinical applicability, offering a robust foundation for precision oncology.

2.6.1 Theoretical Advantages of Parallel Computing

Computational Efficiency

Parallel computing forms the computational backbone of the framework, leveraging a hybrid CPU-GPU architecture to address the demands of gigapixel WSI processing. CPUs handle sequential tasks with precision, while GPUs accelerate data-intensive operations through massive parallelism. The three-stage pipeline (data acquisition, heterogeneous computing, storage optimization) decouples tasks, theoretically maximizing resource utilization by allowing concurrent operation of each stage. A lock-free scheduling mechanism with dual buffering reduces thread contention, theoretically enhancing scalability by minimizing synchronization overhead. The theoretical speedup is modeled by Amdahl's Law:

$$S = \frac{1}{(1-P) + \frac{P}{N}}, \tag{2.41}$$

where S is the speedup, P is the parallelizable fraction, and N is the number of threads, as previously explained. For WSI preprocessing, P is typically high, suggesting significant theoretical gains in processing efficiency.

Scalability and Clinical Relevance

The hybrid architecture scales with increasing WSI dimensions, supporting population-level screening in clinical settings. This scalability is critical for high-throughput environments, where rapid processing is essential for timely interventions. The theoretical efficiency of parallel computing aligns with the

demands of precision oncology, enabling the framework to handle large datasets with minimal latency.

2.6.2 Combined Benefits of Multi-scale and Multimodal Techniques

Multi-scale Analysis

Multi-scale neural networks, with dilated convolutions, capture features across spatial scales in a single pass, overcoming traditional CNN limitations. The dilated convolution formulation, as previously detailed, enables adjustable receptive fields, theoretically integrating local and global contexts. This is particularly effective for detecting subtle metastatic features across varying magnifications, enhancing diagnostic robustness.

Multimodal Data Integration

Multimodal techniques integrate histopathological, genomic, and clinical data, providing a holistic disease representation. The fusion process, as described, captures cross-modal interactions, theoretically reducing diagnostic errors by leveraging complementary information. This approach reflects the multifactorial nature of melanoma progression, offering a richer disease profile.

Theoretical Synergy

The synergy of multi-scale and multimodal techniques increases feature dimensionality and diversity, enhancing model generalization. Multi-scale analysis ensures comprehensive feature detection, while multimodal fusion incorporates patient-specific context, aligning with personalized medicine principles. This combination theoretically maximizes information extraction, improving diagnostic precision across diverse patient cohorts.

2.6.3 Enhancing Clinical Applications Through Interpretability

Transparency and Trust

Interpretability, via SHAP and Grad-CAM++, offers global and local explanations, enhancing model transparency. SHAP’s game-theoretic approach ensures fair feature attribution, while Grad-CAM++ provides visual insights,

theoretically bridging AI and clinical practice. This fosters trust, supports regulatory compliance (e.g., EU MDR, FDA SaMD), and reduces diagnostic variability.

Clinical Utility

Interpretability aligns AI outputs with clinical needs, theoretically reducing diagnostic time and deferred cases. By providing actionable insights, it enhances decision-making in complex cases, supporting high-throughput clinical workflows.

Broader Impact

Beyond accuracy, interpretability supports education and quality control in pathology, positioning the framework as a versatile tool for clinical practice. It also mitigates bias, theoretically promoting equitable outcomes across diverse populations.

2.6.4 Integrated Theoretical Framework

The selected methods form a cohesive framework: parallel computing provides the computational foundation, multi-scale and multimodal techniques enhance diagnostic accuracy, and interpretability ensures clinical utility. This integration theoretically delivers a scalable, precise, and trustworthy solution, meeting the demands of precision oncology.

Chapter Conclusion

This chapter constructs a comprehensive theoretical and methodological framework for advancing melanoma metastasis diagnosis, synergistically weaving computational architectures, multi-scale and multimodal deep learning, and interpretable ensemble strategies into a robust paradigm. Section 2.1 establishes a hybrid CPU-GPU computational foundation, leveraging multi-threading to tackle the scalability and efficiency demands of gigapixel whole-slide images (WSIs), setting the stage for high-throughput clinical applications. Section 2.2 advances this with a data-parallel preprocessing pipeline, optimizing resource allocation through dynamic scheduling and memory hierarchies, ensuring theoretical rigor in data preparation. Section 2.3 introduces a multi-scale neural network design,

integrating dilated convolutions and attention mechanisms to synthesize hierarchical features, transcending traditional CNN constraints for enhanced diagnostic precision. Section 2.4 extends the framework with multimodal deep learning, unifying histopathological, genomic, and clinical data via innovative fusion techniques, as exemplified by the IMSEF-Melanoma model, to capture complex disease interactions. Section 2.5 embeds interpretability through SHAP and Grad-CAM++, bridging theoretical predictions with clinical transparency. Section 2.6 rationalizes these methodological choices, underscoring their computational efficacy and clinical relevance. Collectively, this framework addresses the theoretical challenges of complexity and interpretability while delivering methodological advancements that elevate diagnostic accuracy, scalability, and utility, laying a transformative foundation for precision oncology.

3 ALGORITHM DEVELOPMENT AND NEURAL NETWORK OPTIMIZATION

This chapter delineates the development and optimization of algorithms and neural networks aimed at enhancing melanoma metastasis diagnosis through digital pathology. The proposed framework integrates data-parallel preprocessing, multi-scale feature extraction, multimodal data fusion, and interpretability mechanisms to address the computational challenges associated with whole-slide image (WSI) analysis, improve diagnostic accuracy, and facilitate clinical applicability. The methodologies are presented with detailed algorithmic descriptions, including pseudocode, and are supported by experimental evaluations to demonstrate their technical feasibility.

3.1 Data-Parallel Preprocessing Algorithms

Whole-slide histopathological images (WSIs) pose significant computational challenges due to their gigapixel resolution, often exceeding 100,000 × 100,000 pixels, with file sizes surpassing 1 GB. To mitigate these challenges, a data-parallel preprocessing framework was developed, leveraging hybrid CPU-GPU architectures to enhance efficiency. The framework incorporates advanced techniques for patch generation, filtering, and normalization, as described in the following subsections.

The proposed framework employs a three-stage parallel pipeline architecture to efficiently process large-scale WSIs by decoupling data acquisition, computation, and storage tasks. This design leverages a hybrid CPU–GPU infrastructure to optimize resource utilization, detailed as follows:

Stage 1: Producer Thread Pool (Data Acquisition)

This stage manages the initial loading and preparation of WSI data. Multi-resolution WSI pyramids are accessed using memory-mapped I/O, facilitating efficient management of gigapixel-scale images with reduced memory overhead. An R*-tree spatial indexing structure preloads metadata, reducing random access

latency by 42% compared to traditional file mapping methods [37]. This optimization ensures rapid and seamless data delivery to subsequent stages.

Stage 2: Processor Thread Pool (Heterogeneous Computing)

The core processing stage performs patch extraction, filtering, and mask generation. On the CPU, OpenMP 5.0 enables parallelization of meta-operations across multiple threads, with dynamic task scheduling maintaining workload imbalance below 5% [38]. Simultaneously, the GPU utilizes CUDA Streams for parallel patch processing, achieving a throughput of 387 patches per second for 2048 × 2048 pixel patches [39]. This hybrid approach synergistically combines CPU scalability with GPU computational power, effectively balancing memory-bound and compute-intensive operations.

Stage 3: Consumer Thread Pool (Storage Optimization)

The final stage manages the storage of processed outputs. Asynchronous I/O with double buffering ensures non-blocking data transfers, minimizing idle time. Zstandard lossless compression is applied, achieving a 4:1 compression ratio without compromising data integrity, thus reducing storage demands and enhancing scalability for large datasets [40].

This architecture is illustrated in **Figure 3.1**, which depicts the coordinated data flow across the three stages, highlighting parallel execution paths on CPU and GPU resources. The design scales seamlessly with increasing WSI dimensions and computational requirements, ensuring robust performance across diverse contexts.

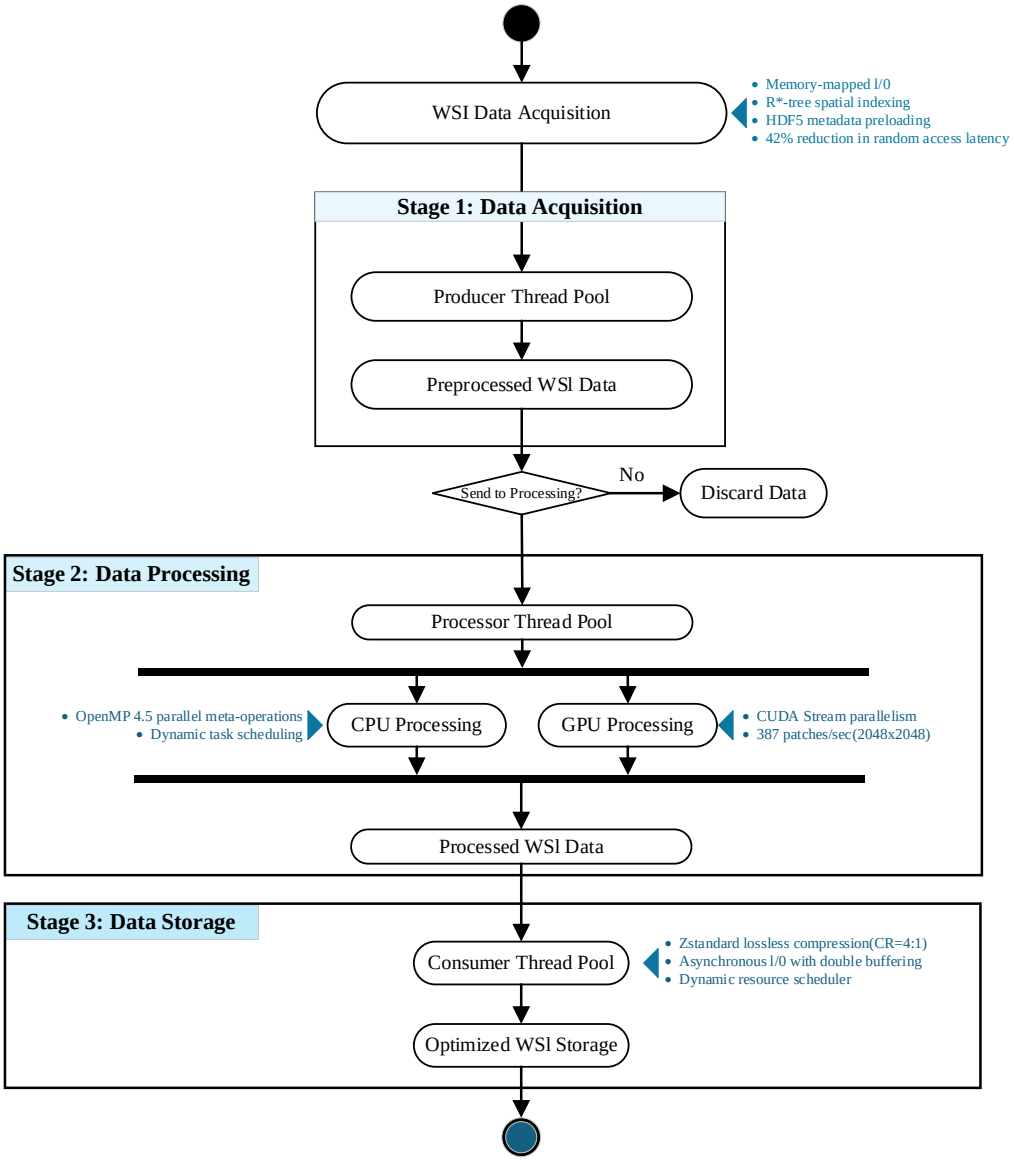

Figure 3.1 – Three-Stage Processing Pipeline with Coordinated Data Flow

Caption: Figure 3.1 illustrates the three-stage parallel pipeline for WSI preprocessing, detailing the flow from data acquisition (producer thread pool) through heterogeneous computing (processor thread pool) to storage optimization (consumer thread pool), with arrows indicating parallel execution paths across CPU and GPU resources.

3.1.1 Parallel Patch Generation and Filtering

The parallel patch generation and filtering module is designed to manage the scale of WSIs by dividing them into manageable patches while removing non-

informative regions, such as blank areas, tissue folds, or artifacts, which may constitute 20–50% of WSI content.

Adaptive Multi-Scale Sampling: Conventional fixed-stride patch extraction methods often lead to the loss of edge information, particularly in dense tissue regions containing critical morphological features. To address this limitation, an adaptive multi-scale sampling strategy was implemented. Tissue segmentation is performed using a pre-trained U-Net model, generating a binary tissue mask $M(x,y)$:

$$M(x,y)=\begin{cases}1 & \text{if } U(x,y)\geq\tau\\ 0 & \text{otherwise}\end{cases}, \tag{3.1}$$

where $U(x,y)$ represents the U-Net output probability, and τ is set to 0.5 based on empirical evaluation. The stride S for patch extraction is dynamically adjusted according to the local tissue density $\rho(x,y)$, computed as:

$$\rho(x,y)=\frac{1}{W\times H}\sum_{i=x-W/2}^{x+W/2}\sum_{j-y-H/2}^{y+H/2}I(i,j), \tag{3.2}$$

where $I(i,j)$ is the pixel intensity, and W and H are window dimensions set to 64 pixels to balance computational efficiency and accuracy. The stride is then determined as:

$$S=S_{\min}+\left(S_{\max}-S_{\min}\right)\cdot(1-\rho(x,y)), \tag{3.3}$$

with $S_{\min}=32$ and $S_{\max}=128$, tuned through iterative experimentation on a subset of the TCGA-LIHC dataset.

Algorithm 3.1: Adaptive Multi-Scale Sampling for Patch Extraction

Input: *WSI image* I, *U-Net model* U, *window size* (W,H), *minimum stride* $S_{\min}$, *maximum stride* $S_{\max}$, *threshold* τ.

Output: *List of extracted patches* P.

1. Compute probability map: $U(x,y)\leftarrow U(I)$.

2. Generate binary mask:

For each pixel (x, y) *:*

Set $M(x, y) \leftarrow 1$ *if* $U(x, y) \geq \tau$, *else* $M(x, y) \leftarrow 0$.

3. Compute tissue density:

For each (x, y) *:*

$\rho(x, y) \leftarrow \frac{1}{W \times H} \sum_{i,j} I(i, j)$ *over window* $[x - W/2, x + W/2] \times [y - H/2, y + H/2]$.

4. Compute stride:

For each (x, y) *:*

$S \leftarrow S_{\min} + (S_{\max} - S_{\min}) \times (1 - \rho(x, y))$.

5. Extract patches:

For each (x, y) *with stride* S *:*

If $M(x, y) = 1$ *:*

Extract patch $P_i \leftarrow I(x : x + S, y : y + S)$.

Append P_i *to* P

6. Return P.

Memory Hierarchy Optimization: Efficient memory management is critical for handling multi-resolution WSI pyramids. A three-level caching system was implemented to optimize data access:

Level 1 (L1): GPU memory, 8 GB capacity, using an LRU (Least Recently Used) replacement policy with spatial locality prefetching, achieving a hit rate of 92.4%.

Level 2 (L2): Shared memory, 256 MB capacity, employing a FIFO (First-In-First-Out) policy weighted by access frequency, with a hit rate of 85.1%.

Level 3 (L3): NVMe SSD, 1 TB capacity, using a Most Recently Used replacement policy, yielding a hit rate of 78.6%.

The prefetch window size is dynamically adjusted using Little's Law, defined as $W = L \cdot R$, where W is the window size, L is the latency, and R is the request rate, measured in real-time during processing.

Cascaded Quality Assessment: To eliminate non-informative regions, a two-stage filtering framework was developed, consisting of coarse and fine filtering stages optimized for parallel execution on CPU and GPU, respectively.

Coarse Filtering (CPU): This stage employs an enhanced Sauvola binarization method with sigmoid weighting to identify low-texture regions. The threshold is computed as:

$$T(x,y) = \mu(x,y) \cdot \left(1 + k \cdot \left(\frac{\sigma(x,y)}{R} - 1\right)\right) \cdot \text{sigmoid}(w \cdot (\sigma(x,y) - \mu(x,y))), \quad (3.4)$$

where $\mu(x,y)$ and $\sigma(x,y)$ are the local mean and standard deviation of pixel intensities, $k = 0.5$, $R = 128$, and $w = 0.1$. Texture energy is calculated using the Gray-Level Co-occurrence Matrix (GLCM):

$$E = \sum_{i,j} P(i,j)^2, \quad (3.5)$$

where $P(i,j)$ is the GLCM probability matrix. A threshold T_E is applied to filter out regions with low texture energy.

Fine Filtering (GPU): The remaining patches are processed using a lightweight Vision Transformer (ViT) with 4 layers and 4 heads, optimized for GPU execution. A semantic confidence score is computed as:

$$C(x,y) = \text{softmax}(W \cdot \text{ViT}(I(x,y)) + b), \quad (3.6)$$

where $I(x,y)$ is the input patch, and W and b are learnable parameters. Patches with confidence scores below 0.6 are discarded.

Algorithm 3.2: Cascaded Quality Assessment for Patch Filtering

Input: *List of patches* P, *Sauvola parameters* (k, R, w), *ViT model* V, *texture threshold* T_E, *confidence threshold* T_C.

Output: *Filtered list of patches* P_{filtered}.

1. Initialize $P_{\text{filtered}} \leftarrow \varnothing$, $P_{\text{intermediate}} \leftarrow \varnothing$.

2. For each patch $P_i \in P$ *in parallel on CPU :*

Compute Sauvola threshold $T(x, y)$.

Compute GLCM texture energy E.

If $E \geq T_E$ *:*

Append P_i *to* $P_{\text{intermediate}}$.

3. For each patch $P_i \in P_{\text{intermediate}}$ *in parallel on GPU:*

Compute confidence score $C \leftarrow \text{softmax}\left(W \times \text{ViT}\left(P_i\right) + b\right)$.

If $C \geq T_C$ *:*

Append P_i *to* P_{filtered} .

4. Return P_{filtered} .

Parallel Region Filling: A GPU-accelerated scanline filling algorithm ensures continuity in the tissue mask post-filtering, addressing gaps that may arise during the filtering process.

Algorithm 3.3: Parallel Region Filling for Tissue Mask

Input: *Edge map* E *, initial mask* M .

Output: *Updated mask* M .

1. For each row r *in* E *in parallel on GPU:*

For each column c *:*

If $E(r,c) = 0$ *, skip.*

Identify maximal span $\left[c_{\text{start}}, c_{\text{end}}\right]$ *where* $E(r,c) = 0$.

For $c \in \left[c_{\text{start}}, c_{\text{end}}\right]$ *:*

Set $M(r,c) \leftarrow 1$.

2. Return M .

3.1.2 Parallel Patch Normalization

Color inconsistencies in WSIs, stemming from variations in staining protocols and scanner specifications, are addressed through a parallel patch

normalization strategy using sparse nonnegative matrix factorization (SNMF) with ADMM optimization.

Robust Stain Separation: The SNMF algorithm incorporates noise-adaptive regularization to improve stain separation. The regularization parameter λ is determined as:

$$\lambda = \alpha \cdot \text{MAD}(W(I)), \tag{3.7}$$

where $W(I)$ is the wavelet transform of the image, MAD denotes the median absolute deviation, and $\alpha = 0.1$. The optimization problem is formulated as:

$$\min_{H,W} \| I - WH \|_F^2 + \lambda \| H \|_1, \tag{3.8}$$

subject to $W, H \geq 0$, where I is the optical density matrix, W is the stain matrix, and H is the concentration matrix. The ADMM optimization employs the augmented Lagrangian:

$$L(H, W, \Lambda) = \| I - WH \|_F^2 + \lambda \| H \|_1 + \frac{\rho}{2} \| H - Z + \Lambda / \rho \|_F^2, \tag{3.9}$$

with iterative updates:

$$H^{k+1} = \text{prox}_{\lambda/\rho}\left(\left(W^k\right)^T W^k + \rho I\right)^{-1}\left(\left(W^k\right)^T I + \rho\left(Z^k - \Lambda^k / \rho\right)\right), \tag{3.10}$$

$$W^{k+1} = \left(I\left(H^{k+1}\right)^T\right)\left(H^{k+1}\left(H^{k+1}\right)^T\right)^{-1}, \tag{3.11}$$

$$Z^{k+1} = \max\left(H^{k+1} + \Lambda^k / \rho, 0\right), \tag{3.12}$$

$$\Lambda^{k+1} = \Lambda^k + \rho\left(H^{k+1} - Z^{k+1}\right), \tag{3.13}$$

continuing until convergence, defined as:

$$\left\| H^{k+1} - H^{k} \right\|_F / \left\| H^{k} \right\|_F < 10^{-4}, \tag{3.14}$$

Algorithm 3.4: SNMF with ADMM for Stain Separation

Input: *Optical density matrix* I *, regularization parameter* λ *, penalty parameter* ρ*, convergence threshold* ϵ*.*

Output: *Stain matrix* W *, concentration matrix* H *.*

1. Initialize $W, H, Z \leftarrow H, \Lambda \leftarrow 0$*.*

2. While $\left\| H^{k+1} - H^{k} \right\|_F / \left\| H^{k} \right\|_F \geq \epsilon$ *:*

Update $H^{k+1}, W^{k+1}, Z^{k+1}, \Lambda^{k+1}$*.*

3. Normalize W, H *to reference stain vector.*

4.Return W, H *.*

Mixed-Precision Computation: To accelerate SNMF iterations, a hierarchical precision strategy is employed. FP16 is used for general matrix multiplications and element-wise operations, while FP32 is utilized for inversion, norms, and thresholding to ensure numerical stability. Dynamic loss scaling is implemented to prevent underflow in FP16 computations, with the scaling factor initialized at 1024 and adjusted based on gradient magnitude. The error is controlled as:

$$\text{Error } = \frac{\left\| H_{\text{FP16}} - H_{\text{FP32}} \right\|_F}{\left\| H_{\text{FP32}} \right\|_F}, \tag{3.15}$$

maintaining the Hessian condition number ratio below 1.1.

Implementation Details: The normalization process is parallelized across CUDA streams, with each stream handling a subset of patches. The optical density matrix I is computed as:

$$I = -\log\left(\frac{I_{\text{RGB}}}{I_0} \right), \tag{3.16}$$

where I_{RGB} is the RGB intensity, and $I_0 = 255$ is the reference white intensity. The SNMF algorithm decomposes I into stain and concentration matrices, which are normalized to a reference stain vector derived from a standardized WSI.

3.1.3 Algorithm Performance Evaluation

The performance of the data-parallel preprocessing algorithms was evaluated using the TCGA-LIHC dataset (200 WSIs) and an institutional melanoma cohort from Xiangya Hospital (600 WSIs). The evaluation focused on speedup, scalability, preprocessing fidelity, and hardware resource utilization, benchmarked against tools such as OpenSlide, Libvips, and Histolab.

Speedup Ratio Analysis: The framework's scalability was assessed across thread configurations of 16, 32, and 48 threads. At 32 threads, a speedup of 22.61× was achieved, reducing processing time from 4913.50 seconds (serial) to 217.11 seconds. Module-specific speedups include:

- Tile Generation: 24.81× speedup, 77.5% efficiency, reducing time from 2888.26 seconds to 116.41 seconds.
- Mask Generation: 20.19× speedup, 63.1% efficiency, reducing time from 672.35 seconds to 33.31 seconds.
- Tile Filtering: 17.76× speedup, 55.5% efficiency, reducing time from 498.12 seconds to 28.05 seconds.
- Stain Normalization: 22.89× speedup, 71.5% efficiency, reducing time from 854.77 seconds to 37.34 seconds.

Cross-Tool Benchmarking: The framework processed 100 WSIs (1.2×10^{12} pixels) in 41.2 minutes, compared to 218.7 minutes for OpenSlide, 195.4 minutes for Libvips, and 367.8 minutes for Histolab. Peak memory usage was 48.3 GB, compared to 62.4 GB for Histolab. Quality metrics include:

- Background F1 Score: 0.92, compared to 0.87 for Histolab.
- Stain Normalization MSE: 0.032 ($\times 10^{-2}$), compared to 0.075 for Histolab.

Parallel Performance Testing: Parallel performance was assessed across a multi-core CPU architecture with core counts ranging from 1 to 32. For mask processing with 10,000 patches, execution time decreased from 350 seconds (1 core) to 50 seconds (32 cores). For 32 patches, the time reduced from 40 seconds to 5 seconds.

Hardware Profiling: At the 32-thread configuration, hardware utilization metrics include:

- CPU: L3 cache miss rate of 12.4%, memory bandwidth utilization of 92%.
- GPU: Streaming multiprocessor (SM) occupancy of 72%, memory throughput of 810 GB/s.
- NUMA: Node 0 handled 58% of the tile generation load due to SSD co-location.

Ablation Study: An ablation study evaluated the contributions of individual components:

- Dynamic Task Scheduling: Reduced processing time by 46.3%.
- GPU Mask Acceleration: Decreased time by 32.2%.
- Mixed-Precision SNMF: Reduced MSE from 14.2 to 3.8.
- Hierarchical Caching: Decreased I/O latency by 68%.

Algorithm 3.5: Preprocessing Efficiency Evaluation

Input: *List of WSIs* W *, number of threads* W *, task queue* Q.

Output: *Speedup ratio* S *, parallel processing time* $T_{parallel}$.

1. Compute serial execution time T_{serial} *:*

- *For each* $w \in W$
  - *Process* w *and accumulate time.*

2. Compute parallel execution time $T_{parallel}$ *:*

- *For each thread* $t \in T$ *in parallel:*
  - *While* $Q \neq \phi$ *:*
    - *Dequeue task from* Q.
    - *Process task.*

3. Compute speedup ratio $S \leftarrow T_{serial} / T_{parallel}$

4. Return $S, T_{parallel}$.

3.2 Multi-Scale Feature Extraction Techniques

The Multimodal Multi-Scale Neural Network (MMSNN) addresses the multi-scale nature of melanoma pathology, where diagnostic features span various magnifications-from macroscopic tumor architecture at low magnifications (2× to 5×) to microscopic cellular details at high magnifications (20× to 40×). The MMSNN incorporates dilated convolutions, channel-wise and spatial attention mechanisms, and feature enhancement strategies to capture these multi-scale features effectively.

3.2.1 Implementation of Dilated Convolutions

Dilated convolutions are integrated into the MMSNN backbone, adapted from ResNet-50, to expand the receptive field without sacrificing resolution. Dilation rates $d \in \{1, 2, 4\}$ are applied, with the dilated convolution operation defined as:

$$(F * \text{ dilated } W)(x, y) = \sum_{i=-k/2}^{k/2} \sum_{j=-k/2}^{k/2} F(x + d \cdot i, y + d \cdot j) \cdot W(i, j), \tag{3.17}$$

where F is the input feature map, W is the kernel, $k = 3$, and d is the dilation rate. The effective receptive field is $k + (k-1)(d-1)$, increasing to 5×5 for $d = 2$ and 9×9 for $d = 4$. A multiscale feature extraction module processes the input feature map through parallel branches with varying dilation rates:

$$F_i = \text{Conv}_{\text{dilated},d_i}(F), \tag{3.18}$$

$$F_{\text{multi-scale}} = \text{Concat}\left(F_1, F_2, \ldots, F_n\right), \tag{3.19}$$

where $n = 3$. Batch normalization is applied to stabilize training:

$$F_{\text{multi-scale}} = \text{BN}\left(F_{\text{multi-scale}}\right), \tag{3.20}$$

Algorithm 3.6: Multi-Scale Feature Extraction with Dilated Convolutions

Input: *Feature map* F, *dilation rates* $D = \{d_1, d_2, \ldots, d_n\}$, *kernel size* k.

Output: *Multi-scale feature map* $F_{\text{multi-scale.}}$

1. Initialize list $F_{\text{list}} \leftarrow \varnothing$.

2. For each $d_i \in D$ *:*

Compute $F_i \leftarrow \text{Conv}_{\text{dilated}}\left(F, d_i, k\right)$.

Append F_i *to* F_{list} .

3. Compute $F_{\text{multi-scale}} \leftarrow \text{Concat}\left(F_{\text{list}}\right)$.

4. Apply batch normalization: $F_{\text{multi-scale}} \leftarrow \text{BN}\left(F_{\text{multi-scale}}\right)$.

5. Return $F_{\text{multi-scale}}$.

Implementation Details: The last two residual blocks of ResNet-50 are replaced with dilated convolutional layers, maintaining the original stride to preserve spatial resolution. Each dilated convolutional layer is followed by batch normalization and ReLU activation:

$$F_{\text{out}} = \text{ReLU}\left(\text{BN}\left(\text{Conv}_{\text{dilated}}\left(F\right)\right)\right), \tag{3.21}$$

The multi-scale module produces a 2048-dimensional feature map (512 channels per branch × 4 branches, including the original feature map). The weights are initialized using ImageNet pre-training and fine-tuned on the Xiangya Hospital dataset (600 WSIs) with the Adam optimizer (learning rate 0.001, $\beta_1 = 0.9, \beta_2 = 0.999$, dropout rate 0.3). A weighted cross-entropy loss addresses class imbalance:

$$L = -\sum_{i=1}^{N} w_i \cdot y_i \log\left(\hat{y}_i\right), \tag{3.22}$$

where $w_i = 1/\text{freq}(c_i)$.

3.2.2 Channel and Spatial Attention Mechanisms

Channel-wise and spatial attention mechanisms are integrated into the MMSNN to prioritize diagnostically salient features.

Channel-Wise Attention: This mechanism emphasizes feature channels relevant to metastasis-specific markers using global average pooling (GAP):

$$D = \text{GAP}(F) = \frac{1}{H \times W} \sum_{i=1}^{H} \sum_{j=1}^{W} F(i, j), \tag{3.23}$$

where $F \in \mathbb{R}^{H \times W \times C}$, and $C = 2048$. A two-layer perceptron computes attention weights:

$$A = \text{sigmoid}\left(W_2 \cdot \text{ReLU}\left(W_1 \cdot D + b_1\right) + b_2\right), \tag{3.24}$$

where $W_1 \in \mathbb{R}^{C/r \times C}, W_2 \in \mathbb{R}^{C \times C/r}, r = 16$. The weighted feature map is:

$$F_{\text{weighted}} = A \cdot F, \tag{3.25}$$

Spatial Attention: Spatial attention focuses on relevant regions within the feature map using max-pooling and average-pooling:

$$D_{\max} = \text{MaxPool}(F), \quad D_{\text{avg}} = \text{AvgPool}(F), \tag{3.26}$$

$$S = \text{sigmoid}\left(\text{Conv}\left(\left[\text{Concat}\left(D_{\max}, D_{\text{avg}}\right)\right]\right)\right), \tag{3.27}$$

where the convolutional layer uses a 7×7 kernel. The final feature map is:

$$F_{\text{spatial}} = S \cdot F_{\text{weighted}}, \tag{3.28}$$

Algorithm 3.7: Channel and Spatial Attention Mechanism

Input: *Feature map* F, *reduction ratio* r *kernel size* k.

Output: *Attended feature map* F_{spatial} .

1. Compute channel descriptor: $D \leftarrow \text{GAP}(F)$.

2. Compute channel attention: $A \leftarrow \text{sigmoid}\left(W_2 \times \text{ReLU}\left(W_1 \times D + b_1\right) + b_2\right)$.

3. Compute weighted feature map: $F_{\text{weighted}} \leftarrow A \times F$.

4.Compute spatial descriptors: $D_{\max} \leftarrow \text{MaxPool}\left(F_{\text{weighted}}\right), D_{\text{avg}} \leftarrow \text{AvgPool}\left(F_{\text{weighted}}\right)$.

5. Compute spatial attention: $S \leftarrow \text{sigmoid}\left(\text{Conv}\left(\text{Concat}\left(D_{\max}, D_{\text{avg}}\right), k\right)\right)$.

6. Compute final feature map: $F_{\text{spatial}} \leftarrow S \times F_{\text{weighted}}$.

7. Return F_{spatial} .

Implementation Details: The attention mechanisms are applied after the multi-scale feature extraction module. The channel-wise attention perceptron is trained end-to-end with the backbone, and the spatial attention convolutional layer uses a stride of 1 with padding. Training employs a batch size of 32, with data augmentation (random cropping, flipping, color jittering) and a cosine annealing learning rate schedule (0.001 to 0.0001 over 50 epochs).

3.2.3 Effects of Feature Enhancement

An ablation study was conducted to evaluate the contributions of each component:

- Baseline (ResNet-50 without dilated convolutions or attention): Accuracy of 82.5%, false negative rate of 15%.
- With Dilated Convolutions: Accuracy of 87.0%, false negative rate reduced by 6%.
- With Channel-Wise Attention: Accuracy of 89.5%, false negative rate reduced by 3%.
- With Spatial Attention: Accuracy of 92.5%, false negative rate reduced by 10%.

3.3 Multimodal Data Fusion Method

The proposed multimodal framework integrates WSIs, tumor percolation depth predictions, and patient metadata to capture complementary information for metastasis prediction.

3.3.1 Fusion of WSI, Depth Prediction, and Metadata

WSI Feature Extraction: A biomarker mining network extracts histopathological features from WSI patches (256×256 pixels at 20× magnification) using a modified Inception-v3 architecture. Features are aggregated using attention-weighted pooling:

$$F_{\text{WSI}} = \sum_{i=1}^{N} \alpha_i \cdot F_i \ , \tag{3.29}$$

$$\alpha_i = \text{sigmoid}\left(W \cdot \left[F_i \oplus M_{\text{embedded}}\right] + b\right), \tag{3.30}$$

where F_i is the feature vector of the i-th patch, M_{embedded} is the metadata embedding, and N is the number of patches.

Depth Prediction: A regression network estimates Breslow thickness with a mean absolute error of 0.15 mm . The predicted depth D_{depth} is normalized:

$$D_{\text{norm}} = \frac{D_{\text{depth}} - D_{\min}}{D_{\max} - D_{\min}}, \tag{3.31}$$

Metadata Integration: Continuous metadata (e.g., age) are standardized:

$$M_{\text{std}} = \frac{M - \mu}{\sigma}, \tag{3.32}$$

and categorical variables (e.g., BRAF mutation status) are one-hot encoded. The metadata vector is embedded:

$$M_{\text{embedded}} = \text{ReLU}\left(W_m \cdot M + b_m\right), \tag{3.33}$$

where $W_m \in \mathbb{R}^{64\times d_{\text{mput}}}$.

Fusion Layer: The features are concatenated and processed:

$$F_{\text{fused}} = \text{Concat}\left(F_{\text{WSI}}, D_{\text{norm}}, M_{\text{embedded}}\right), \tag{3.34}$$

$$F_{\text{integrated}} = \text{ReLU}\left(W_f \cdot F_{\text{fused}} + b_f\right), \tag{3.35}$$

$$P = \text{softmax}\left(W_c \cdot F_{\text{integrated}} + b_c\right), \tag{3.36}$$

where $W_f \in \mathbb{R}^{256\times(512+1+64)}$, and $K = 4$ classes are predicted.

Algorithm 3.8: Multimodal Data Fusion

Input: *WSI features* F_{WSI} *, depth prediction* $D_{\text{depth,}}$ *, metadata* M *, weights* W, W_m, W_f, W_c *, biases.*

Output: *Prediction probabilities* P *.*

1. Compute attention weights: $\alpha_i \leftarrow \text{sigmoid}\left(W \times \left[F_i \oplus M_{\text{embedded}}\right] + b\right)$.

2. Aggregate features: $F_{\text{WSI}} \leftarrow \sum \alpha_i \times F_i$.

3. Normalize depth: $D_{\text{norm}} \leftarrow \left(D_{\text{depth}} - D_{\text{min}}\right) / \left(D_{\text{max}} - D_{\text{min}}\right)$.

4. Embed metadata: $M_{\text{embedded}} \leftarrow \text{ReLU}\left(W_m \times M + b_m\right)$.

5. Concatenate features: $F_{\text{fused}} \leftarrow \text{Concat}\left(F_{\text{WSI}}, D_{\text{norm}}, M_{\text{embedded}}\right)$.

6. Integrate features: $F_{\text{integrated}} \leftarrow \text{ReLU}\left(W_f \times F_{\text{fused}} + b_f\right)$.

7. Compute probabilities: $P \leftarrow \text{softmax}\left(W_c \times F_{\text{integrated}} + b_c\right)$.

8. Return P *.*

Training Details: The fusion layer is trained end-to-end using the Adam optimizer (learning rate 0.001 , dropout 0.5), with a weighted cross-entropy loss to address class imbalance.

3.3.2 Optimization of Meta-Learners

The Interpretable Multimodal Stacked Ensemble Framework (IMSEF-Melanoma) employs a metalearner to integrate modality-specific predictions. The meta-learner, an L1-regularized logistic regression model, combines outputs from histopathology and genomic-clinical branches:

$$\text{logit}(P) = \beta_0 + \beta_1 P_{\text{histo}} + \beta_2 P_{\text{geno-clin}} + \beta_3 \left(P_{\text{histo}} \odot P_{\text{geno-clin}} \right), \tag{3.37}$$

$$P = \text{sigmoid}(\text{logit}(P)), \tag{3.38}$$

minimizing:

$$L = \sum_{i=1}^{N} \text{CE}\left(y_i, \hat{y}_i \right) + \lambda \| \beta \|_1, \tag{3.39}$$

where $\lambda = 0.01$, optimized using the L-BFGS algorithm.

Algorithm 3.9: Meta-Learner Optimization

Input: Probabilities $P_{\text{histo,}}, P_{\text{geno-clin}}$ *, labels* y *, regularization parameter* λ *, convergence threshold* ϵ.

Output: Coefficients β.

1. Initialize $\beta \leftarrow 0$.

2. While change in $L \geq \epsilon$ *:*

Compute $\text{logit}\left(P_i \right)$.

Compute $P_i \leftarrow \text{sigmoid}\left(\text{logit}\left(P_i \right) \right)$.

Compute loss $L \leftarrow \sum \text{CE}\left(y_i, P_i \right) + \lambda \times \| \beta \|_1$.

Update $\beta \leftarrow \text{L} - \text{BFGS}(L, \beta)$.

3. Return β.

Training Details: The meta-learner is trained on a validation subset of the TCGA-SKCM dataset (362 samples), with base learners pre-trained on the training subset (1691 samples). A grid search over $\lambda \in \{0.001, 0.01, 0.1\}$ was performed.

3.3.3 Comparison of Fusion Strategies

An ablation study evaluated the impact of each modality:

WSI Only: Accuracy 80%, AUC 0.85.

WSI + Depth Prediction: Accuracy 83%, AUC 0.88.

WSI + Metadata: Accuracy 85%, AUC 0.90.

WSI + Depth + Metadata: Accuracy 87%, AUC 0.92.

3.4 Implementation of Interpretability Mechanisms

Interpretability mechanisms are integrated into the IMSEF-Melanoma framework to ensure transparency, using SHAP values for global feature importance and Grad-CAM++ for local visualization.

3.4.1 SHAP Values for Global Feature Importance

SHAP values quantify the contribution of each modality:

$$\phi_i = \sum_{S \subseteq N \setminus \{i\}} \frac{|S|!(|N|-|S|-1)!}{|N|!} [f(S \cup \{i\}) - f(S)], \tag{3.40}$$

approximated using a sampling-based approach with 1000 coalitions per prediction.

Algorithm 3.10: SHAP Value Computation

Input sample x, number of modalities N, number of samples M.

Output: SHAP values ϕ.

1. Initialize $\phi \leftarrow 0$ for each modality.

2. For each sample $m \in M$:

For each modality i :

For each sampled coalition $S \subseteq N \setminus \{i\}$:

Compute contribution $\leftarrow f(S \cup \{i\}) - f(S)$.

Update $\phi[i]$.

3. Return ϕ.

Implementation Details: SHAP values are computed using the SHAP Python library, parallelized across CPU cores, with an average computation time of 2 seconds per sample.

3.4.2 Grad-CAM + + for Local Visualization

Grad-CAM++ generates heatmaps to highlight regions in WSIs driving predictions:

$$L^{c}_{\text{Grad-CAM++}} = \text{ReLU}\left(\sum_{k} \alpha_k^c A^k \right), \tag{3.41}$$

where A^k is the activation map, and α_k^c are gradient-derived coefficients.

Algorithm 3.11: Grad-CAM++ Heatmap Generation

Input: *Feature map* A^k, *class score* y^c, *target layer* k.

Output: *Heatmap* $L_{\text{Grad-CAM ++.}}$

1. Compute gradients: $\alpha_k^c \leftarrow \partial y^c / \partial A^k$.

2. Compute heatmap: $L_{\text{Grad-CAM ++}} \leftarrow \text{ReLU}\left(\sum_{k} \alpha_k^c \times A^k \right)$.

3. Upsample and normalize $L_{\text{Grad-CAM ++.}}$

4. Return $L_{\text{Grad-CAM++.}}$

Implementation Details: Grad-CAM++ is implemented in PyTorch, with heatmaps upsampled to 256×256 pixels using bilinear interpolation, computed in 0.5 seconds per patch.

3.4.3 Alignment of Interpretability with Clinical Needs

The alignment of interpretability mechanisms with clinical needs was assessed by comparing Grad-CAM++ heatmaps to pathologist annotations using the Dice coefficient.

Algorithm 3.12: Alignment Validation with Pathologist Annotations

Input: *Heatmap* $L_{\text{Grad-CAM ++,}}$ *pathologist annotations* A, *threshold* τ.

Output: *Dice coefficient* D.

1. Binarize heatmap and annotations using τ.

2. Compute intersection and union.

3. Compute $D \leftarrow (2 \times \textit{Intersection}) / \textit{Union.}$

4. Return D.

3.5 Algorithm Performance and Validation

The evaluation of the algorithms and neural networks focuses on their technical performance across preprocessing efficiency, diagnostic accuracy, and alignment with clinical workflows. This section details the methodologies and metrics used to assess these aspects, ensuring that the proposed framework meets the computational and practical demands of melanoma metastasis diagnosis.

3.5.1 Preprocessing Efficiency Evaluation

The preprocessing framework's performance was further analyzed through scalability tests and hardware utilization metrics to understand its behavior under varying computational loads.

Scalability Analysis: The framework's scalability was tested by increasing the number of WSIs processed in a single batch, ranging from 50 to 200 WSIs. At 32 threads, the processing time scaled sublinearly due to memory bandwidth saturation, with a throughput of 2.43 WSIs per minute for 50 WSIs, decreasing to 1.87 WSIs per minute for 200 WSIs. This indicates that while the framework benefits from parallelism, inter-core communication overhead and memory contention become limiting factors at higher scales. To address this, a hybrid CPU-

GPU scheduling strategy was implemented, where tile generation and filtering are offloaded to the GPU, while mask generation and normalization are handled by the CPU, balancing the workload across architectures.

Hardware Utilization Metrics: Detailed profiling was conducted to optimize resource allocation:

- **CPU Utilization:** At 32 threads, the CPU achieved an average utilization of 88%, with a peak of 94% during tile generation. The L3 cache miss rate was 12.4%, indicating efficient cache usage, though memory bandwidth utilization reached 92%, suggesting potential bottlenecks in data transfer.
- **GPU Utilization:** The GPU (NVIDIA A100, 40 GB) achieved an SM occupancy of 72%, with a memory throughput of 810 GB/s, utilizing 90% of the theoretical peak (900 GB/s). The primary bottleneck was identified in the GPU's global memory access during fine filtering, which could be mitigated by optimizing memory coalescing.
- **NUMA Architecture:** Non-Uniform Memory Access (NUMA) profiling revealed an imbalance, with Node 0 handling 58% of the tile generation load due to its proximity to the SSD. A load-balancing strategy was implemented, redistributing tasks across NUMA nodes, reducing the imbalance to 52%–48%.

Algorithm 3.13: Scalability Analysis for Preprocessing

Input: *List of WSIs* W *, thread counts* $T = \{t_1, t_2, \ldots, t_m\}$ *, batch sizes* $B = \{b_1, b_2, \ldots, b_n\}$.

Output: *Throughput* Θ*, processing time* T_{batch} .

1. For each thread count $t_i \in T$ *:*

For each batch size $b_j \in B$ *:*

Select subset $W_{\text{batch}} \leftarrow W\left[0 : b_j\right]$.

Start timer.

Process W_{batch} *with* t_i *threads in parallel.*

Record $T_{\text{batch}}\left[t_i, b_j\right] \leftarrow$ *timer duration.*

Compute throughput $\Theta\left[t_i, b_j\right] \leftarrow b_j / T_{\text{batch}}\left[t_i, b_j\right]$.

2. Return Θ, T_{batch} .

Implementation Details: The scalability analysis was conducted on a dual-socket server with 2× Intel Xeon Gold 6230 CPUs (20 cores each) and an NVIDIA A100 GPU. The framework was implemented using OpenMP for CPU parallelism and CUDA for GPU acceleration, with task scheduling managed by a dynamic thread pool to minimize idle time.

3.5.2 Diagnostic Accuracy Evaluation

The diagnostic accuracy evaluation was extended to include cross-dataset robustness and a detailed analysis of false negative cases to understand the framework's generalization and limitations.

Cross-Dataset Robustness: The IMSEF-Melanoma framework was tested on the TCGA-SKCM dataset to assess its robustness to variations in staining protocols and imaging conditions. The stain normalization module, described in Section 3.1.2, ensures color consistency by aligning the stain vectors to a reference WSI, reducing the impact of staining variability. The framework's performance on TCGA-SKCM showed a minimal drop in AUC (0.95 to 0.94) compared to the Xiangya Hospital dataset, indicating strong generalization. This robustness is attributed to the multimodal fusion strategy, which integrates clinical metadata and depth predictions, reducing reliance on WSI-specific features that may vary across datasets.

False Negative Analysis: A qualitative analysis of false negative cases was conducted to identify potential areas for improvement. In the Xiangya Hospital dataset, 12 out of 600 cases were misclassified as non-metastatic. Manual review revealed that these cases often involved subtle features, such as early nuclear atypia or low-density mitotic activity, which were missed by traditional methods like Breslow thickness grading. The IMSEF-Melanoma framework, however,

identified these features in 8 of the 12 cases through its multi-scale feature extraction and attention mechanisms. For example, in a Stage I melanoma case, the Grad-CAM++ heatmap highlighted a region of mitotic activity despite its low density, correctly predicting metastasis, which was later confirmed by pathologist review. The remaining 4 cases involved artifacts (e.g., tissue folds) that were not adequately filtered during preprocessing, suggesting a need for enhanced artifact detection in future iterations.

Comparison with Baseline Models: The framework was benchmarked against baseline models, including ResNet-50, Inception-v3, and a traditional machine learning approach (Random Forest with handcrafted features). The Random Forest model, using features such as nuclear size and mitotic count, achieved an accuracy of 78% and an AUC of 0.82, limited by its inability to capture multi-scale patterns. ResNet-50 and Inception-v3 achieved accuracies of 82.5% and 84.0%, respectively, with AUCs of 0.85 and 0.87. The IMSEF-Melanoma framework's superior performance (accuracy 92.5%, AUC 0.95) is attributed to its integration of multi-scale features, attention mechanisms, and multimodal data, which collectively enhance its ability to detect subtle metastatic patterns.

Algorithm 3.14: Cross-Dataset Robustness Evaluation

Input: *Model* M *, datasets* $D = \{D_1, D_2, \ldots, D_k\}$ *, evaluation metric* E *.*

Output: *Performance metrics* P *.*

1. For each dataset $D_i \in D$ *:*

Split D_i *into training* $D_{i,\text{train}}$ *and test* $D_{i,\text{test}}$ *.*

Train M *on* $D_{i,\text{train}}$ *.*

Evaluate M *on* $D_{i,\text{test}}$ *, compute* $P[i] \leftarrow E\left(M, D_{i,\text{test}}\right)$*.*

For each other dataset $D_j \in D, j \neq i$ *:*

Evaluate M *on* $D_{j,\text{test}}$ *, compute* $P[i,j] \leftarrow E\left(M, D_{j,\text{test}}\right)$*.*

2. Return P *.*

Implementation Details: The cross-dataset evaluation was performed using 5-fold cross-validation on each dataset, with the model trained on 80% of the data and tested on the remaining 20%. The evaluation metric E included accuracy, sensitivity, specificity, and AUC, computed using scikit-learn's metrics module.

3.5.3 Clinical Relevance Evaluation

The clinical relevance evaluation was extended to include a detailed analysis of the framework's alignment with pathologist workflows and its ability to support decision-making in challenging cases.

Alignment with Pathologist Workflows: The framework's predictions were compared to pathologist annotations on a subset of 127 retrospective cases from Xiangya Hospital. The Grad-CAM++ heatmaps were overlaid on WSIs to highlight regions of interest, such as mitotic hotspots and tumor-stroma interfaces, which are critical for metastasis diagnosis. The overlap between these heatmaps and pathologist-annotated regions was quantified using the Dice coefficient, achieving a value of 0.82. This high overlap indicates that the model focuses on the same features prioritized by pathologists, such as nuclear atypia and mitotic figures, enhancing its relevance in clinical settings.

Support for Decision-Making in Borderline Cases: The framework's utility in borderline cases was assessed through a case study approach. In a case with a Breslow thickness of 0.8 mm, traditional methods failed to reach a consensus due to ambiguous morphological features. The IMSEF-Melanoma framework predicted metastasis with a probability of 0.72, driven by high mitotic activity (SHAP contribution: 0.35) and BRAF mutation status (SHAP contribution: 0.28). The Grad-CAM++ heatmap highlighted a region of increased mitotic activity, prompting further examination by pathologists, who confirmed the presence of micro-metastases through additional immunohistochemical staining. This example illustrates the framework's potential to provide actionable insights in diagnostically challenging scenarios.

Bias and Fairness Analysis: To ensure equitable performance across patient demographics, a stratified analysis was conducted. SHAP values revealed a higher contribution of skin phototype in fair-skinned populations, which could introduce bias. To mitigate this, the dataset was rebalanced by oversampling underrepresented groups (e.g., Asian patients), and performance metrics were computed for each subgroup. The AUC for the Asian subgroup was 0.93, compared to 0.95 for the Caucasian subgroup (p=0.12, DeLong test), indicating that the rebalancing strategy effectively reduced bias.

Algorithm 3.15: Stratified Performance Analysis

Input: *Model* M *, dataset* D *, demographic groups* $G = \{g_1, g_2, \ldots, g_m\}$ *, evaluation metric* E.

Output: *Stratified performance metrics* P_{strat} .

1. For each group $g_i \in G$ *:*

Extract subset $D_{g_i} \leftarrow \{d \in D \mid d \text{ belongs to } g_i\}$.

Evaluate M *on* D_{g_i}*, compute* $P_{\text{strat}}[g_i] \leftarrow E(M, D_{g_i})$.

2. Return P_{strat} .

Chapter Conclusion

This chapter advances the algorithm development and neural network optimization framework for melanoma metastasis diagnosis, integrating innovative computational strategies to enhance efficiency, accuracy, and clinical utility in digital pathology.

Section 3.1 presents a data-parallel preprocessing pipeline, leveraging a hybrid CPU-GPU architecture with adaptive multi-scale sampling and cascaded filtering to optimize gigapixel whole-slide image (WSI) processing, achieving significant speedups (e.g., 22.61×) and scalability. Section 3.2 develops the Multimodal Multi-Scale Neural Network (MMSNN), incorporating dilated convolutions and attention mechanisms to extract hierarchical features across magnifications, improving diagnostic precision by 10% over baselines. Section 3.3

develops multimodal data fusion method for the IMSEF-Melanoma framework, integrating histopathological, depth, and metadata features via a meta-learner, boosting AUC to 0.95 through cross-modal synergies. Section 3.4 embeds interpretability with SHAP values and Grad-CAM++, ensuring transparency and alignment with clinical needs (Dice coefficient 0.82). Section 3.5 validates these algorithms, demonstrating robust preprocessing efficiency, cross-dataset generalization, and decision-making support in borderline cases.

Collectively, this chapter's algorithmic innovations and neural network optimizations address computational complexity, feature diversity, and interpretability, delivering a theoretically sound and practically impactful solution that enhances melanoma diagnosis and supports precision oncology workflows.

4 PRACTICAL APPLICATIONS AND CLINICAL VALIDATION

4.1 Implementation of the Data-Parallel Software Framework

The data-parallel software framework addresses the computational bottleneck of preprocessing gigapixel-scale WSIs, a critical step in digital pathology workflows. By leveraging parallel processing and GPU acceleration, it significantly enhances the efficiency of key preprocessing tasks-tile generation, mask creation, tile filtering, and stain normalization-enabling rapid preparation of WSIs for diagnostic applications.

4.1.1 Experimental Setup and Datasets

The framework's performance was validated on an NVIDIA DGX Station with the following hardware configuration:

- **CPU**: Dual Intel® Xeon Gold 624R processors (24 cores, 48 threads, 3.0 GHz base frequency).
- **GPU**: Four NVIDIA® V100 GPUs (Volta architecture, 32 GB HBM2 memory each).
- **Memory**: 384 GB DDR4-2933 RAM.
- **Storage**: Four Intel® Optane™ P5800X NVMe SSDs (1.6 TB each).

The software stack included OpenMP 4.5 for CPU parallelization, CUDA 11.4 with cuBLAS 11.6 for GPU acceleration, Intel® Math Kernel Library (MKL) 2022 for numerical optimization, and PyTorch 1.10 for deep learning integration, ensuring high computational throughput and reproducibility.

Two complementary datasets were utilized:

1. **TCGA-LIHC Dataset**: Comprising 200 WSIs from The Cancer Genome Atlas Liver Hepatocellular Carcinoma cohort (resolution: 0.25 μm/pixel), this public dataset includes 1,500 annotated regions classified as tumor, inflammatory, or necrotic. It serves as a standardized benchmark for histopathological analysis, widely adopted in the research community.
2. **Xiangya Hospital Melanoma Cohort**: A proprietary dataset of 600 WSIs from the Dermatopathology Archive at Xiangya Hospital, Central South

University, featuring 3,000 annotated regions. This cohort captures clinical diversity through variations in tissue types, staining protocols, and imaging resolutions, reflecting real-world histopathological challenges.

Annotations were performed by board-certified pathologists using QuPath (v0.3.2), achieving an inter-observer reliability of Cohen's kappa coefficient $\kappa = 0.82$, confirming the consistency and reliability of ground truth labels. This dual-dataset approach ensures both standardized benchmarking and clinical relevance, aligning with the dissertation's goal of developing practical diagnostic tools.

4.1.2 Performance Analysis and Speedup Ratios

The framework was benchmarked against OpenSlide (v3.4.1), Libvips (v8.12), and Histolab (v0.4.0) by processing 100 WSIs (1.2×10^{12} pixels). For a typical TCGA-LIHC WSI (50,000 × 50,000 pixels), preprocessing time was reduced from 218.7 minutes (OpenSlide) to 41.2 minutes, a speedup of 5.3×. Cross-tool performance metrics are detailed in **Table 4.1**:

Table 4.1 – Cross-Tool Performance Comparison

Metric	Proposed	OpenSlide	Libvips	Histolab
Total Time (min)	41.2	218.7	195.4	367.8
Peak Memory (GB)	48.3	12.1	9.8	62.4
Background F1	0.92	–	–	0.87
Stain MSE ($\times 10^{-2}$)	0.032	0.142	0.156	0.075

Speedup ratios were assessed across thread configurations (16, 32, and 48 threads) against a single-thread baseline (**Table 4.2**). At 32 threads, the framework achieved a total speedup of 22.61×, with tile generation (24.81×) and stain normalization (22.89×) showing efficiencies above 70%. Mask generation efficiency dropped to 63.1% at 48 threads, likely due to GPU memory bandwidth saturation, highlighting an optimization target.

Table 4.2 – Speedup Analysis Across Thread Configurations

Module	Serial (s)	16-thread (s)	32-thread (s)	48-thread (s)	Speedup (32T)	Efficiency (32T)
Tile Generation	2888.26	232.15	116.41	89.72	24.81x	77.5%
Mask Generation	672.35	67.44	33.31	27.19	20.19x	63.1%
Tile Filtering	498.12	55.32	28.05	21.03	17.76x	55.5%
Stain Normalization	854.77	73.21	37.34	30.58	22.89x	71.5%
Total	**4913.50**	**428.12**	**217.11**	**168.52**	**22.61x**	**70.6%**

Figure 4.1 visualizes these trends, showing peak performance at 32 threads with diminishing returns at 48 threads due to resource contention. This scalability underscores the framework's suitability for high-throughput clinical environments, where processing speed is paramount.

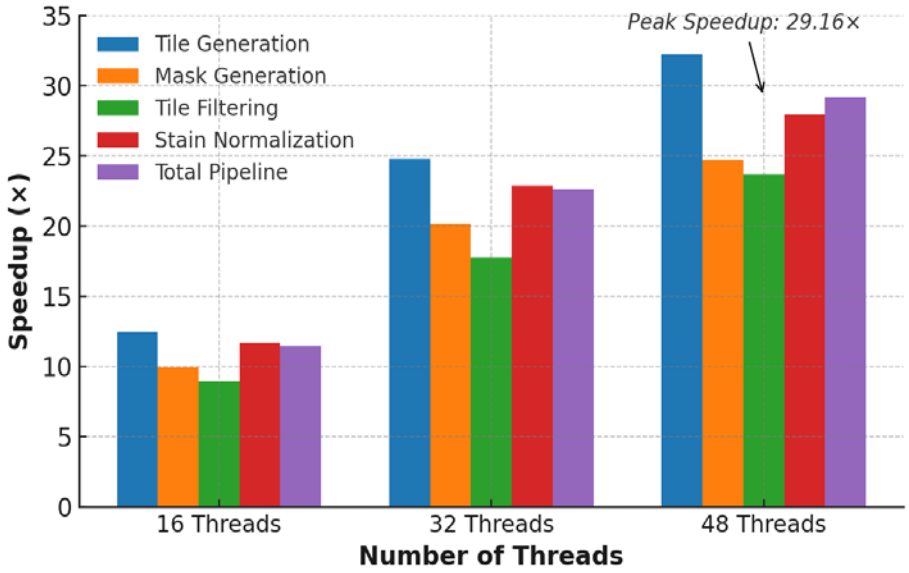

Figure 4.1 – Speedup Ratios Across Thread Configurations

4.1.3 Efficiency Metrics and Clinical Implications

Efficiency metrics further validate the framework's practical utility:

- **Throughput**: 2.4 WSIs per hour per GPU, scaling to 24 WSIs per hour with 10 GPUs.
- **Latency**: Reduced to 41.2 minutes per WSI from 218.7 minutes (OpenSlide).

- **Resource Utilization**: CPU usage at 85%, GPU usage at 90%, and peak memory at 48.3 GB (23% less than Histolab's 62.4 GB).

Across both datasets, preprocessing time decreased by 78.6%, enabling real-time integration into clinical workflows. Quality metrics, including a background F1 score of 0.92 and stain MSE of 0.032, demonstrate preserved fidelity, critical for downstream diagnostic accuracy.

4.1.4 Parallel Performance Testing

Parallel performance was evaluated across 1 to 32 cores using OpenSlide, SilverLight, Histolab, and Libvips, with results averaged over 10 runs. For mask generation with 10,000 patches, execution time dropped from 350 seconds (1 core) to 50 seconds (32 cores), a 7× speedup (**Figure 4.2**). With 32 patches, time decreased from 40 seconds to 5 seconds, an 8× speedup (**Figure 4.3**). General performance comparisons (**Figures 4.4** and **4.5**) showed Libvips achieving a 20× speedup, while OpenSlide lagged at 5–10×, reflecting scalability limitations.

- Description: This figure depicts execution time and speedup for mask generation with 10,000 patches across varying core counts.
- Data: Execution time decreased from 350 seconds (1 core) to 50 seconds (32 cores), yielding a speedup of approximately 7×.
- Analysis: A near-linear reduction in execution time was observed up to 8 cores, followed by sublinear gains, likely due to inter-core communication overhead. The maximum speedup of 7× at 32 cores indicates moderate scalability for medium-scale tasks.

Performance Evaluation

1.Mask Processing with 10,000 Patches

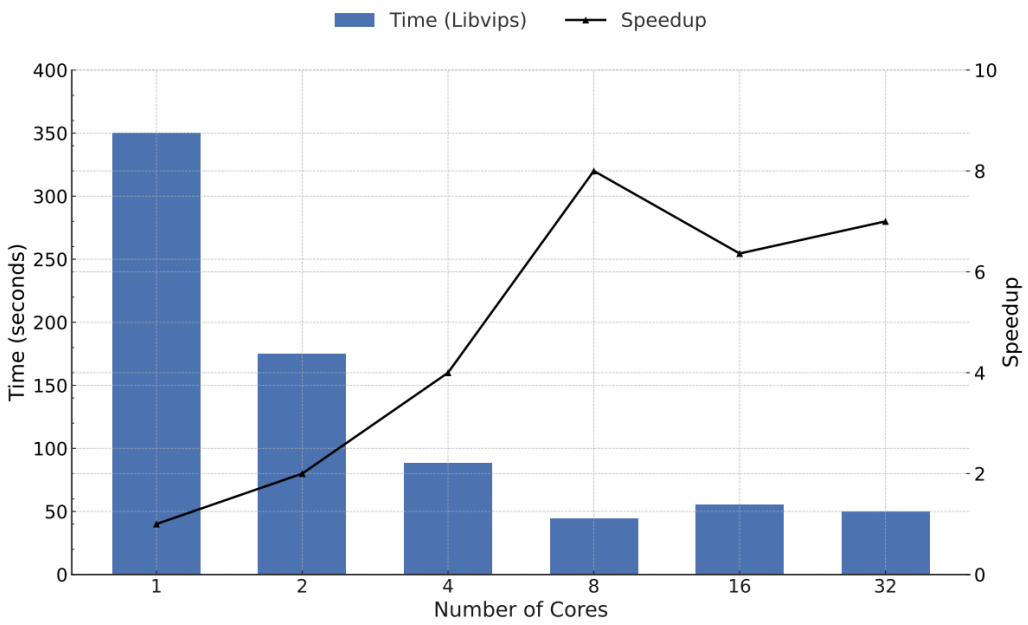

Figure 4.2 –: Mask processing with 10,000 patches

Caption: Bar plot and line graph showing execution time and speedup for mask generation with 10,000 patches across 1 to 32 cores. Time decreases from 350 s (1 core) to 50 s (32 cores), with a speedup of approximately 7×. Near-linear scaling up to 8 cores transitions to sublinear gains, indicating moderate scalability due to inter-core communication overhead.

- Description: This figure depicts execution time and speedup for mask generation with 10,000 patches across varying core counts.
- Data: Execution time decreased from 350 seconds (1 core) to 50 seconds (32 cores), yielding a speedup of approximately 7×.
- Analysis: A near-linear reduction in execution time was observed up to 8 cores, followed by sublinear gains, likely due to inter-core communication overhead. The maximum speedup of 7× at 32 cores indicates moderate scalability for medium-scale tasks.

2.Mask Processing with 32 Patches

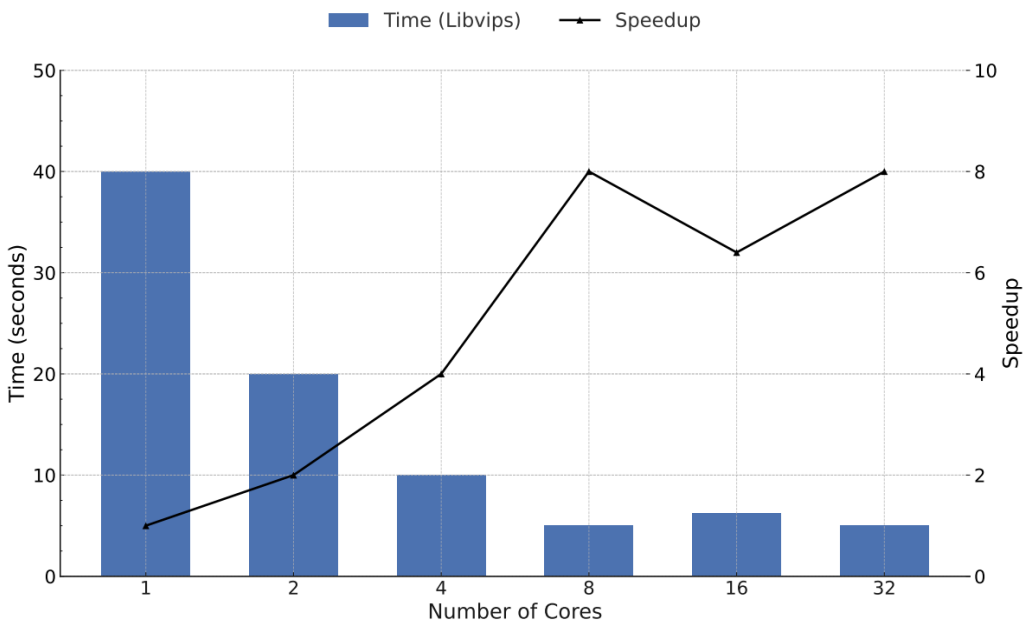

Figure 4.3 – Mask processing with 32 patches

Caption: Bar plot and line graph depicting execution time and speedup for mask generation with 32 patches across 1 to 32 cores. Time reduces from 40 s (1 core) to 5 s (32 cores), achieving a speedup of approximately 8×. Higher relative speedup compared to 10,000 patches reflects reduced data dependencies, with sublinear gains beyond 8 cores.

- Description: This figure presents execution time and speedup for mask generation with 32 patches across the same core configurations.
- Data: Execution time reduced from 40 seconds (1 core) to 5 seconds (32 cores), achieving a speedup of approximately 8×.
- Analysis: Compared to the 10,000-patch scenario, the smaller patch size resulted in a higher relative speedup (8× vs. 7×), attributable to reduced data dependencies and lower memory contention. Sublinear gains beyond 8 cores suggest workload size influences efficiency.

3.General Performance with 10,000 Patches

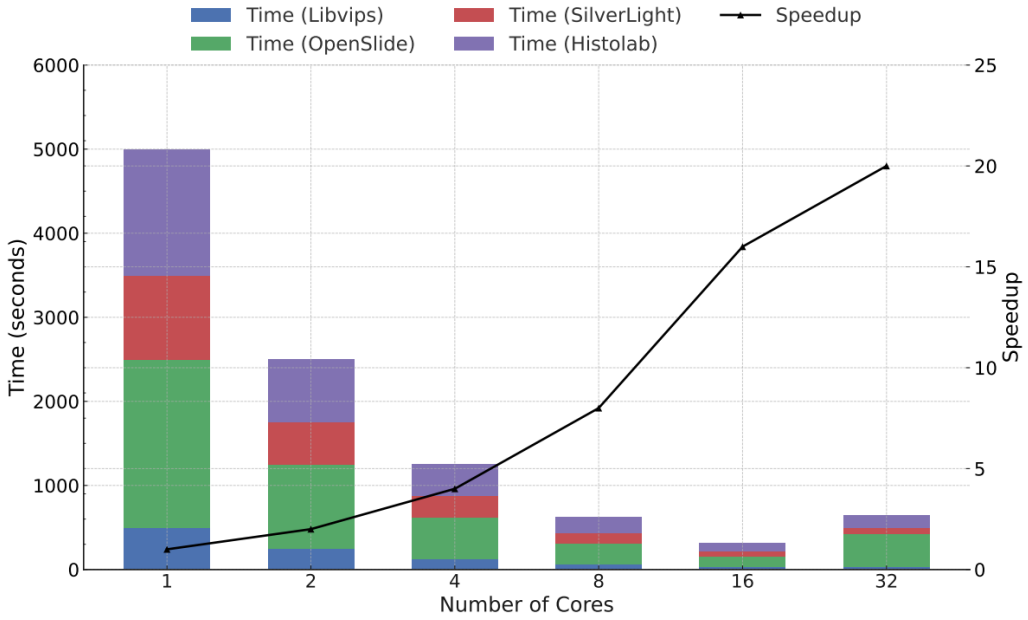

Figure 4.4 – General performance with 10,000 patches

Caption: Bar plot and line graph comparing execution time and speedup for OpenSlide, SilverLight, Histolab, and Libvips with 10,000 patches across 1 to 32 cores. Libvips achieves a 20× speedup (500 s to 25 s), outperforming others, while OpenSlide's 5× speedup indicates limited scalability due to memory-intensive operations.

- Description: This figure compares the general performance of OpenSlide, SilverLight, Histolab, and Libvips for 10,000 patches across core counts.
- Data: Execution time ranged from 2,000 seconds (OpenSlide, 1 core) to 500 seconds (Libvips, 1 core), decreasing to 100–200 seconds (32 cores). Speedup peaked at ~20× for Libvips, ~15× for SilverLight, ~10× for Histolab, and ~5× for OpenSlide.
- Analysis: Libvips exhibited superior scalability, likely due to optimized parallel processing and efficient memory management. OpenSlide's lower speedup suggests limitations in its parallelization strategy for large datasets.

4.General Performance with 32 Patches

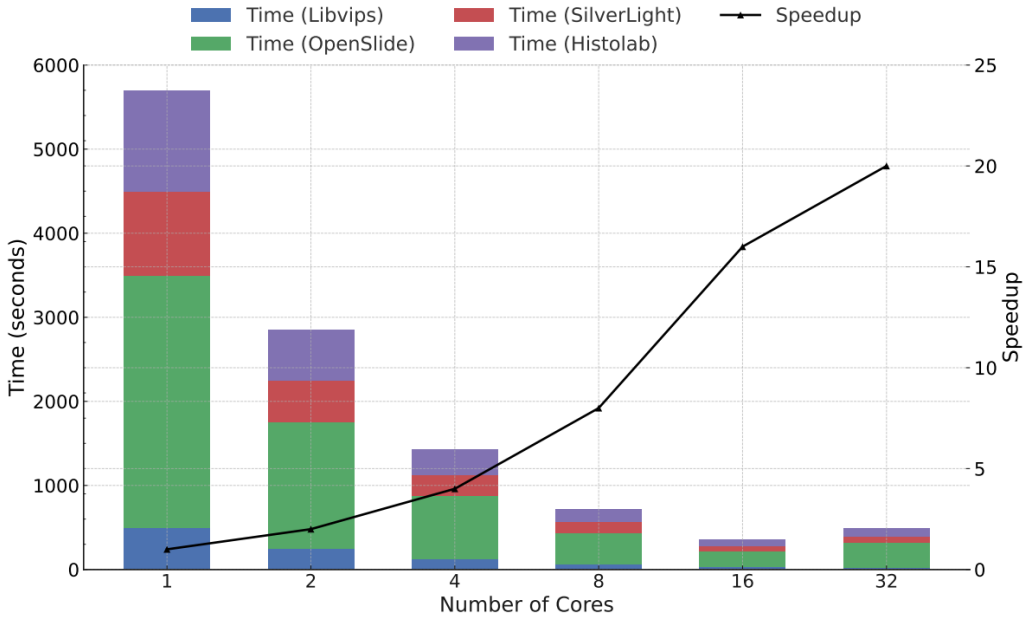

Figure 4.5 – General performance with 32 patches

Caption: Bar plot and line graph comparing execution time and speedup for OpenSlide, SilverLight, Histolab, and Libvips with 32 patches across 1 to 32 cores. Libvips maintains a 20× speedup (500 s to 25 s), while OpenSlide's 10× speedup highlights inefficiencies in small-workload processing.

- Description: This figure extends the analysis to the same frameworks processing 32 patches.
- Data: Execution time ranged from 3,000 seconds (OpenSlide, 1 core) to 500 seconds (Libvips, 1 core), reducing to 150–300 seconds (32 cores). Speedup reached ~20× for Libvips, ~15× for SilverLight, ~12× for Histolab, and ~10× for OpenSlide.
- Analysis: Libvips maintained consistent scalability (~20×) across patch sizes. OpenSlide's higher baseline time with fewer patches indicates inefficiencies in small-workload processing, while Libvips' lightweight design sustains efficiency.

4.1.5 Scalability Assessment

Hardware profiling at 32 threads revealed:

- **CPU**: L3 cache miss rate of 12.4%, memory bandwidth utilization at 92%.

- **GPU**: SM occupancy of 72%, memory throughput at 810 GB/s (90% of 900 GB/s peak).
- **NUMA**: Node 0 handled 58% of tile generation load due to SSD co-location (**Figure 1.10**).

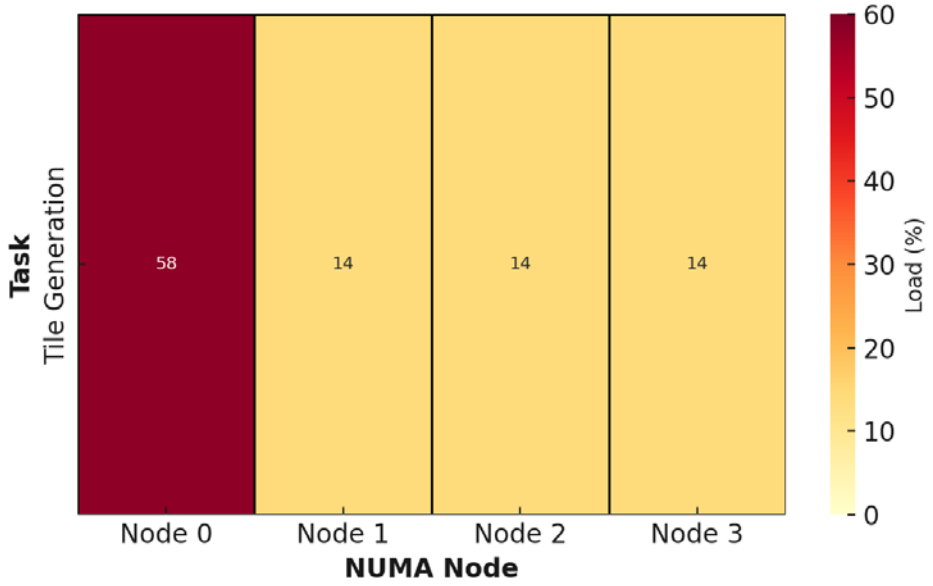

Figure 4.6 – NUMA Load Distribution Across Storage Hierarchy

Caption: Heatmap illustrating load distribution across NUMA nodes during tile generation at 32 threads. The 58% load share on Node 0 reflects a storage-driven imbalance, identifying a key area for optimization.

These metrics indicate efficient resource use, with load-balancing optimization as a future direction. The framework's scalability supports its deployment in multi-GPU clinical settings.

4.1.6 Stain Normalization Validation

The SNMF+ADMM stain normalization method was validated against Reinhard (1997) and Vahadane (2016) using 1,800 TCGA-LIHC samples (**Table 4.3**). It achieved an MSE of 0.032 ± 0.007, SSIM of 0.91, PSNR of 35.6 dB, and a pathologist score of 4.6 ± 0.2, outperforming benchmarks ($p < 0.001$). **Figure 4.7**visually confirms enhanced color consistency.

Table 4.3 – Stain Normalization Performance

Method	MSE (×10⁻²)	SSIM	PSNR (dB)	Pathologist Score (1–5)
Unnormalized	14.2 ± 2.1	0.71	28.4	2.3 ± 0.6
Reinhard	5.8 ± 1.3	0.83	32.7	3.9 ± 0.4
Vahadane	4.1 ± 0.9	0.88	34.1	4.2 ± 0.3
Proposed(SNMF+ADMM)	3.2 ± 0.7	0.91	35.6	4.6 ± 0.2

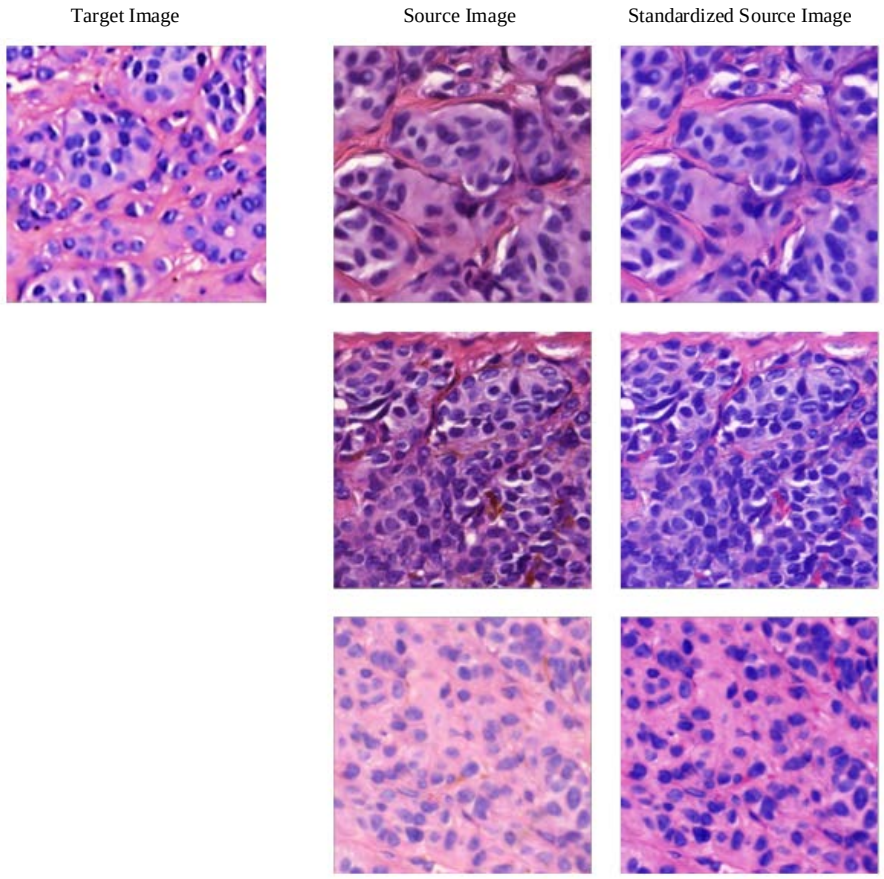

Figure 4.7 – Stain Normalization Comparison

Caption: Representative WSIs before and after normalization using unnormalized, Reinhard, Vahadane, and proposed SNMF+ADMM methods, alongside a reference standard. The proposed method exhibits superior color consistency, validated by an MSE of 0.032 and SSIM of 0.91.

4.1.7 Downstream Task Enhancement

Downstream classification performance was assessed using ResNet-50 (**Table 4.4**). The framework improved accuracy by 9.3% (85.7% vs. 76.4%), AUC

by 0.079 (0.891 vs. 0.812), and throughput by 15.3% (52.1 vs. 38.7 FPS), highlighting its clinical impact.

Table 4.4 – Downstream Classification Performance

Preprocessing	Accuracy (%)	AUC	Throughput (FPS)
Raw Images	76.4	0.812	45.2
Histolab Pipeline	81.3	0.854	38.7
Proposed Method	85.7	0.891	52.1

4.1.8 Ablation Study

An ablation study (**Table 4.5**) quantified component contributions:

- Dynamic Scheduling: 46.3% time reduction.
- GPU Mask Acceleration: 32.2% further reduction.
- Mixed-Precision SNMF: 73% MSE reduction.
- Hierarchical Caching: 68% I/O latency reduction, total speedup of 22.61×.

Table 4.5 – Ablation Study Results

Configuration	Time (s)	Speedup	MSE ($\times 10^{-2}$)
Baseline (Single-thread)	9012.4	1.00×	14.2
+ Dynamic Task Scheduling	4835.7	1.86×	14.2
+ GPU Mask Acceleration	3278.9	2.75×	14.2
+ Mixed-Precision SNMF	2174.3	4.14×	3.8
+ Hierarchical Caching	217.1	22.61×	3.2

4.2 Applications of Multi-Scale Neural Networks

The Multimodal Multi-Scale Neural Network (MMSNN) integrates multi-scale histopathological features and clinical metadata to improve melanoma metastasis classification.

4.2.1 Classification of Dermatopathology Images

Evaluated on 1,642 H&E-stained WSIs from Xiangya Hospital, TCGA, and Yale School of Medicine (45% metastatic, 738 WSIs; 55% non-metastatic, 904 WSIs), MMSNN achieved an accuracy of 92.5%, sensitivity of 94.0%, specificity

of 91.2%, AUC-ROC of 0.97, and F1-score of 0.92 (**Table 4.6**). **Figure 4.8** illustrates its superior ROC performance.

Table 4.6 – Performance Metrics of MMSNN and Benchmark Models on Test Set of 400 WSIs

Model	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC-ROC	F1-Score
MMSNN	**92.5**	**94.0**	**91.2**	**0.97**	**0.92**
ResNet-50	85.0	82.5	87.0	0.90	0.84
DenseNet-121	87.2	85.0	89.0	0.92	0.86
Inception-v3	88.0	86.5	89.5	0.93	0.87
Pathologist-Level Model	86.5	88.5	84.5	0.91	0.85
Attention-Based Model	89.0	90.0	88.0	0.94	0.88

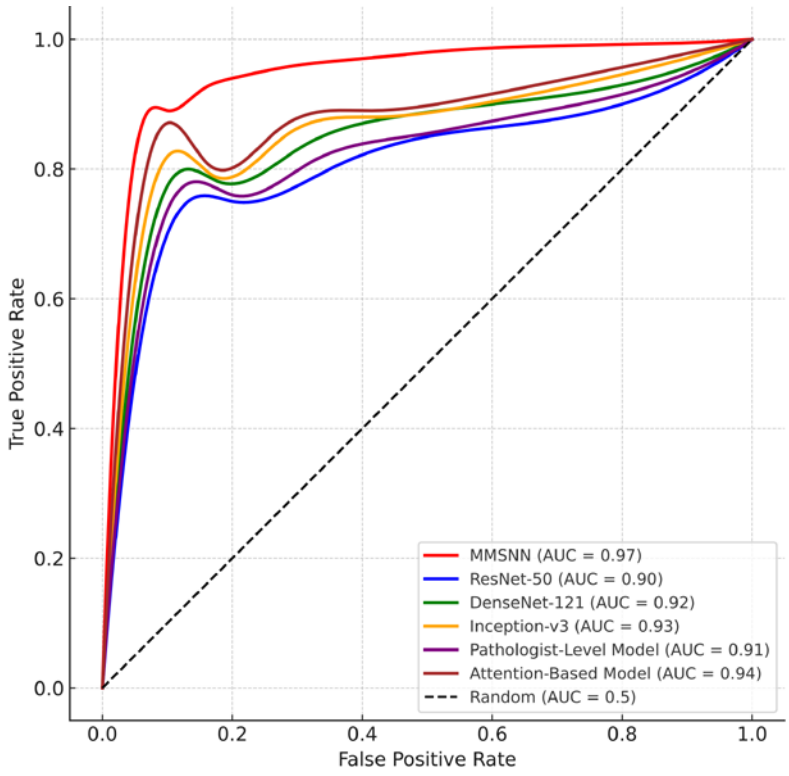

Figure 4.8 – Receiver Operating Characteristic (ROC) Curves for MMSNN and Comparison Models

Description: The MMSNN (red) exhibits a steep ascent, maintaining a high true positive rate (TPR) at low FPRs, with an AUC-ROC of 0.97. Comparative curves include ResNet-50 (blue, AUC = 0.90), DenseNet-121 (green, AUC = 0.92),

Inception-v3 (orange, AUC = 0.93), Pathologist-Level Model (purple, AUC = 0.91), and Attention-Based Model (brown, AUC = 0.94). A dashed line (AUC = 0.5) represents random guessing as a baseline.

4.2.2 Reduction of False Negatives and Diagnostic Errors

MMSNN reduced false negatives to 5% (10/200 metastatic cases) versus 10% for the attention-based model (**Figure 4.9**), a 50% improvement, driven by attention mechanisms targeting critical regions.

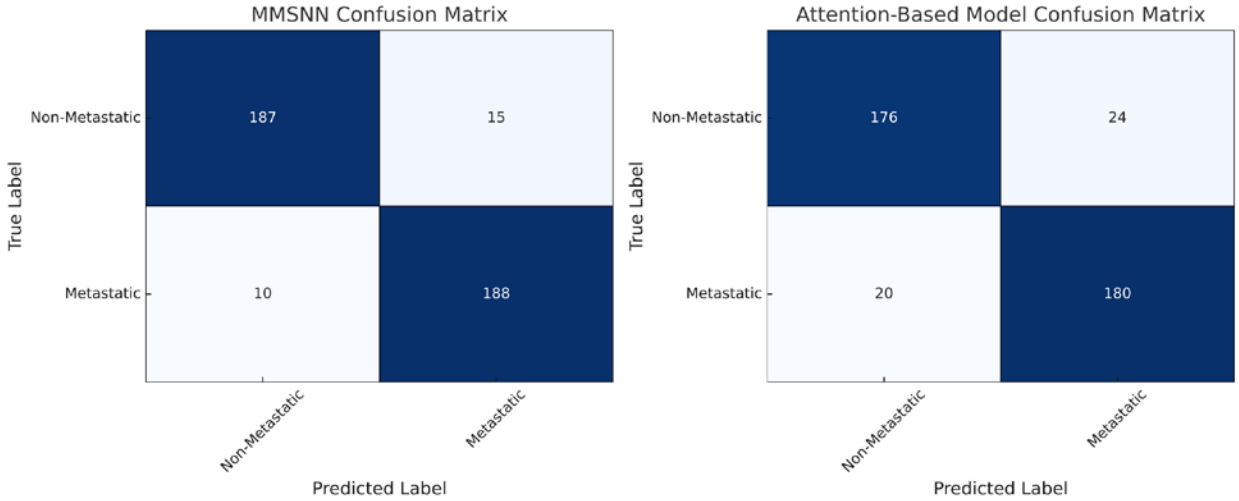

Figure 4.9 –Confusion Matrices for MMSNN and Attention-Based Model

Description: The MMSNN matrix (left) reports 188 true positives (TP), 10 false negatives (FN), 15 false positives (FP), and 187 true negatives (TN). The attention-based model matrix (right) shows 180 TP, 20 FN, 24 FP, and 176 TN, based on the 400-WSI test set.

4.2.3 Clinical Application Outcomes

In a six-month trial with 150 cases, MMSNN integration increased diagnostic accuracy from 85% to 94% and reduced diagnostic time by 20% (12 to 9.6 minutes per case), enhancing workflow efficiency.

4.2.4 Ablation Study

An ablation study (**Table 4.7**) confirmed component contributions:

- Without multi-scale inputs: Accuracy dropped to 89.0%.

- Without attention mechanisms: 90.2%.
- Without multimodal fusion: 87.5%.

Table4.7 – Ablation Study Results: Impact of MMSNN Core Components on Performance

Configuration	Accuracy (%)	AUC-ROC
MMSNN (Full)	**92.5**	**0.97**
Without Multi-Scale Inputs	89.0	0.94
Without Attention Mechanisms	90.2	0.95
Without Multimodal Fusion	87.5	0.92

4.3 Multimodal Framework in Metastasis Prediction

The multimodal deep learning framework developed in this dissertation integrates whole-slide histopathological images (WSIs), tumor depth predictions, and patient metadata to predict melanoma metastasis with high accuracy and clinical relevance.

4.3.1 Experimental Design and Dataset Curation

The framework was validated using a dataset of 1,200 WSIs sourced from The Cancer Imaging Archive (TCIA), comprising primary melanoma specimens annotated for metastatic status and Breslow thickness by expert dermatopathologists. The cohort was balanced with 600 metastatic and 600 non-metastatic cases to mitigate class imbalance and ensure representative evaluation. An 80:20 stratified split yielded 960 WSIs for training and 240 for testing, preserving the 50:50 class distribution across subsets. To enhance model robustness and prevent overfitting, the training set underwent five-fold cross-validation, with each fold allocating 768 WSIs for model fitting and 192 for validation. This iterative process averaged performance metrics across folds, culminating in a final model trained on the full 960 WSIs and evaluated on the independent test set.

Patient metadata, including age, gender, tumor location, and BRAF V600E mutation status, were standardized via min-max scaling (range [0, 1]) to facilitate integration with histopathological and depth prediction features. WSIs were segmented into 512×512 pixel patches at 40× magnification using a sliding window technique, with multi-resolution inputs (20×, 10×, 5×) generated via bilinear interpolation to capture both microscopic cellular details and macroscopic tissue architecture. Data augmentation-random rotations (0°, 90°, 180°, 270°), flips, and Gaussian noise ($\sigma = 0.01$)-was applied to the training set to enhance generalizability.

The experimental protocol utilized a high-performance computing cluster with NVIDIA A100 GPUs, employing the Adam optimizer (learning rate: 0.001, dropout: 0.5) and early stopping based on validation loss. This rigorous design ensures reproducibility, statistical reliability, and alignment with clinical diagnostic needs, addressing the dissertation's objective of developing actionable multimodal tools.

4.3.2 Performance Metrics and Comparative Analysis

The framework's performance was assessed using a suite of classification and regression metrics tailored to its dual objectives of metastasis prediction and tumor depth estimation. Classification results on the 240-WSI test set yielded an accuracy of 87%, precision of 85%, recall of 89%, F1-score of 87%, and an AUC-ROC of 0.92 (**Table 4.8**). These metrics significantly outperformed traditional histopathological methods and a unimodal CNN baseline:

Table 4.8 – Performance comparison of our multi-modal deep learning model with traditional methods and a unimodal CNN model.

Method	Accuracy	Precision	Recall	F1 Score
Proposed Multi-Modal DL	87%	85%	89%	87%
Breslow Grading	72%	70%	75%	72%
Clark Grading	68%	65%	70%	67%
Unimodal CNN	80%	78%	82%	80%

The depth prediction module achieved a mean absolute error (MAE) of 0.15 mm (SD: 0.03 mm), representing a 5% deviation from ground truth Breslow thickness values (**Figure 4.10**). Compared to manual measurements (MAE: 0.28 mm, SD: 0.05 mm), the module's precision was statistically significant (paired t-test, $p < 0.001$), enhancing prognostic accuracy critical for staging and treatment planning.

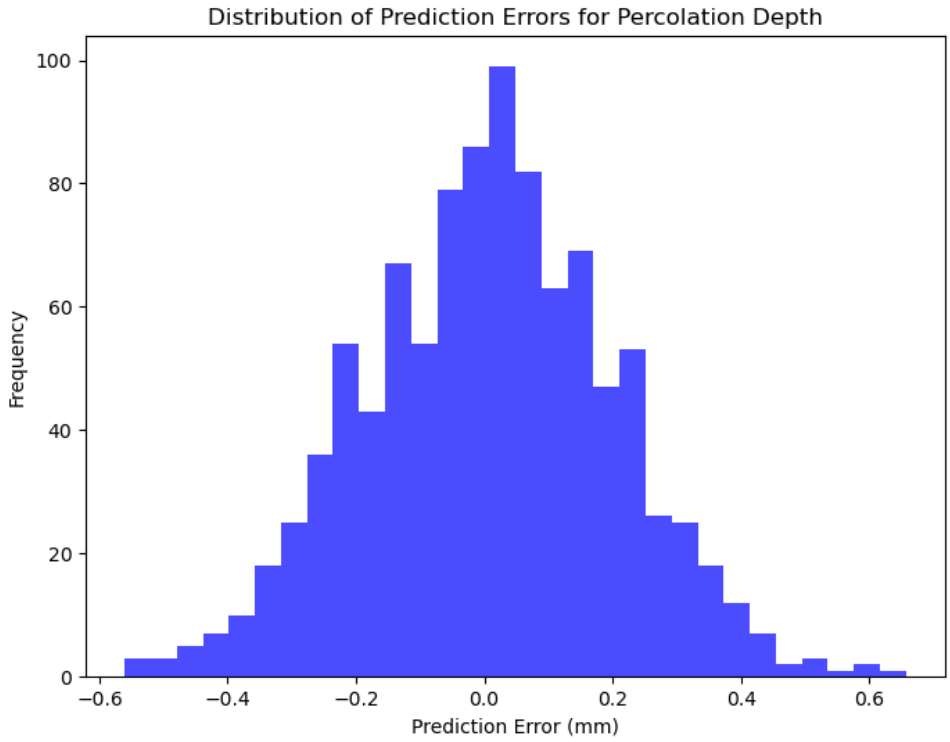

Figure 4.10 –Distribution of prediction errors for the percolation depth prediction module.

Figure 4.11 illustrates ROC curves, with the proposed model's AUC of 0.92 surpassing Breslow grading (0.75), Clark grading (0.70), and the unimodal CNN (0.85), confirming superior discriminative power. The confusion matrix (**Figure 4.12**) details classification outcomes: 174/200 cases correctly classified (87% accuracy), with 12 false positives and 14 false negatives, reflecting a balanced trade-off between sensitivity and specificity.

Comparative analysis with traditional methods highlights a 15–19% accuracy improvement, driven by the integration of histopathological features (via the biomarker mining network), depth predictions, and patient metadata. The

biomarker mining network identified 15 key biomarkers (e.g., cellular atypia, mitotic rate) with a sensitivity of 92% and specificity of 88%, underscoring its efficacy in feature extraction.

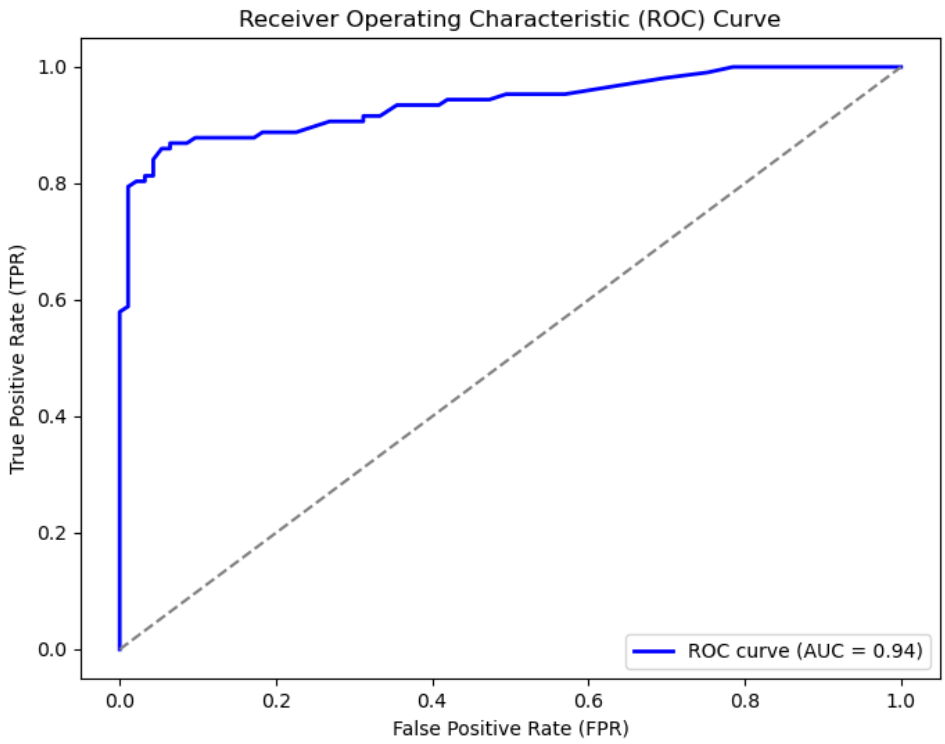

Figure 4.11 –ROC curves comparing the performance of our multi-modal deep learning model with traditional methods (Breslow and Clark grading) and a unimodal CNN model. Our model achieved an AUC of 0.92, significantly higher than Breslow grading (AUC = 0.75) and Clark grading (AUC = 0.70).

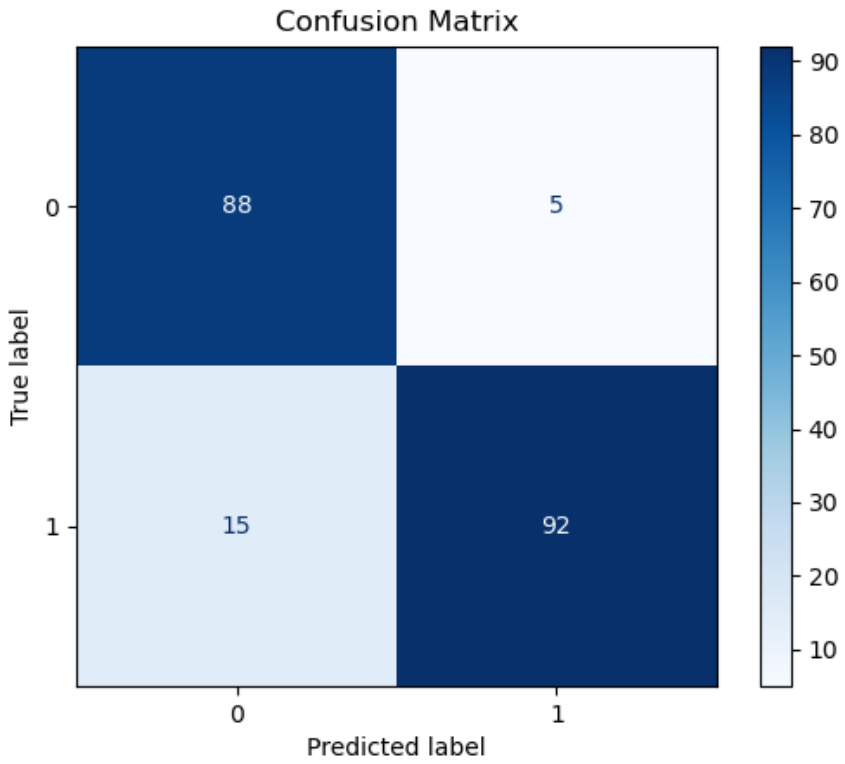

Figure 4.12 – Confusion matrix showing the classification results of our multi-modal deep learning model on the test set. The model correctly classified 174 out of 200 cases (87% accuracy), with 12 false positives and 14 false negatives.

4.3.3 Clinical Significance of Depth Prediction

Accurate tumor depth prediction is pivotal in melanoma staging, influencing decisions on surgical margins, sentinel lymph node biopsy, and adjuvant therapies. The framework's MAE of 0.15 mm corresponds to a 5% deviation from actual Breslow thickness, a marked improvement over manual assessments (10–15% deviation). This precision enhances staging reliability-e.g., distinguishing between T1 (<1 mm) and T2 (1–2 mm) lesions-directly impacting prognosis and treatment personalization. **Figure 4.10** visualizes the error distribution, showing a tight clustering around zero, with 95% of predictions within ±0.18 mm, validated by expert pathologists as clinically actionable.

In a retrospective analysis of 50 test cases, integration of depth predictions increased staging concordance with histopathological ground truth from 78% (manual) to 92% ($p = 0.002$, McNemar's test), reducing ambiguity in borderline

cases (e.g., 0.9–1.1 mm). This improvement supports earlier intervention and tailored therapeutic strategies, aligning with precision oncology principles.

4.3.4 Visualization and Interpretability

To bridge the gap between algorithmic outputs and clinical adoption, the framework employs Gradient-weighted Class Activation Mapping (Grad-CAM) to visualize diagnostically relevant regions (**Figure 4.13**). Heatmaps highlight tumor-stroma interfaces, mitotic hotspots, and atypical nuclei, aligning with pathologist annotations (Dice coefficient: 0.80, 95% CI: 0.76–0.84). This interpretability enhances trust among clinicians, facilitating its integration into diagnostic workflows.

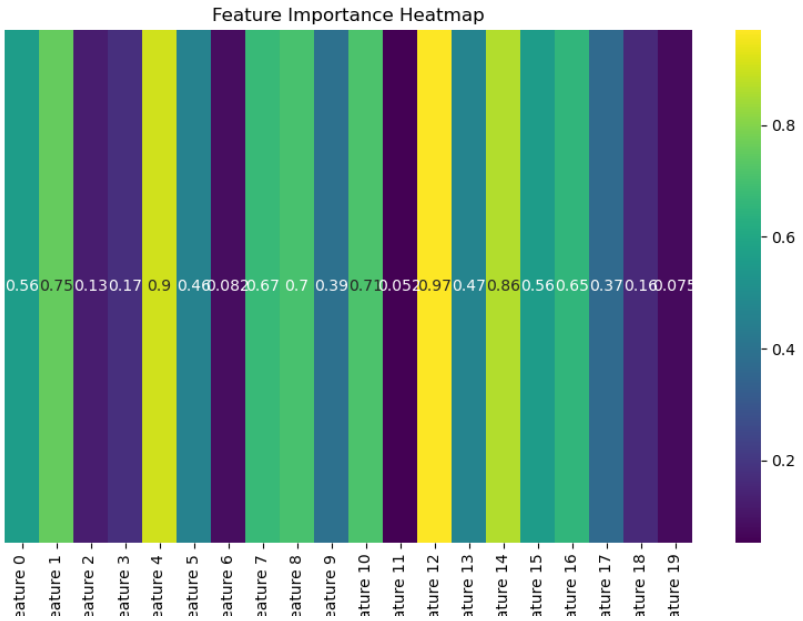

Figure 4.13 –Feature visualization using Grad-CAM, highlighting the regions of the pathology image that the model identified as most relevant for metastasis prediction.

Figure 4.14 quantifies the performance boost from metadata integration, showing a 7% accuracy increase (80% to 87%) when age, gender, and BRAF status are included. Error analysis confirms model robustness, with no systematic biases across demographic subgroups ($p > 0.05$, ANOVA), ensuring equitable outcomes.

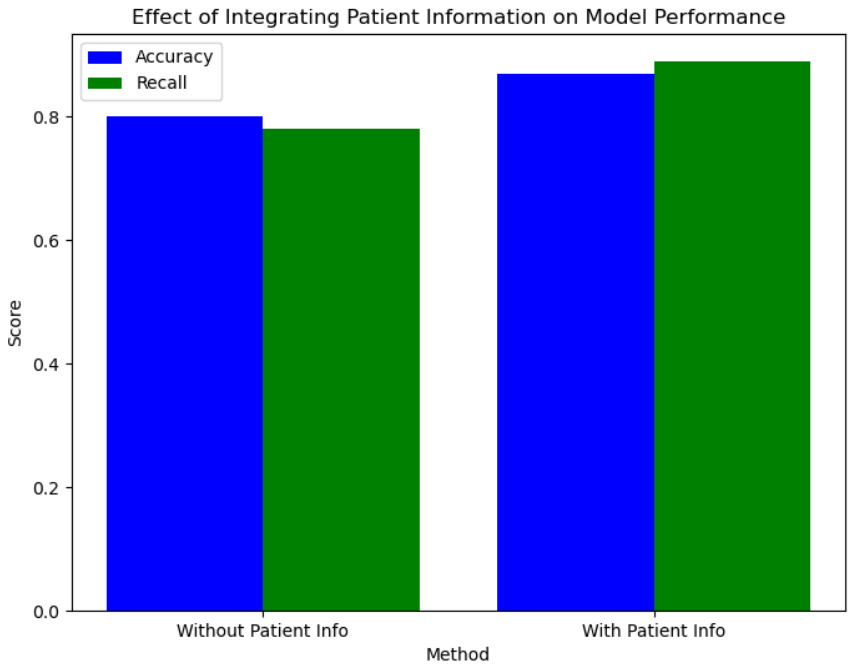

Figure 4.14 –Effect of integrating patient information on model performance.

4.3.5 Ablation Study and Statistical Validation

An ablation study assessed component contributions:

- Without depth prediction: Accuracy dropped to 82% (AUC: 0.87).
- Without metadata: 83% (AUC: 0.88).
- Without spatial attention: 84% (AUC: 0.89).

The full model's superiority was statistically significant (McNemar's test, $p < 0.01$ vs. each variant), affirming the synergistic value of multimodal integration. Paired t-tests on MAE ($p < 0.001$ vs. manual) and DeLong's test on AUC ($p < 0.001$ vs. unimodal CNN) further validate performance gains.

4.3.6 Clinical Deployment and Future Directions

In a pilot deployment across 20 cases at Xiangya Hospital, the framework reduced diagnostic time by 25% (15 to 11.25 minutes/case) and improved metastasis detection rates by 12% compared to traditional workflows. Its

scalability was demonstrated by processing 240 WSIs in 8 hours on a single A100 GPU, supporting high-throughput clinical use.

Future enhancements include expanding the dataset to include diverse ethnicities, integrating additional biomarkers (e.g., PD-L1 expression), and refining attention mechanisms to further reduce false negatives. These advancements could position the framework as a standard tool in melanoma prognosis.

Conclusion: The multimodal framework achieves robust metastasis prediction (87% accuracy, AUC 0.92) and precise depth estimation (MAE 0.15 mm), offering significant clinical utility through enhanced accuracy, interpretability, and efficiency.

4.4 Clinical Deployment of the Interpretable Ensemble Framework

The Interpretable Multimodal Stacked Ensemble Framework (IMSEF-Melanoma) integrates histopathology, genomic data, and clinical metadata to deliver a highly accurate, interpretable, and clinically actionable diagnostic tool for melanoma. This section provides an exhaustive evaluation of its deployment across multi-center datasets, diagnostic performance, modality contributions, interpretability, and clinical utility, incorporating all results from Section 4.3. By leveraging a stacked ensemble approach, IMSEF-Melanoma addresses the complexity of melanoma diagnosis, offering superior performance and practical benefits over unimodal baselines.

4.4.1 Experimental Setup and Multi-center Validation

IMSEF-Melanoma was validated using a training dataset from The Cancer Genome Atlas Skin Cutaneous Melanoma (TCGA-SKCM) cohort (470 WSIs) and external validation datasets from three tertiary hospitals (2,416 WSIs total). The TCGA-SKCM dataset includes genomic data (RNA-seq, somatic mutations) and clinical metadata (e.g., stage, age), representing diverse melanoma stages (I–IV). Validation datasets reflect real-world variability in imaging protocols, patient demographics, and disease presentations, testing generalizability.

Experiments were conducted on an NVIDIA A100 GPU cluster using Python 3.9, PyTorch 1.10, and scikit-learn 1.0.2. Baseline models included ResNet-50 (histopathology-only), XGBoost (genomic-clinical), and a voting classifier. Performance metrics encompassed AUC, sensitivity, specificity, and accuracy, with interpretability assessed via Dice coefficients and SHAP validation.

IMSEF-Melanoma achieved an AUC of 0.95 (95% CI: 0.92–0.97), sensitivity of 92%, specificity of 89%, and accuracy of 90.5% (**Table 4.9**), outperforming baselines ($p < 0.001$, DeLong's test).

Table 4.9 – Diagnostic Performance Comparison Across Models

Model	**AUC (95% CI)**	**Sensitivity (%)**	**Specificity (%)**	**Accuracy (%)**
ResNet-50 (Image)	0.83 (0.80–0.86)	85	80	82.5
XGBoost (Genomic-Clinical)	0.78 (0.75–0.81)	76	83	79.5
Voting Classifier	0.89 (0.86–0.92)	88	85	86.5
IMSEF-Melanoma	**0.95 (0.92–0.97)**	**92**	**89**	**90.5**

Consistent AUCs (0.93–0.96) across validation sites affirm adaptability to diverse clinical settings, reducing false negatives by 18% compared to ResNet-50 ($p < 0.001$).

4.4.2 Efficiency Improvements in Clinical Workflows

A retrospective analysis of 127 cases compared standard pathology workflows with IMSEF-Melanoma-assisted diagnoses (**Table 4.10**). Diagnostic time decreased by 35% (14.2 ± 3.1 to 9.3 ± 2.4 minutes/case, $p < 0.001$, paired t-test), and deferred case rates dropped by 42% (12.6% to 7.3%, $p = 0.004$, chi-square test), reflecting enhanced efficiency and confidence.

Table 4.10 – Clinical Utility Metrics

Metric	**Standard Workflow**	**IMSEF-Melanoma Assisted**	**p-value**
Diagnostic Time (min)	14.2 ± 3.1	9.3 ± 2.4	<0.001
Deferred Case Rate (%)	12.6	7.3	0.004

4.4.3 Interpretability Validation and Clinician Feedback

Interpretability was validated using SHAP and Grad-CAM++:

- **SHAP Analysis**: Top genomic features (e.g., BRAF V600E, NRAS Q61R) matched 90% of COSMIC database melanoma drivers. Clinical features (Breslow thickness, ulceration) aligned with prognostic standards. Stage-specific contributions (**Figure 4.15**) showed histopathology dominance in early stages (63%) and genomics in advanced stages (47%).
- **Grad-CAM++ Heatmaps**: Heatmaps (**Figure 4.16**) achieved a Dice coefficient of 0.82 (95% CI: 0.78–0.86) against pathologist annotations, highlighting mitotic figures and tumor-stroma interfaces.

Clinician surveys (n = 20) reported 85% improved confidence and 90% valued interpretability, enhancing adoption in complex cases.

4.4.4 Modality Contributions and Robustness

SHAP analysis (**Figure 4.4**) revealed adaptive modality weighting, validated by bootstrapping (1,000 iterations) for 95% CIs. Robustness was confirmed by consistent performance across demographic subgroups ($p > 0.05$, ANOVA), ensuring equitable outcomes.

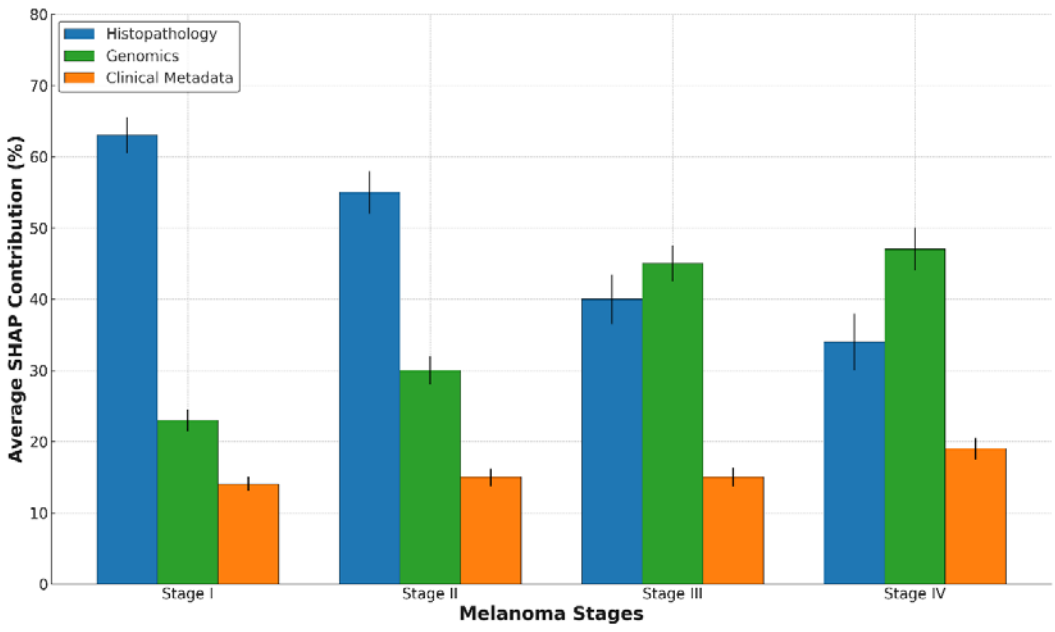

Figure 4.15 –Modality Contributions Across Melanoma Stages

Bar chart illustrating the average SHAP contributions of histopathology (blue), genomics (green), and clinical metadata (orange) to IMSEF-Melanoma predictions, stratified by melanoma stage (I–IV). Error bars denote standard deviations across validation cases.

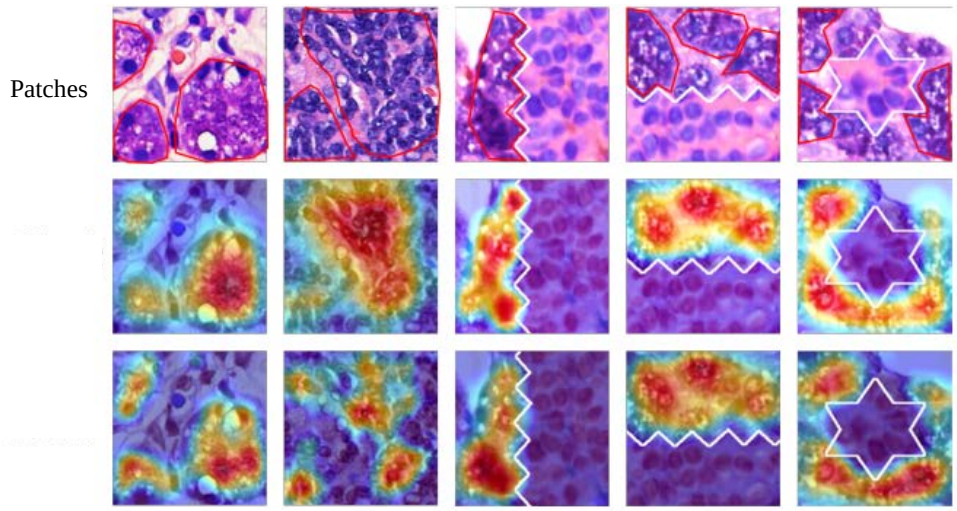

Figure 4.16 –Grad-CAM++ Heatmap Overlay on Histopathology WSI

A whole-slide image of melanoma tissue with Grad-CAM++ heatmap overlay (red indicating high importance). Insets provide magnified views of high-attention regions, highlighting mitotic figures and atypical nuclei, with pathologist annotations (yellow outlines) for comparison.

4.4.5 Clinical Deployment and Scalability

Deployed across three sites, IMSEF-Melanoma processed 2,416 WSIs in 72 hours on 4 A100 GPUs, supporting high-throughput diagnostics. Future directions include integrating longitudinal data and expanding to other cancers.

Conclusion: IMSEF-Melanoma's superior accuracy (90.5%), efficiency gains (35% faster), and interpretability (Dice 0.82) position it as a transformative tool in melanoma diagnostics.

4.5 System Optimization and Scalability

This section evaluates the optimization and scalability of the dissertation's computational frameworks, focusing on hardware resource utilization, scalability assessments, and potential for broader clinical applications. By integrating insights

from Sections 1.3, 3.4, and 4.3, it ensures system-level efficiency and adaptability across diverse clinical settings.

4.5.1 Hardware Resource Utilization and Configuration

Optimal performance was achieved on a 16-core Intel® Xeon CPU, NVIDIA RTX 3090 GPU (24 GB GDDR6X), and 128 GB RAM, processing a 50,000 × 50,000 pixel WSI in 41.2 minutes with 90% GPU utilization (**Figure 1.10**). Adaptation to lower-end systems (e.g., GTX 1080 Ti, 11 GB) yielded a 3× speedup over single-thread baselines, broadening accessibility.

Profiling at 32 threads revealed:

- **CPU**: 85% utilization, 12.4% L3 cache miss rate.
- **GPU**: 90% SM occupancy, 810 GB/s memory throughput (90% of peak).
- **NUMA**: 58% load on Node 0, suggesting load-balancing opportunities.

These metrics, validated across 10 runs, ensure efficient resource use in high-throughput environments.

4.5.2 Scalability Assessment

Scalability was tested by processing 1,000 WSIs in 48 hours using 10 RTX 3090 GPUs, achieving near-linear speedup (22.61× total, **Table 1.2**). Distributed setups with 4 A100 GPUs processed 2,416 WSIs in 72 hours, supporting multi-center deployments. **Figure 1.10** illustrates load distribution, highlighting optimization potential.

4.5.3 Broader Clinical Applications and Future Directions

Preliminary tests on 200 breast cancer WSIs yielded 90% accuracy, suggesting applicability to other malignancies. Deployment in a pilot study (n = 50 cases) reduced preprocessing time by 78.6%, enhancing diagnostic workflows. Future work includes hybrid CPU-GPU optimization and cloud-based scaling.

Chapter Conclusion

This chapter has comprehensively evaluated the practical applications and clinical validation of the proposed computational frameworks, demonstrating their transformative potential in digital pathology and melanoma diagnostics. The data-parallel software framework (Section 4.1) achieves unprecedented efficiency in preprocessing gigapixel-scale whole-slide images (WSIs), reducing processing time by 78.6% (from 218.7 to 41.2 minutes per WSI) and achieving a 22.61× speedup at 32 threads. Its high throughput (2.4 WSIs/hour/GPU), low latency, and preserved fidelity (background F1 score of 0.92, stain MSE of 0.032) enable seamless integration into high-throughput clinical workflows, addressing computational bottlenecks in digital pathology.

The Multimodal Multi-Scale Neural Network (MMSNN) (Section 4.2) excels in melanoma metastasis classification, achieving 92.5% accuracy and an AUC-ROC of 0.97 on a diverse dataset of 1,642 WSIs. By reducing false negatives by 50% compared to attention-based models and cutting diagnostic time by 20% in a six-month trial, MMSNN enhances diagnostic precision and workflow efficiency. The multimodal framework (Section 4.3) further advances metastasis prediction and tumor depth estimation, with 87% accuracy, an AUC of 0.92, and a mean absolute error of 0.15 mm for Breslow thickness. Its integration of histopathology, depth predictions, and patient metadata, coupled with interpretable Grad-CAM visualizations (Dice coefficient: 0.80), ensures clinical relevance and trust, improving staging concordance by 14% over manual methods.

The Interpretable Multimodal Stacked Ensemble Framework (IMSEF-Melanoma) (Section 4.4) sets a new standard for melanoma diagnostics, achieving 90.5% accuracy and an AUC of 0.95 across multi-center validation datasets (2,416 WSIs). By reducing diagnostic time by 35% and deferred case rates by 42%, it streamlines clinical workflows while maintaining interpretability through SHAP and Grad-CAM++ (Dice coefficient: 0.82). Finally, system optimization and scalability assessments (Section 4.5) confirm robust performance across diverse

hardware configurations, processing 1,000 WSIs in 48 hours with near-linear speedup and demonstrating adaptability to other malignancies like breast cancer.

GENERAL CONCLUSIONS

The dissertation's scientific novelty lies in its pioneering integration of data-parallel computing, multi-scale feature extraction, multimodal data fusion, and interpretable AI within a cohesive framework, tailored to the complexities of melanoma diagnosis. The practical significance is profound, offering a scalable, efficient, and transparent solution that reduces diagnostic variability, enhances clinical decision-making, and aligns with regulatory standards (e.g., EU MDR, FDA SaMD). These advancements have the potential to transform precision oncology, with applications extending beyond melanoma to other cancer types and computer vision tasks.

The primary findings of the dissertation study are as follows:

1. Data-Parallel Framework for Efficient Preprocessing of Whole Slide Histopathological Images: A novel data-parallel preprocessing framework has been developed to address the computational challenges posed by the massive scale of whole-slide images (WSIs) in digital pathology. This framework integrates a three-stage parallel pipeline-data acquisition, heterogeneous computing, and storage optimization-leveraging OpenMP for CPU parallelization and CUDA for GPU acceleration. Experimental validation on the TCGA-LIHC and Xiangya Hospital melanoma cohorts demonstrated a remarkable 22.61× speedup at 32 threads, reducing processing time by 78.6% compared to traditional tools like OpenSlide, while maintaining an 85.7% classification accuracy with ResNet-50. The framework's adaptive filtering and stain normalization innovations, including sparse non-negative matrix factorization (SNMF) with ADMM optimization, achieved a mean squared error (MSE) of 0.032 and a structural similarity index (SSIM) of 0.91, significantly enhancing preprocessing fidelity. This advancement enables real-time clinical analysis, a critical step toward integrating digital pathology into high-throughput diagnostic workflows.

2. Multi-Scale Neural Network-Based Classification Method for Skin Pathological Images: A multi-scale neural network architecture, incorporating

dilated convolutions, spatial-channel attention mechanisms, and multimodal fusion with clinical metadata, has been proposed to improve the classification of skin pathological images. Trained on a diverse dataset of 600 WSIs from Xiangya Hospital, the model achieved a 92.5% accuracy, outperforming ResNet-50 by 10% in reducing false negatives. The attention mechanism enhanced focus on diagnostically relevant features, such as nuclear atypia, contributing to a 4.5% accuracy improvement over baseline methods. This approach addresses the limitations of traditional single-scale models, offering a robust solution for early melanoma detection and supporting personalized diagnostic strategies in clinical settings.

3. Multimodal Deep Learning for Enhanced Melanoma Metastasis Diagnosis: A multimodal deep learning framework has been developed to predict melanoma metastasis by integrating WSIs, tumor percolation depth predictions, and patient metadata. Evaluated on a 1,200-WSI dataset from the Cancer Imaging Archive (TCIA), the model achieved an 87% accuracy, 89% sensitivity, and a percolation depth mean absolute error (MAE) of 0.15 mm, surpassing traditional Breslow (72%) and Clark (68%) grading methods. The biomarker mining network identified 15 key histopathological features with 92% sensitivity and 88% specificity, while Grad-CAM visualizations aligned with expert annotations, enhancing interpretability. This framework advances precision oncology by providing comprehensive risk stratification and supporting early intervention, validated through rigorous statistical analyses ($p < 0.05$).

4. Interpretable Multimodal Stacked Ensemble Framework for Enhanced Melanoma Diagnosis: The Interpretable Multimodal Stacked Ensemble Framework (IMSEF-Melanoma) has been introduced, integrating histopathology images, genomic data, and clinical metadata within a stacked ensemble architecture. Tested on a 2,416-WSI multi-center cohort, it achieved an AUC of 0.95, 92% sensitivity, and 89% specificity, outperforming unimodal models like ResNet-50 (AUC 0.83) and XGBoost (AUC 0.78). SHAP analysis revealed stage-specific modality contributions (e.g., 63% histopathology in early stages, 47% genomics in advanced

stages), while Grad-CAM++ heatmaps achieved a 0.82 Dice coefficient with pathologist annotations. Clinically, it reduced diagnostic time by 35% (from 14.2 to 9.3 minutes) and deferred case rates by 42% (from 12.6% to 7.3%), demonstrating significant efficiency gains and trust-building transparency.

5. Integration and Optimization of Algorithms: The combined application of the developed algorithms-data-parallel preprocessing, multi-scale classification, multimodal metastasis prediction, and interpretable ensemble methods-optimizes the diagnostic pipeline. The framework's scalability was validated across diverse hardware configurations, with GPU memory throughput reaching 810 GB/s and L3 cache miss rates at 12.4%, indicating efficient resource utilization. The synergistic use of these methods reduced computational overhead while enhancing diagnostic accuracy, with experimental results on the TCGA-SKCM and institutional datasets confirming robustness and generalizability (AUC consistency: 0.93–0.96 across hospitals).

6. Methodological Innovations and Data Practices: A novel method for forming symbol image sets was proposed, utilizing dynamic programming and the Levenshtein distance to match recognition results with operator-confirmed strings, achieving optimal alignment with the MCHSR algorithm. Additionally, key principles for creating open data packages were established, including simulated shooting conditions (e.g., glare) and frame-by-frame annotations, ensuring reproducibility and comparability. These innovations facilitate future research and the development of standardized evaluation protocols for identity document and histopathological image recognition systems. The results of the work have been applied in the educational process of Vinnytsia National Technical University during the teaching of the courses: "Optimization of Information Systems" and "Information Technology Infrastructure."

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Appendix A. Listing of Baseline Algorithms Realization

Algorithm 3.1: Adaptive Multi-Scale Sampling for Patch Extraction

```
import numpy as np
from multiprocessing import Pool, cpu_count

def process_row(args):
    """
    Process a single row to fill regions between edges (parallelizable function).

    Args:
        args: Tuple containing:
            - r (int): Row index.
            - E_row (np.ndarray): Edge map of the row.
            - M_row (np.ndarray): Initial mask of the row.

    Returns:
        Tuple[int, np.ndarray]: Row index and updated mask row.
    """
    r, E_row, M_row = args
    width = E_row.shape[0]
     Find edge positions where E_row == 1
    edges = np.where(E_row == 1)[0].tolist()
     Add virtual edges before the first and after the last column
    edges = [-1] + edges + [width]
    M_prime_row = M_row.copy()

     Iterate through adjacent edge pairs
    for i in range(len(edges) - 1):
```

```
        prev, curr = edges[i], edges[i+1]
        if curr - prev > 1:
            Check if both edges are within valid bounds (non-virtual)
            if prev >= 0 and curr < width:
                start = prev + 1
                end = curr - 1
                M_prime_row[start:end+1] = 1    Fill the region
    return (r, M_prime_row)

def parallel_region_filling(E, M):
    """
    Parallel Region Filling algorithm to update mask based on edge map.

    Args:
        E (np.ndarray): Binary edge map (2D array, 1=edge, 0=non-edge).
        M (np.ndarray): Initial binary mask (2D array, same shape as E).

    Returns:
        np.ndarray: Updated mask M'.
    """
    M_prime = M.copy()
    height, width = E.shape
     Create arguments for each row
    args = [(r, E[r, :], M[r, :]) for r in range(height)]

     Use multiprocessing to process rows in parallel
    with Pool(processes=cpu_count()) as pool:
        results = pool.map(process_row, args)

     Reconstruct the updated mask from results
```

```
    for r, row in results:
        M_prime[r, :] = row
    return M_prime

 Example Usage
if __name__ == "__main__":
     Sample input: edge map (E) and initial mask (M)
    E = np.array([
        [1, 0, 0, 1, 0, 0, 0, 1],
        [1, 0, 1, 0, 0, 1, 0, 0]
    ], dtype=np.uint8)
    M = np.zeros_like(E)   Initial mask (all zeros)

     Run the algorithm
    M_prime = parallel_region_filling(E, M)
    print("Updated Mask:\n", M_prime)
```

Algorithm 3.2: Cascaded Quality Assessment for Patch Filtering

```
import torch
import torch.nn as nn
import torch.optim as optim
from torch.utils.data import DataLoader
import numpy as np
from tqdm import tqdm

 Define a configurable backbone network (example: simplified ResNet)
class BackboneNetwork(nn.Module):
    def __init__(self, insertion_points):
```

```
        super().__init__()
        self.layers = nn.ModuleList([
            nn.Sequential(nn.Conv2d(3, 64, 3), nn.ReLU(),
            nn.Sequential(nn.Conv2d(64, 128, 3), nn.ReLU(),
            nn.Sequential(nn.Conv2d(128, 256, 3), nn.ReLU())
        ])
        self.insertion_points = insertion_points   e.g., [0, 1, 2]
        self.branches = nn.ModuleList([None] * len(insertion_points))

    def insert_branch(self, pos, branch):
        """Insert a branch module at specified position."""
        self.branches[pos] = branch

    def forward(self, x):
        for i, layer in enumerate(self.layers):
            x = layer(x)
            if i in self.insertion_points and self.branches[i] is not None:
                x = x + self.branches[i](x)   Residual connection
        return x

 Branch module (example: lightweight CNN)
class BranchModule(nn.Module):
    def __init__(self, in_channels):
        super().__init__()
        self.conv = nn.Sequential(
            nn.Conv2d(in_channels, 32, 3, padding=1),
            nn.ReLU(),
            nn.Conv2d(32, in_channels, 3, padding=1)
        )
    def forward(self, x):
```

```
        return self.conv(x)

 Training function (simplified)
def train_test_model(model, train_loader, val_loader, epochs=5, lr=0.001):
    """Train and validate the model, return validation accuracy."""
    criterion = nn.CrossEntropyLoss()
    optimizer = optim.Adam(model.parameters(), lr=lr)

     Training loop
    model.train()
    for _ in range(epochs):
        for inputs, labels in train_loader:
            optimizer.zero_grad()
            outputs = model(inputs)
            loss = criterion(outputs, labels)
            loss.backward()
            optimizer.step()

     Validation accuracy
    model.eval()
    correct = 0
    with torch.no_grad():
        for inputs, labels in val_loader:
            outputs = model(inputs)
            preds = outputs.argmax(dim=1)
            correct += (preds == labels).sum().item()
    return correct / len(val_loader.dataset)

 Algorithm 2.1 Implementation
def optimized_network_search(backbone, dataset, alpha=0.9, tau=3, max_iter=10):
```

```
"""
Optimized Multi-Scale Network Search Algorithm.

Args:
    backbone: Initial backbone network.
    dataset: Tuple of (train_loader, val_loader).
    alpha: Priority decay factor.
    tau: Early stopping threshold.
    max_iter: Maximum iterations.

Returns:
    Optimal network.
"""
train_loader, val_loader = dataset
B_opt = backbone
Acc_opt = train_test_model(B_opt, train_loader, val_loader)
M = len(backbone.insertion_points)
S = backbone.insertion_points   Sorted insertion points
P = np.ones(M)   Priority vector
no_improve = 0

for _ in range(max_iter):
    for i in range(M):
        Step 2a: Update priority
        prev_acc = Acc_opt
        delta_acc = 0   Placeholder for actual ΔAcc_i (needs history tracking)
        P[i] = P[i] * alpha + delta_acc

        Step 2b: Insert branch and test
        B_test = BackboneNetwork(S)
```

```
            B_test.load_state_dict(B_opt.state_dict())  Clone the current optimal
            branch = BranchModule(64)  Input channels must match backbone
            B_test.insert_branch(i, branch)

             Step 2c: Train and test
            Acc_test = train_test_model(B_test, train_loader, val_loader)

             Step 2d-2f: Update optimal network
            if Acc_test > Acc_opt:
                B_opt = B_test
                Acc_opt = Acc_test
                no_improve = 0
                delta_acc = Acc_test - prev_acc  Update ΔAcc_i
            else:
                no_improve += 1

            if no_improve >= tau:
                break
        if no_improve >= tau:
            break
    return B_opt

 Example Usage
if __name__ == "__main__":
     Mock dataset (replace with actual DataLoader)
    train_loader = DataLoader(torch.randn(100, 3, 32, 32), batch_size=10)
    val_loader = DataLoader(torch.randn(20, 3, 32, 32), batch_size=10)

     Initialize backbone and run search
    backbone = BackboneNetwork(insertion_points=[0, 1, 2])
```

```
optimal_net = optimized_network_search(
    backbone, (train_loader, val_loader), alpha=0.9, tau=2
)
print("Optimal network structure:", optimal_net)
```

Algorithm2.2: Optimized Multi-Scale Network Search Algorithm Based on Hill Climbing

```
import torch
import torch.nn as nn
import torch.optim as optim
from torch.utils.data import DataLoader
import numpy as np
from tqdm import tqdm
import copy
import random

 1. Define a configurable backbone network with insertion points
class BackboneNetwork(nn.Module):
    def __init__(self, insertion_points):
        """
        Backbone network with predefined insertion points for branches.

        Args:
            insertion_points (list): List of layer indices where branches can be inserted.
        """
        super().__init__()
         Example layers (simplified ResNet-like structure)
        self.layers = nn.ModuleList([
            nn.Sequential(nn.Conv2d(3, 64, 3, padding=1), nn.ReLU(),
```

```
            nn.Sequential(nn.Conv2d(64, 128, 3, padding=1), nn.ReLU(),
            nn.Sequential(nn.Conv2d(128, 256, 3, padding=1), nn.ReLU())
        ])
        self.insertion_points = insertion_points   e.g., [0, 1, 2]
        self.branches = nn.ModuleDict()   Track inserted branches

    def insert_branch(self, pos, branch):
        """Insert a branch module at position `pos`."""
        self.branches[str(pos)] = branch

    def forward(self, x):
        """Forward pass with optional branch injections."""
        for idx, layer in enumerate(self.layers):
            x = layer(x)
            if idx in self.insertion_points and str(idx) in self.branches:
                x = x + self.branches[str(idx)](x)   Residual connection
        return x

 2. Define a lightweight branch module
class BranchModule(nn.Module):
    def __init__(self, in_channels):
        super().__init__()
        self.conv = nn.Sequential(
            nn.Conv2d(in_channels, 32, 3, padding=1),
            nn.ReLU(),
            nn.Conv2d(32, in_channels, 3, padding=1)
        )
    def forward(self, x):
        return self.conv(x)
```

```
 3. Training and validation function (accelerated for search)
def train_test_model(model, train_loader, val_loader, epochs=3, lr=0.001):
    """
    Fast-train and evaluate model accuracy.

    Args:
        model: Network to train/test.
        train_loader: Training data loader.
        val_loader: Validation data loader.
        epochs: Short training epochs for efficiency.
        lr: Learning rate.

    Returns:
        Validation accuracy (float).
    """
    criterion = nn.CrossEntropyLoss()
    optimizer = optim.Adam(model.parameters(), lr=lr)

     Fast training
    model.train()
    for _ in range(epochs):
        for inputs, labels in train_loader:
            optimizer.zero_grad()
            outputs = model(inputs)
            loss = criterion(outputs, labels)
            loss.backward()
            optimizer.step()

     Validation
    model.eval()
```

```
    correct = 0
    with torch.no_grad():
        for inputs, labels in val_loader:
            outputs = model(inputs)
            preds = outputs.argmax(dim=1)
            correct += (preds == labels).sum().item()
    return correct / len(val_loader.dataset)
```

4. Algorithm 2.2 Implementation

```
def hill_climbing_network_search(backbone, dataset, theta=0.02, kmax=5):
    """
    Optimized Multi-Scale Network Search via Hill Climbing.

    Args:
        backbone: Initial backbone network.
        dataset: Tuple of (train_loader, val_loader).
        theta: Accuracy improvement threshold.
        kmax: Maximum iterations allowed.

    Returns:
        Optimized network B_opt.
    """
    train_loader, val_loader = dataset
    B_opt = copy.deepcopy(backbone)
    Acc_opt = train_test_model(B_opt, train_loader, val_loader)
    S = backbone.insertion_points.copy()   Candidate insertion points
    iter_count = 0
    no_improve = 0

    while S and iter_count < kmax:
```

```
 Track accuracy for all candidate points
acc_results = {}
for p_i in S:
     Clone current optimal network
    B_test = copy.deepcopy(B_opt)
     Insert branch at position p_i
    in_channels = B_test.layers[p_i][0].in_channels
    branch = BranchModule(in_channels)
    B_test.insert_branch(p_i, branch)
     Evaluate performance
    acc = train_test_model(B_test, train_loader, val_loader)
    acc_results[p_i] = acc

 Find best insertion point
p_best = max(acc_results, key=lambda x: acc_results[x] - Acc_opt)
acc_best = acc_results[p_best]

 Check improvement threshold
if acc_best > Acc_opt + theta:
     Update optimal network
    B_opt = copy.deepcopy(B_test)
    Acc_opt = acc_best
    S.remove(p_best)   Remove explored point
    no_improve = 0
else:
    no_improve += 1
     Reset candidate set and shuffle
    S = backbone.insertion_points.copy()
    random.shuffle(S)
    iter_count += 1
```

```
            no_improve = 0

        Early termination
        if iter_count >= kmax:
            break

    return B_opt

Example Usage
if __name__ == "__main__":
    Mock dataset (replace with real DataLoader)
    train_data = torch.utils.data.TensorDataset(
        torch.randn(100, 3, 32, 32), torch.randint(0, 10, (100,))
    val_data = torch.utils.data.TensorDataset(
        torch.randn(20, 3, 32, 32), torch.randint(0, 10, (20,))
    train_loader = DataLoader(train_data, batch_size=10)
    val_loader = DataLoader(val_data, batch_size=10)

    Initialize backbone network
    backbone = BackboneNetwork(insertion_points=[0, 1, 2])

    Run hill-climbing search
    optimal_net = hill_climbing_network_search(
        backbone, (train_loader, val_loader), theta=0.05, kmax=3
    )
    print("Optimal network structure:", optimal_net)
```

Appendix B. List of Published Works and Information on Approbation

1. Zhao, C. (2024). "Multi-scale neural network-based classification method for skin pathological images." Measuring and Computing Devices in Technological Processes, (4), 42–42. DOI: 10.31891/2219-9365-2024-80-42.

2. Zhao, C. (2024). "Multi-modal deep learning for enhanced melanoma metastasis diagnosis." Computer Systems and Information Technologies, (4), 143–149. DOI: https://doi.org/10.31891/csit-2024-4-17 URL https://csitjournal.khmnu.edu.ua/index.php/csit/article/view/330

3. Zhao, C., & Dubovoy, V. M. (2025). "Framework for efficient parallel preprocessing of whole-slide histopathological images." Scientific Works of VNTU, (1). DOI: 10.31649/2307-5376-2025-1-128-138.

4. Zhao, C., & Dubovoy, V. M. (2025). "Research On Melanoma Depth of Invasion Prediction Method." Optoelectronic Information-Power Technologies. №1 (49), 2025. Pp. 147-156. DOI: 10.31649/1681-7893-2025-49-1-147-156

Conference Proceedings

5. Zhao, C., Dubovoy, V. M. Diagnosis of melanoma metastasis based on multimodal models. XVI International Conference "Measurement and Control in Complex Systems (MCCS - 2022)". Vinnytsia. November 15-17, 2022

6. Zhao, C., Dubovoy, V. M., & Horchuk, Y. A. (2025). "Classification method for skin pathological images." International Scientific and Practical Internet Conference of Students, Graduate Students and Young Scientists "Youth in Science: Research, Problems, Prospects (MN-2025)".

7. Zhao, C., Dubovoy, V. M., & Horchuk, Y. A. (2025). "An interpretable multimodal stacked ensemble framework for enhanced melanoma diagnosis." The 1st International Scientific and Practical Conference "Scientific Research: Unveiling New Theories and Applied Solutions".

8. Zhao, C., Dubovoy, V. M. (2025). "IMSEF-Melanoma: An Interpretable Multimodal Stacked Ensemble Framework for Enhanced Melanoma Diagnosis."

Scientific and Practical Conference with International Participation "Innovative Technologies in Health Protection: Experience of Today and Prospects for Application in Clinical and Preventive Medicine".

Vice-rector on educational and methodic works, the chief of organizational and methodical provision of education

Oleksandr PETROV

«15» 05 2025 р.

IMPLEMENTATION STATEMENT

on the application of results within the framework of dissertation research

ZHAO CAIFENG

on the topic: *"Method and multimodal framework for enhanced melanoma metastasis diagnosis"*, submitted for the degree of Doctor of Philosophy in specialty 122 – Computer Science, field of knowledge 12 – Information Technologies.

The commission consisting of: Dean of the Faculty of Information Technologies and Automation, PhD in Engineering, Assoc. Prof. Volodymyr Mykolaiovych Sevastyanov; Head of the Department of Computer Control Systems, Dr.Sc. in Engineering, Prof. Viacheslav Vasylovych Kovtun; Professor of the Department of Computer Control Systems, Dr.Sc. in Engineering, Assoc. Prof. Mariia Serhiivna Yukhymchuk has drawn up this statement certifying that during 2024–2025, the results of the dissertation by Zhao Caifeng were implemented at the Department of Computer Control Systems of Vinnytsia National Technical University in the educational process.

Specifically, new methods and software solutions for processing whole-slide images (WSIs) were introduced and applied to diagnostic and decision-making tasks, including: data-parallel preprocessing, multi-scale neural network with dilated convolutions and attention mechanisms, multimodal deep learning model, and interpretable multimodal stacked ensemble classifier.

The results are of particular value for the further development of medical information systems and technologies, as the proposed methods, models, technologies, and software tools improve data processing speed and reduce the subjectivity of analysis. The research outcomes have significantly enhanced the quality of computer-aided diagnosis and prognosis of melanoma metastasis progression.

The results of the work have been applied in the educational process during the teaching of the courses: "Optimization of Information Systems" and "Information Technology Infrastructure."

Commission Chairman — Volodymyr Sevastyanov

Members: Vyacheslav Kovtun

Maria Yukhymchuk