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Review Article

Data Fusion in Pathology: Integrating Morphologic, Molecular, and Clinical Data for a Unified Disease Atlas

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Abstract

The field of computational pathology is increasingly reliant on the integration of diverse data modalities to advance beyond traditional diagnostic paradigms. This integration is critical for deciphering complex disease mechanisms and enabling personalized medicine, yet the rapidly evolving landscape of fusion techniques necessitates a consolidated overview. This mini review addresses the pressing need to synthesize current methodologies, applications, and challenges in multimodal data fusion within pathology. We explore the pivotal role of multimodal deep learning in pan-cancer integration for tasks such as cancer origin identification, survival prediction, and biomarker discovery. The review further examines the field of pathogenomics, which fuses pathology, genomic, and clinical data, and details computational frameworks for inferring molecular profiles directly from histology images. Additionally, we cover the integration of multiomics data to characterize the tumor microenvironment, survey emerging computational frameworks and foundation models, and present key clinical studies validating these integrative approaches. Finally, the review discusses significant challenges, including data heterogeneity and standardization, that must be overcome for clinical translation. Future progress in this domain will depend on the development of explainable and federated artificial intelligence models, innovative architectures to handle data complexity, and robust interdisciplinary collaborations. By addressing these frontiers, data fusion is poised to fundamentally transform pathology into a more precise and predictive discipline, ultimately culminating in the realization of unified disease atlases for research and clinical care.

Keywords: Computational pathology, Data fusion, Digital pathology, Disease atlas, Multimodal deep learning, Pathogenomics, Spatial transcriptomics, Tumor microenvironment

Introduction

The integration of diverse data modalities in pathology has emerged as a pivotal approach to advancing disease understanding, diagnosis, and prognosis [1-7]. Data fusion techniques (Table 1) that combine morphologic, molecular, and clinical information are increasingly recognized for their potential to create comprehensive disease atlases, thereby enabling more precise and personalized medical interventions. The recent literature underscores the significance of multimodal deep learning frameworks and fusion models in achieving this integration, particularly within the context of cancer and complex diseases [8-12].

A prominent theme across the studies is the utilization of multimodal deep learning to analyze pathology whole-slide images alongside molecular profile data [13-17]. For instance, pan-cancer integrative analyses employing multimodal deep learning have demonstrated the capacity to jointly examine histological features and genomic data across 14 cancer types [17]. This approach involves a sophisticated fusion layer, extended from the Pathomic Fusion model, which effectively integrates whole-slide images with molecular profiles, thereby capturing the complex interplay between morphology and molecular alterations [17]. Such models facilitate a more holistic understanding of tumor heterogeneity and enable the identification of molecular signatures associated with specific histological patterns.

The integration of imaging and genomic data is not limited to cancer but extends to other complex diseases, where multimodal deep learning has been employed to predict patient prognosis [18-23]. For example, a recent study highlights how combining imaging data with genomic information can reveal distinct disease characteristics, ultimately improving prognostic accuracy [24]. This underscores the importance of multimodal data fusion in capturing the multifaceted nature of disease processes, which single-modality analyses might overlook. Clinical data further enriches the fusion landscape, providing context that enhances diagnostic and prognostic models. Pathogenomics exemplifies this integration by combining pathology, genomic, and clinical data to improve disease diagnosis, treatment planning, and prognosis [3]. The fusion models in this domain

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Table 1: Core data modalities in pathology and their roles in data fusion for a unified disease atlas.

Data modality	Sub-type/technology	Description	Key features/data output	Role in data fusion and contribution to disease atlas
Morphologic	Histology (hematoxylin and eosin (H&E), IHC)	Whole-slide images of stained tissue sections	Tissue architecture, cellular morphology, protein localization (via IHC)	Provides the foundational structural and phenotypic context; essential for linking form to function
	Spatial phenotyping (e.g., co-detection by indexing, Cell DIVE)	Multiplexed imaging for high-plex protein detection	Spatial distribution and co-expression of dozens of proteins at single-cell resolution	Enables deep characterization of the tumor microenvironment and cell-cell interactions
Molecular	Genomics (DNA-seq)	Seq-DNA to identify variations	Somatic mutations, copy number variations, structural variants	Reveals fundamental genetic drivers and alterations that initiate and propel disease
	Transcriptomics (RNA-seq, scRNA-seq)	Seq of RNA to measure gene expression	Bulk or single-cell gene expression profiles, expression signatures	Uncovers functional activity states, cellular heterogeneity, and molecular subtypes
	Spatial transcriptomics (e.g., 10x Visium, Xenium)	Seq of RNA within its native tissue context	Gene expression data mapped directly to histological locations	Bridges the gap between morphology and molecular biology; crucial for spatially informed fusion
	Proteomics/metabolomics	Mass spectrometry-based profiling of proteins/metabolites	Protein/metabolite abundance, post-translational modifications	Provides a functional readout of cellular processes and metabolic activity
Clinical	Electronic health records	Structured and unstructured patient data from clinical care	Demographics, lab values, treatments, comorbidities, family history	Provides patient-level context and ground truth for diagnostic, prognostic, and predictive models
	Radiology/radiology reports	Medical imaging and their diagnostic reports	3D tumor volume, texture, metabolic activity, and radiological assessments	Enables a whole-body perspective and integration across diagnostic disciplines (Radiomics)
	Longitudinal outcomes	Data collected over time during patient follow-up	Overall survival, disease-free survival, recurrence, treatment response	Serves as the ultimate validation endpoint for training and evaluating prognostic models
Digital and derived	Pathologist annotations	Expert-derived labels on whole-slide images (e.g., regions of interest, cell types)	Semantic segmentation masks, bounding boxes, clinical scores (e.g., grade)	Provides high-quality, expert-curated labels for training and validating AI models
	Artificial intelligence generated features	Features extracted by deep learning models from raw data	Latent feature vectors, attention scores, predicted scores (e.g., for risk)	Creates compact, information-rich representations that facilitate downstream fusion tasks

require access to matched datasets encompassing clinical features and molecular expression profiles, emphasizing the necessity of comprehensive data collection for effective integration [3].

Advances in transcriptome prediction from pathology images exemplify the power of multimodal data fusion to infer molecular states directly from morphological features [25-29]. Multimodal data fusion technologies have been shown to enhance model performance by integrating medical imaging with molecular data, thereby facilitating transcriptome prediction and disease characterization [30]. Such approaches demonstrate the potential to reduce reliance on invasive procedures by extracting molecular insights solely from histological images. The capacity of models to infer fine-grained cellular information from histology images further exemplifies the benefits of multimodal integration. A notable example is cross-modal unified representation learning framework, a model trained on paired morphology and spatial transcriptomics data, which can accurately predict cell types from pathology images alone [31]. This capability underscores the potential of multimodal fusion to bridge the gap between morphological observations and underlying molecular identities, enabling more detailed cellular analyses without the need for extensive molecular assays.

Challenges in pathomics, particularly in liver cancer, highlight the importance of integrating multiomics data to link tumor morphology with molecular pathways such as EZH2 dysregulation and immune evasion mechanisms [32]. Despite these advances, key obstacles remain, including data heterogeneity, standardization issues, and the need for robust fusion algorithms capable of handling diverse data types effectively. The development of unified disease atlases through data integration is further exemplified by efforts to consolidate morphological, developmental, imaging, and clinical data into comprehensive frameworks. A recent proposal advocates for a tabular integration approach, aiming to create a unified platform that synthesizes all relevant data sources for better disease understanding [33]. Such integrations can serve as valuable resources for research and clinical decision-making.

In the realm of computational pathology, multi-modal foundation models are emerging as powerful tools for integrating diverse data modalities [34-38]. These models leverage biomedical terminologies, such as the Unified Medical Language System, to harmonize terminology across datasets, facilitating more effective data fusion [39]. This standardization is crucial for building scalable and interoperable models capable of handling complex, multimodal data. Finally, multimodal data fusion has demonstrated its utility in uncovering tumor microenvironment characteristics by integrating lncRNA data, immune-cell scores, clinical information, and pathology images [40]. Such comprehensive models enable nuanced prognostic predictions and deepen our understanding of tumor-immune interactions, which are critical for immunotherapy strategies.

In summary, the current literature emphasizes that data fusion in pathology-integrating morphologic, molecular, and clinical data-is fundamental to constructing detailed disease atlases. Multimodal deep learning and fusion models are at the forefront of this effort, offering enhanced diagnostic, prognostic, and therapeutic insights. Despite existing challenges, ongoing advancements promise to refine these integrative approaches, ultimately transforming pathology into a more precise and personalized discipline.

Multimodal Deep Learning for pan-cancer Integration

Multimodal deep learning for pan-cancer integration is a rapidly evolving field that leverages the combination of histology and genomic data to improve cancer diagnosis, prognosis, and treatment strategies (Table 2) [41-46]. This approach aims to integrate diverse data types to enhance the accuracy and interpretability of cancer predictions, addressing the limitations of unimodal models. The integration of multimodal data has shown significant promise in improving the prediction of cancer origins, survival outcomes, and the discovery of prognostic biomarkers. Below are key aspects of multimodal deep learning in pan-cancer integration.

Table 2: Multimodal deep learning architectures for pan-cancer analysis.

Model name/type	Fused modalities	Primary task(s)	Key innovation/fusion method
Pathomic fusion	Whole-slide images, genomics (e.g., mutations, copy number alterations)	Survival prediction, cancer subtyping	A sophisticated cross-modal attention layer that allows histology and genomic features to interact and gate each other
MultiSurv	Whole-slide images, clinical, molecular (e.g., gene expression, methylation)	Long-term pan-cancer survival prediction	Employs dedicated submodels per modality and a data fusion layer. Explicitly designed to handle missing data modalities
Deep orthogonal fusion	Radiology (MRI), pathology (whole-slide images), genomics, clinical	Glioma overall survival prediction	Uses attention-gated tensor fusion combined with a multimodal orthogonalization loss, forcing embeddings to be complementary
Graph deep learning	Multi-omics data (e.g., mRNA, miRNA, methylation)	Survival prediction, biomarker discovery	Model's biological data as a graph, capturing complex, non-linear interactions between molecular features
Robust multimodal fusion (discrete late fusion)	Clinical, RNA-seq, miRNA, DNA methylation, etc. (up to 6 modalities)	Survival prediction	A late fusion approach using synthetic data generation to compute time-dependent weights for each modality's contribution
MPath-Net	Whole-slide images, pathology report text	Cancer subtype classification	End-to-end fusion of image features and text embeddings (from Sentence-BERT) for joint classification
Deep attention-based multiple-instance learning	Radiology, histology (whole-slide images), genomics	Immunotherapy response prediction in non-small cell lung cancer	Integrates features from multiple domains using an attention-based multiple-instance learning framework
Pancancer deep learner (with multimodal dropout)	Clinical, mRNA, miRNA, whole-slide images	Pan-cancer overall survival prediction	Use an unsupervised encoder for each modality and employs 'multimodal dropout' during training to build resilience to missing data

Cancer origin prediction

- A multimodal deep learning algorithm was developed to classify tumors into 18 different primary origins by integrating histology slides, genomics data, and patient sex. This model achieved an accuracy of 88.1% on a held-out test set and 92.0% on an external test set, outperforming unimodal models that use either histology or genomic data alone [47].
- The model also demonstrated an 85.5% agreement with differential diagnoses in cases of cancers of unknown primary, highlighting its potential utility in clinical settings where data may be incomplete [47].

Survival prediction

- Multimodal deep learning models have been constructed to predict patient survival using multi-omics data, achieving higher accuracy than single-modality models. These models utilize unsupervised learning to extract high-level feature representations from different omics data, which are then integrated using attention-based methods [48]. The MultiSurv model, for instance, combines histopathology slides with clinical and molecular data to predict survival across 33 cancer types, demonstrating high predictive performance and the ability to handle missing data [49, 50].
- Pan-cancer survival prediction model: A deep learning model was developed to predict patient survival using multi-omics data. This model employs an unsupervised learning approach to extract high-level feature representations from different omics data modalities, followed by an attention-based integration method to produce a compact vector for survival prediction. The model demonstrated higher prediction accuracy compared to single-modal data approaches, achieving better performance across various cancer types using the concordance index and 5-fold cross-validation methods [48].
- Robust multimodal fusion model: This model uses a discrete late fusion approach with synthetic data generation to compute time-dependent weights for different modalities. Robust multimodal fusion model integrates up to six data modalities from the cancer genome atlas (TCGA) datasets, outperforming unimodal models by a significant margin in terms of the concordance index. The model highlights the complex relationships in multimodal fusion and sets a new benchmark for survival prediction in pan-cancer settings [51].
- MultiSurv: A method designed for long-term pan-cancer survival prediction, MultiSurv uses dedicated submodels for each data modality and a data fusion layer to aggregate multimodal representations. It provides accurate survival curves and can handle missing data, offering insights into cancer characteristics and heterogeneity. MultiSurv achieved the best results when combining clinical information with gene expression or DNA methylation data [50].

Prognostic biomarker discovery

- The integration of multimodal data allows for the identification of explainable morphological and molecular descriptors that govern prognosis. For instance, the presence of tumor-infiltrating lymphocytes was associated with favorable outcomes in several cancer types.
- An integrative platform was developed to discover prognostic features from histology and molecular data, using a weakly supervised, interpretable multimodal deep learning algorithm. This approach improved risk stratification in 9 out of 14 cancer types and identified significant associations between tumor-infiltrating lymphocytes and favorable prognosis [52].

- The platform also provides an open-access database for further exploration and biomarker discovery, facilitating the identification of morphological and molecular markers responsible for prognostic predictions [52].
- A graph deep learning algorithm that enhances survival prediction accuracy by integrating multimodal information. It achieved superior performance compared to single-modality models, highlighting the benefits of multimodal integration [53].

While multimodal deep learning offers significant improvements over traditional methods, challenges such as data heterogeneity, integration complexity, and the need for large, annotated datasets remain. Addressing these challenges will be essential for realizing the full potential of multimodal approaches in precision oncology. The ongoing research and development in this field are likely to yield more sophisticated models that can provide actionable insights for personalized cancer treatment.

Pathogenomics: Fusing Pathology, Genomics, and Clinical Data

Pathogenomics represents a transformative approach in the integration of pathology, genomics, and clinical data, aiming to enhance the precision and effectiveness of medical diagnostics and treatment [54-58]. This interdisciplinary field leverages advanced molecular diagnostics, histopathological imaging, and clinical data to discover new biomarkers and improve patient outcomes, particularly in oncology and infectious diseases. The fusion of these data types is facilitated by emerging technologies and methodologies, such as artificial intelligence and digital pathology, which enable a more comprehensive understanding of diseases and their progression.

Integration of multimodal data

- Pathogenomics involves synthesizing genomic data with histopathological and clinical information to identify novel cancer biomarkers, which can significantly advance precision oncology [59].
- The integration of digital pathology with genomics, known as histo-genomics, provides a spatial and microenvironmental context to molecular data, enhancing the understanding of cancer progression and aiding in personalized treatment plans [60].
- In infectious disease management, pathogen genomics facilitates improved diagnosis, tracking of antimicrobial resistance, and outbreak control by integrating genomic and epidemiological data [61].
- Gene-centric integration: The genome-scale integrated analysis of gene networks in tissues method exemplifies a gene-centric approach to integrating multimodal data by converting datasets into gene graphs and embedding them into a unified latent space. This method allows for the discovery of diverse gene functions and regulatory mechanisms across tissues and modalities, as demonstrated with the human biomolecular atlas program (HuBMAP) datasets [62].
- Single-cell and spatial genomics: In Alzheimer's disease research, multimodal integration of single-cell and spatial genomics data has been used to map disease progression and identify vulnerable cell populations. This approach provides insights into the molecular and cellular mechanisms driving disease progression, highlighting the importance of integrating transcriptomic, epigenomic, and spatial data [63].
- Pathogen profiling: The integration of microbial genomics with phenotypic and sequence-based data aids in understanding transmission patterns and epidemic dynamics, which is crucial for disease management and surveillance [64].

Technological and methodological advances

- The development of multimodal transformers, such as pathomics, allows for the integration of pathology and genomics data to predict cancer survival outcomes, demonstrating superior performance over traditional methods [65].
- The use of Fast Healthcare Interoperability Resources and Clinical Quality Language standards enhances data interoperability, crucial for integrating complex genomic data at the point of care [66].
- Advances in multi-modal deep learning enable the integration of incomplete data across radiological, pathological, genomic, and demographic domains, improving survival predictions in brain cancer [67].

While pathogenomics holds immense promises for revolutionizing healthcare, it also presents challenges that need to be addressed to fully realize its potential. The integration of diverse data types requires robust infrastructure, standardized methodologies, and collaborative efforts across disciplines. Moreover, the application of pathogenomics in resource-limited settings remains a critical area for development, as tailored approaches are necessary to optimize its impact on public health. As the field continues to evolve, it will be crucial to balance technological advancements with practical considerations to ensure equitable access and effective implementation.

Inferring Molecular Profiles from Histology Images

Inferring molecular profiles from histology images is a transformative approach that aims to bridge the gap between traditional histopathology and molecular profiling, offering a unified disease atlas. This integration is crucial for advancing precision medicine by providing insights into disease mechanisms and enabling personalized treatment strategies. Several computational frameworks have been developed to achieve this integration, leveraging advanced machine learning techniques to infer molecular data from histological images. These methods not only enhance the understanding of disease biology but also offer cost-effective alternatives to traditional molecular assays. Below are key approaches and methodologies discussed in the literature.

- Histology-enhanced contrastive learning (HECLIP): HECLIP is a deep learning framework designed to infer gene expression profiles directly from H&E-stained images, bypassing the need for expensive spatial transcriptomics assays. It employs an image-centric contrastive loss function to optimize image representation learning, capturing critical morphological patterns that correlate with gene expression profiles. Extensive benchmarking has shown HECLIP's superior performance in predicting gene expression, making it a scalable and cost-efficient tool for research and clinical applications [68].

- Single-cell omics from histology (SCHAF): SCHAF utilizes adversarial machine learning to generate spatially resolved single-cell omics datasets from H&E histology images. It has been demonstrated on human tumors, effectively generating single-cell profiles that align well with ground-truth scRNA-Seq data and expert pathologist annotations. This framework facilitates an integrated understanding of cell and tissue biology, paving the way for next-generation histology analyses [69].
- Connecting tumor histology with gene expression (PathOmCLIP): PathOmCLIP integrates morphological and expression features by creating a joint-embedding space between histopathology and single-cell RNA-seq models. It incorporates a set transformer to enhance performance by gathering localized tumor architecture, validated across multiple tumor types for improved gene expression prediction [70].
- Molecularly informed histopathology (SpotWhisperer): SpotWhisperer links histopathological images to spatial gene expression profiles using natural language processing, enabling molecularly grounded histopathology analysis. It outperforms existing models on spatially resolved H&E annotation benchmarks, allowing interactive exploration of cell types and disease mechanisms [71].
- Multimodal representation learning (MORPHEUS): MORPHEUS is a transformer-based framework that encodes both histopathology and multi-omics data into a shared latent space. It supports any-to-any omics generation, allowing inference of omics profiles from H&E images alone, and consistently outperforms state-of-the-art methods across diverse tasks [72].
- Hypergraph neural networks for gene expression prediction (HGGEP): HGGEP addresses limitations in existing methods by enhancing the model's perception of cell morphology and utilizing hypergraph neural networks to capture higher-order associations among features. It demonstrates superior performance in predicting gene expressions from histology images, particularly in cancer and tumor disease samples [72].

While these methods show promise in integrating histology and molecular data, challenges remain in ensuring robust algorithm development and clinical application. The complexity of biological systems and the variability in histological and molecular data necessitate further research to refine these computational models. Additionally, the ethical and practical implications of deploying artificial intelligence-driven diagnostics in clinical settings must be carefully considered to ensure patient safety and data privacy.

Multiomics and the Tumor Microenvironment

The integration of multiomics with the tumor microenvironment is pivotal in creating a unified disease atlas, which can significantly enhance our understanding of cancer biology and improve therapeutic strategies. Multiomics approaches, which include genomics, transcriptomics, proteomics, and metabolomics, provide a comprehensive view of the molecular landscape of tumors and their microenvironments. This integration allows for a more detailed characterization of the tumor microenvironment, which is crucial for understanding cancer progression, immune evasion, and therapy resistance. The development of a unified disease atlas through multiomics can facilitate personalized medicine by identifying specific molecular targets and biomarkers for individual patients.

Multiomics approaches in tumor microenvironment characterization

- Multiomics technologies enable the integration of various omics data, such as transcriptome, genome, and proteome, to provide a holistic view of the tumor microenvironment. This approach helps in understanding the complex interactions between cancer cells and their microenvironment, which includes immune cells, stromal cells, and secreted molecules [73].
- A novel multiomic spatial assay has been developed to simultaneously profile gene and protein expression in formalin-fixed paraffin-embedded tissue sections. This method allows for the spatial resolution of cellular behaviors within the tumor microenvironment, providing insights into disease progression and potential therapeutic targets [74].
- The creation of an omics and multidimensional spatial atlas from serial biopsies of metastatic breast cancer patients has demonstrated the potential of multiomics in tracking tumor evolution and identifying mechanisms of therapeutic resistance and vulnerability [75].

Applications in cancer research and therapy

- Multiomics profiling has been used to construct a diffuse large B-cell lymphoma atlas, which maps the spectrum of tumor microenvironments across samples and establishes a robust model for predictive modeling. This approach aids in understanding cancer evolution and tumor immune contexture from a personalized medicine perspective [76].
- The integration of over 50 single-cell RNA datasets into a unified atlas has revealed novel axes of tumor microenvironment variation, such as the enrichment of T-cells in naïve states and variations in macrophage signatures. This large-scale integration enhances the understanding of tumor microenvironment biology and supports therapeutic development [77].
- Multiomics data are being leveraged to identify actionable targets and design novel immunotherapeutic and molecular precision strategies tailored to the metastatic niche, providing a scientific rationale for tumor microenvironment targeted approaches in advanced-stage cancers [78].

Challenges and future directions

- Despite the advancements, challenges such as data standardization, integration, and interpretation remain. The development of comprehensive analytical tools, like immuno-oncology biological research 2, facilitates the integration of multiomics data and provides insights into tumor-immune interactions [79].

- The PACIFIC framework exemplifies the integration of genetic cancer drivers with immune cell infiltration profiles to identify clinically relevant immunogenomic interactions, highlighting the potential of multiomics in prognostic assessments and therapeutic target development [80].

While multiomics approaches offer significant potential in understanding and treating cancer, the complexity of the tumor microenvironment and the vast amount of data generated pose challenges in data integration and interpretation. Collaborative efforts and the development of standardized protocols are essential to overcome these challenges and fully realize the potential of a unified disease atlas. Additionally, while precision medicine has improved outcomes for some cancer patients, the variability in individual responses underscores the need for a deeper understanding of resistance mechanisms and the development of more effective, personalized therapeutic strategies [75].

Computational Frameworks and Foundation Models

The development of a unified disease atlas through computational frameworks and foundation models represents a significant advancement in the integration and analysis of complex biomedical data. This approach leverages the power of multivariate disease mapping and foundation models to create comprehensive, scalable, and interpretable representations of disease mechanisms and cellular states. By synthesizing information from various data sources, these models facilitate the discovery of novel insights into disease pathology and potential therapeutic targets.

- Multivariate disease mapping: Multivariate disease mapping involves joint analysis of multiple diseases, accounting for correlations among them. This approach is crucial for understanding complex disease interactions and patterns. A unifying framework for multivariate disease mapping has been proposed, which subsumes existing models and offers computational efficiency, enabling the analysis of numerous diseases simultaneously. This framework provides insights into the statistical properties of disease mapping models, enhancing the ability to interpret and predict disease patterns across different regions [81].

- Foundation models in healthcare: Foundation models, such as large-scale pre-trained models, are transforming the integration of heterogeneous medical data, including electronic health records, clinical notes, and medical imaging [82]. These models excel in capturing intricate patterns across diverse data modalities, supporting cross-modal understanding with minimal customization [82]. In oncology, the Harmonized ONcologY Biomedical Embedding Encoder framework uses foundation models to generate high-dimensional data representations, improving cancer-type separability and survival prediction [83].

- Single-cell data integration: The similarity framework provides a scalable representation of single-cell RNA-seq data, enabling the integration and querying of cellular states across millions of profiles. This approach facilitates the discovery of commonalities in cell states across different diseases and tissues, offering a unified view of the human cell atlas [84].

- Data discovery and exploration: Foundation models are also applied to data discovery and exploration tasks, outperforming task-specific models in table-class detection, column-type annotation, and join-column prediction. These models demonstrate superior performance and generalizability, suggesting a future where disparate data management tasks are unified under foundation models [84].

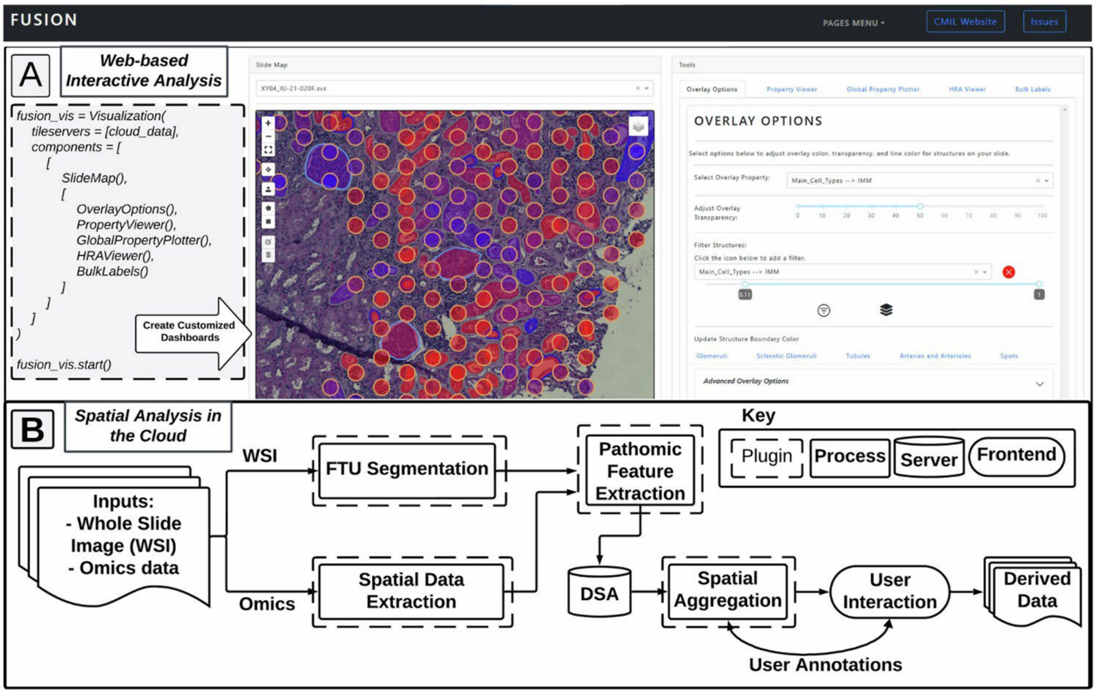
- Computational pathology: In computational pathology, foundation models like Virchow enable the detection of both common and rare cancers with high accuracy, even with limited training data. These models enhance the ability to model diverse patterns in pathology images, supporting clinical decision-making and precision medicine [85].

While the integration of computational frameworks and foundation models offers significant advancements in creating a unified disease atlas, challenges remain. These include the need for ethical considerations in data use, the complexity of integrating diverse data types, and the computational demands of large-scale models. Additionally, the development of these models requires careful validation and standardization to ensure their reliability and applicability across different healthcare settings. Despite these challenges, the potential of these models to transform disease understanding and treatment is immense, paving the way for more personalized and effective healthcare solutions.

Clinical Studies

The concept of a unified disease atlas through data fusion is an emerging field that leverages multi-source data integration to enhance disease understanding, diagnosis, and treatment. This approach involves combining diverse datasets, such as genomic, phenotypic, and clinical data, to create a comprehensive map of disease associations and characteristics. The integration of these datasets can lead to more accurate disease classification, improved prediction of disease associations, and enhanced diagnostic processes.

A study by Border et al. [86] reported functional unit state identification in whole slide images (FUSION) is a web-based, open-source platform designed for the in-depth exploration of multi-omics data integrated with brightfield histology. It offers a comprehensive suite of tools and functionalities for researchers. FUSION enables (Figure 1) the visualization and analysis of spatial-omics data alongside high-resolution histology, allowing for a combined understanding of molecular insights and tissue morphology. The platform provides specific workflows for various analytical tasks, including assessing cell compositions, performing quantitative morphometrics, and conducting comparative tissue analyse. FUSION has demonstrated applicability across a range of spatial assays. These include 10x Visium, Visium HD, 10x Xenium, Cell DIVE, and PhenoCycler. The platform has been applied to both healthy and diseased tissues from various organs, such as the kidney, small intestine, lung, and skin, within HuBMAP. In a series of use cases, FUSION has shown its capacity to: (i) distinguish renal glomeruli injury states, (ii) quantify morphometric changes within tissues, and (iii) characterize fibrosis with immune infiltration. FUSION is a cloud-based and open-source application, making it



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            [
                OverlayOptions(),
                PropertyViewer(),
                GlobalPropertyPlotter(),
                HRAViewer(),
                BulkLabels()
            ]
        ]
    ]
)
fusion_vis.start()
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Select options below to adjust overlay color, transparency, and line color for structures on your slide.

Select Overlay Property: Main_Cell_Types --> IMM

Adjust Overlay Transparency: 50

Filter Structures:

Click the icon below to add a filter.

Main_Cell_Types --> IMM

Update Structure Boundary Color

Figure 1: The cloud-based FUSION platform enables both unimodal and multimodal analysis of histology and spatial-omics data. Its processing pipeline first handles histological tissue units and spatial-omics data separately **(A)**. Following spatial aggregation, a custom interactive dashboard allows users to visualize the data, for instance, by overlaying a colormap on segmented kidney structures alongside spatial spots and applying data filters **(B)** [86].

widely accessible. It is accessible at https://fusion.hubmapconsortium.org/ and hosts over 50 paired datasets along with tutorials to guide users. In summary, FUSION provides an intuitive and interactive platform for integrating spatial omics data with histological context, facilitating detailed exploration of cellular and tissue-level features across diverse biological samples and experimental setups.

A study by Braman et al. [87] reported that the deep orthogonal fusion model was developed to predict the overall survival of glioma patients. This model integrates diverse multimodal data, including radiology scans, pathology slides, genomic information, and clinical factors. The deep orthogonal fusion model demonstrated significantly improved performance in predicting overall survival. It achieved a median C-index of 0.788 ± 0.067, which significantly outperformed ($p = 0.023$) the best performing unimodal model, which had a median C-index of 0.718 ± 0.064. The model effectively combines information from various data sources: multiparametric magnetic resonance imaging (MRI) exams (providing radiological insights), biopsy-based modalities (including H&E slide images and/or DNA sequencing (seq) for pathological and genomic data), and clinical variables (incorporating relevant patient-specific clinical factors). Prognostic embeddings from each modality are learned and then combined using attention-gated tensor fusion. To enhance the information gleaned from each modality and improve model performance, a multimodal orthogonalization loss term was introduced. This term incentivizes the constituent embedding to be more complementary. The prognostic model successfully stratifies glioma patients by overall survival within various clinical subsets. This capability adds further granularity to existing prognostic clinical grading and molecular subtyping methods. In summary, the deep orthogonal fusion model provides a robust framework for integrating diverse data types to predict glioma patient survival, showcasing superior performance and offering more detailed prognostic stratification than traditional unimodal approaches.

A study by Song et al. [88] introduces MPath-Net, a multimodal framework designed for enhanced cancer subtype classification and reports significant improvements over baseline models (Figure 2). MPath-Net achieved a classification accuracy of 94.65%. The model demonstrated a precision of 0.9553. A recall score of 0.9472 was obtained. The F1-score, a harmonic mean of precision and recall, was 0.9473. MPath-Net significantly outperformed baseline models, with a statistical significance of $p < 0.05$. This indicates that the multimodal approach provides a substantial advantage in cancer subtype classification. The framework provides attention to heatmaps, which offer interpretable tumor tissue localization. This feature enhances the clinical utility of the approach by allowing pathologists to understand which regions of the whole-slide images contribute most to the classification decision. The study utilized the TCGA dataset, comprising 1684 cases (916 kidneys and 768 lungs). For whole-slide images that feature extraction, multiple-instance learning was applied. Pathology reports were encoded using Sentence-BERT. The framework involved joint fine-tuning of these components for tumor classification. In summary, MPath-Net demonstrated superior performance in cancer subtype classification by effectively integrating whole-slide images and pathology reports, offering both high accuracy and valuable interpretability for clinical application.

A study by Bao et al. [89] reported PathoFusion platform, an open-source artificial intelligence framework, demonstrated significant capabilities in recognizing pathomorphological features and mapping immunohistochemical data, particularly in glioblastoma cases. PathoFusion achieved high accuracy in patch-level recognition of six typical pathomorphological features, with an area under the curve (AUC) of 0.985 ± 0.011. The system also showed strong performance in detecting associated immunoreactivity, yielding an AUC of 0.988 ± 0.001. The system successfully correlated CD276

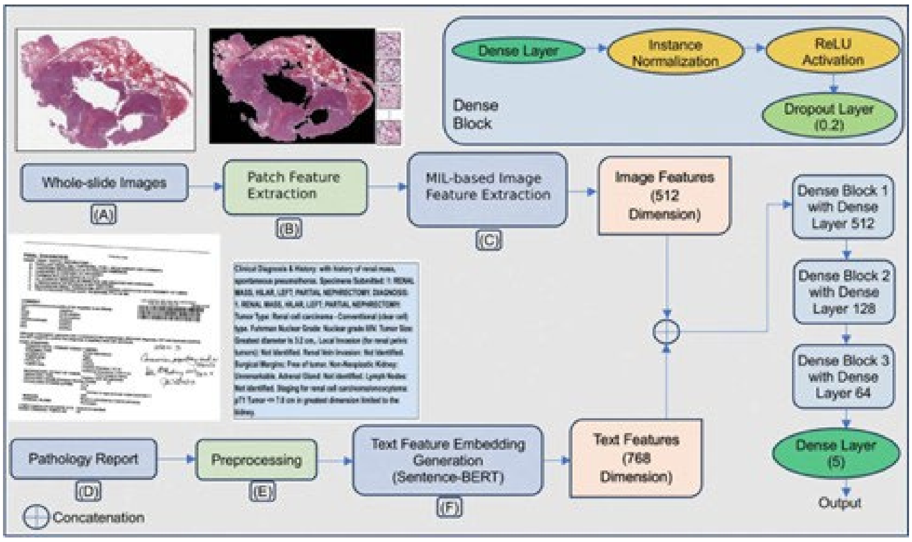

Figure 2: This diagram illustrates MPath-Net, our end-to-end multi-modal model for whole slide image classification. The workflow begins with **(A)** a raw whole slide image and **(B)** patch extraction, followed by **(C)** image feature extraction. Simultaneously, it processes **(D)** a pathology report in PDF format through **(E)** text preprocessing and **(F)** feature embedding generation using a Sentence-BERT model [88].

immunoreactivity with abnormal tumor vasculature. PathoFusion utilizes heatmaps to visualize corresponding feature distributions and overlaps. This allows for high-resolution qualitative and quantitative morphological analyses across entire histological slides. The system is designed to allow for the addition of more user-defined pathomorphological features, which can be included in future tissue analyses. In summary, PathoFusion proved effective in autonomously recognizing malignant neuropathological features and simultaneously mapping immunohistochemical data, achieving high accuracy metrics and providing detailed visualization tools for comprehensive tissue analysis.

A study by Wang et al. [90] results highlights the effectiveness of the deep learning clinical medicine based pathological gene multi-modal (DeepClinMed-PGM) model in predicting disease-free survival for breast cancer patients by integrating multi-modal data. The DeepClinMed-PGM model significantly improved the AUC values for disease-free survival predictions. In the training cohort, AUC values reached 0.979 for 1 year, 0.957 for 3 years, and 0.871 for 5 years disease-free survival predictions. For the external testing cohort, the AUC values were 0.851 for 1-year, 0.878 for 2-years, and 0.938 for 3-years disease-free survival predictions. The DeepClinMed-PGM model consistently demonstrated robust discriminative capabilities across various cohorts, indicated by significant hazard ratios (HR): (i) training cohort: HR of 0.027 (95% confidence interval (CI) 0.0016 to 0.046, $p < 0.0001$), (ii) internal validation cohort: HR of 0.117 (95% CI 0.041 to 0.334, $p < 0.0001$), and (iii) external cohort: HR of 0.061 (95% CI 0.017 to 0.218, $p < 0.0001$). The model also showed strong concordance (C-index) values, which measure the model's discriminative ability: (i) Training cohort: 0.925, (ii) internal validation cohort: 0.823, and (iii) external cohort: 0.864. In summary, the DeepClinMed-PGM model, by integrating imaging, molecular, and clinical data, achieved high predictive accuracy for breast cancer disease-free survival across different cohorts, as evidenced by improved AUC, significant HR, and strong C-index values.

A study by Vanguri et al. [91] successfully integrated multimodal data from radiology, pathology, and genomics to predict immunotherapy response in patients with non-small cell lung cancer, demonstrating improved predictive capacity compared to unimodal approaches. The study included 247 patients with advanced non-small cell lung cancer who received programmed death-ligand 1 (PD-(L)1) blockade therapy. Consistent with real-world proportions, only 25% of this cohort responded to immunotherapy. The best overall response was retrospectively assessed using response evaluation criteria in solid tumors (v.1.1) criteria, showing 55% progressive disease, 20% stable disease, 23% partial response, and 2% complete response. For analysis, the cohort was binarized into responders (complete response/partial response) and nonresponders (stable disease/progressive disease). The median progression-free survival was 2.7 months (95% CI 2.5 to 3.0), and overall survival was 11.4 months (95% CI 10.3 to 12.8). Standard clinical biomarkers like PD-L1 tumor proportion score and tumor mutational burden were significantly different between responders and nonresponders but were only modestly helpful in predicting response. For example, PD-L1 expression only modestly distinguished long-term response in the 5 year overall survival report of keynote-001. Classification models using tumor proportion score (AUC = 0.73) and tumor mutational burden (AUC = 0.61) were unable to fully separate the two groups. CT-based predictions of response were modest, primarily driven by texture in lung parenchymal lesions. The logistic model built from features derived from pleural nodules alone was unsuccessful (AUC = 0.28), while models for lung parenchymal nodules (AUC = 0.64) and pathologically enlarged lymph nodes (AUC = 0.63) showed better performance. Aggregating individual lesion predictions resulted in an overall AUC of 0.65. Automated feature extraction with immunohistochemistry (IHC) texture could approximate expert thoracic pathologist assessment. Logistic regression modeling using 18 features from the autocorrelation matrix and pixel intensity distribution resulted in a prediction accuracy of AUC = 0.62, which was comparable to lesion-wide radiological averaging but inferior to pathologist-assessed PD-L1 tumor proportion score (AUC = 0.73). Gray level co-occurrence matrix autocorrelation means (AUC = 0.67), and skewness (AUC = 0.69) were consistent with the multimodal cohort. Alterations in EGFR and STK11, along with tumor mutational burden, exhibited significantly adjusted HR in multivariable analysis. Tumor mutational burden showed a predictive ability of AUC = 0.61 for response. A model using tumor mutational burden and genomic alterations achieved an AUC of 0.65, outperforming the model trained with tumor mutational burden alone. The deep attention-based multiple-instance learning model (DyAM) integrated features from radiology, histology, and genomics. The DyAM model's multimodal integration significantly improved prediction of immunotherapy response. The multimodal model (AUC = 0.80, 95% CI 0.74 to 0.86) outperformed unimodal measures, including tumor mutational burden (AUC = 0.61) and programmed death ligand-1 IHC score (AUC = 0.73). The DyAM model was more effective at separating high- and low-risk patients than standard clinical biomarkers. Progression in 4 months was 21% for the lowest quartile and 79% for the highest quartile, demonstrating early stratification capabilities. The model was robust to the removal of IHC texture and PD-L1 tumor proportion score, though the removal of lung parenchymal nodule CT texture and genomic alterations had the greatest effect on AUC. In summary, the study highlights that integrating multimodal data through advanced machine learning techniques, such as the DyAM model, significantly enhances the prediction of immunotherapy response in non-small cell lung cancer patients. This approach provides a more robust and comprehensive understanding of patient response compared to using individual data modalities or standard biomarkers alone.

A research study by Cheerla and Gevaert [92] presented a deep learning model that leverages multimodal data for pan-cancer prognosis prediction, demonstrating several significant results. The model, trained in pan-cancer data, achieved an overall C-index of 0.78 for predicting both pan-cancer and single cancer survival overall. This indicates its robust predictive capability across various cancer types. The model effectively integrates and processes multiple data modalities, including clinical data, mRNA expression, microRNA expression, and histopathology whole slide images. The system efficiently analyzes whole slide images, which are typically high-resolution and complex, by using a stochastic sampling approach to select relevant regions of interest. It samples 200 224x224 pixel patches, computes their color balance, and selects the top 20% (40 patches) as regions of interest, ensuring non-representative areas like whitespace are ignored. These regions of interest represent, on average, 15% of the tissue region within the whole slide images. It represents patient multimodal data flexibly into an unsupervised, informative feature vector. This unsupervised encoding acts as a pan-cancer 'patient profile' that can summarize information from various modalities. The model is designed to handle missing data through a resilient, multimodal dropout method, which involves dropping entire feature vectors for a given modality during training. This improves the network's ability to build accurate representations even with incomplete data. Multimodal dropout consistently improved the validation C-index during training, leading to better performance. For instance, in models integrating all modalities, many cancer types (15 out of 20) showed a higher C-index with multimodal dropout, resulting in an average improvement of 2.8%. The overall C-index for the pan-cancer model integrating all four modalities (clinical, mRNA, miRNA, whole slide images) with multimodal dropout was 0.78, compared to 0.75 without dropout. Training the model on pan-cancer data generally improved survival prediction across individual cancer sites compared to training on single cancer datasets. For example, for cervical squamous cell carcinoma, pan-cancer training led to a 48% improvement over single cancer training, and for thyroid carcinoma, it showed a 69% improvement. Only one cancer site (KIRC) showed a decrease in performance with pan-cancer training. The study found that miRNA is the most informative modality for prognosis prediction in a pan-cancer setting, while mRNA is the least informative when all modalities are integrated. For specific cancers, different combinations of modalities were optimal; for example, integrating clinical, miRNA, and whole slide images data was sufficient and necessary for prognosis determination in kidney renal papillary cell carcinoma (KIRP), ovarian serous cystadenocarcinoma (OV), and lung adenocarcinoma (LUAD). The model achieves comparable or better results than previous research, particularly by handling incomplete data and predicting across 20 different cancer types. In summary, the paper introduces a powerful automated tool that effectively integrates diverse data types, handles missing information, and provides accurate prognosis predictions across multiple cancer types, marking a significant step towards personalized cancer treatment.

Challenges and Future Directions

The development of a unified disease atlas through data fusion presents both significant challenges and promising future directions. The integration of diverse datasets, such as electronic health records, imaging, and wearable device data, is crucial for creating comprehensive disease models. However, this process is fraught with difficulties, including data quality issues, interoperability, and the need for models that can generalize across different populations. Addressing these challenges requires innovative approaches in data harmonization, model architecture, and interdisciplinary collaboration. The following sections delve into the specific challenges and potential future directions in data fusion for a unified disease atlas.

Challenges in data fusion

- Data quality and standardization: The integration of heterogeneous data sources, such as electronic health records, imaging, and wearable devices, often suffers from inconsistencies and lack of standardization, which can lead to biased and unreliable outcomes. Ensuring data quality and compatibility is a significant hurdle in data fusion efforts [93].

- Interoperability and semantic integrity: Cross-institutional data sharing requires maintaining semantic integrity, which is challenging due to varying data standards and terminologies. Ontology-driven integration, such as the mondo disease ontology, is essential for harmonizing disease data across different platforms [94].

- Computational and ethical constraints: The computational demands of processing large-scale, multimodal datasets are substantial, and ethical considerations, such as data privacy and consent, further complicate data fusion efforts [95].

Future directions in data fusion

- Multimodal data integration: Emerging techniques in multimodal data fusion, such as early, intermediate, and late fusion methods, offer promising avenues for integrating diverse data types to enhance medical analysis and decision-making [96].

- Explainable and federated artificial intelligence: The development of explainable artificial intelligence models and federated learning approaches can address the need for interpretable models that respect data privacy while enabling collaborative data analysis across institutions [97].

- Innovations in model architecture: Advances in model architecture, including the use of quantum computing and hybrid models, can improve the efficiency and reliability of data fusion processes, reducing computational costs and complexity [97].
- Interdisciplinary collaboration: Cross-disciplinary efforts are crucial for developing generalized solutions to data fusion challenges, enabling more effective and efficient data analysis tools across various sectors [98].

While the integration of diverse datasets for a unified disease atlas presents numerous challenges, it also offers significant opportunities for advancing healthcare. The development of standardized frameworks and collaborative efforts across disciplines can facilitate the creation of more robust and reliable disease models. However, it is essential to address ethical considerations and ensure data privacy to gain the trust of stakeholders and promote the responsible use of data fusion technologies.

Conclusion

In conclusion, the integration of morphologic, molecular, and clinical data through advanced fusion techniques represents a paradigm shift in pathology. By leveraging multimodal deep learning and sophisticated computational frameworks, the field is moving decisively beyond subjective, single-modality assessments toward a future of objective, holistic disease profiling. The reviewed methodologies—from pan-cancer models and pathogenomics to molecular inference from histology—demonstrate a powerful capacity to unravel the complex interplay between tissue structure, genomic drivers, and clinical outcomes. This synergy is not merely additive but multiplicative, unlocking insights into tumor heterogeneity, the tumor microenvironment, and patient prognosis that were previously inaccessible, thereby paving the way for truly personalized therapeutic strategies.

Looking ahead, the full clinical translation of these integrative approaches hinges on overcoming persistent challenges. Key among these are the critical needs for robust data standardization, the development of scalable and interoperable foundation models, and the creation of explainable artificial intelligence (AI) systems that build clinical trust. Future research must prioritize federated learning solutions to navigate data privacy concerns and foster collaborative, cross-institutional model training. As these technical and ethical hurdles are addressed, the continued refinement of data fusion will undoubtedly cement its role as the cornerstone of next-generation pathology, ultimately fulfilling the promise of a unified disease atlas that seamlessly connects microscopic findings to patient-specific care.

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Conflict of Interest

None.

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