

# Machine Learning and Domain Knowledge in Biomedical Imaging

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## ABSTRACT

This analysis explores the integration of machine learning techniques and domain knowledge within the realm of biomedical imaging, emphasizing three pivotal areas: feature extraction, computational modeling, and annotation-efficient learning. Biomedical images contain complex and high-dimensional data, wherein effective feature extraction methods that incorporate expert insights can substantially improve downstream analysis. Computational models leveraging both data-driven algorithms and domain-specific information enable more accurate interpretation and predictive capabilities in various biomedical applications.

The primary objective of this study is to investigate how combining machine learning with domain expertise enhances the efficacy and robustness of biomedical image analysis. Specifically, it addresses challenges related to limited labeled datasets by focusing on annotation-efficient learning approaches that reduce dependency on extensive manual annotation while maintaining performance. The methodology includes an extensive literature review, quantitative evaluations, and case study analyses, highlighting recent advances and practical implementations.

Key findings demonstrate that the fusion of domain knowledge and machine learning significantly improves feature representation quality, model interpretability, and generalization across diverse biomedical imaging tasks. Annotation-efficient strategies, such as semi-supervised and weakly supervised learning, effectively leverage sparse labels without sacrificing accuracy. Moreover, computational modeling that synergizes mechanistic understanding with statistical learning contributes to more reliable diagnostic and prognostic tools.

Overall, this comprehensive examination underscores the critical role of integrating expert knowledge with advanced machine learning frameworks in biomedical imaging. The insights gained can guide future research and development efforts aimed at enhancing image-based healthcare solutions through efficient and scalable analytical pipelines.

## INTRODUCTION

Biomedical imaging has revolutionized modern healthcare by providing non-invasive visualization of anatomical structures and physiological processes. Techniques such as magnetic resonance imaging (MRI), computed tomography (CT), ultrasound, and fluorescence microscopy generate vast quantities of complex data that are essential for diagnosis, treatment planning, and biomedical research. However, the inherently high dimensionality, variability, and noise present in biomedical images pose significant challenges to accurate and efficient analysis. Traditional image analysis techniques often struggle to fully capture these complexities, which limits their reliability and clinical utility.

In recent years, machine learning (ML) has emerged as a transformative approach for biomedical image analysis. By learning patterns directly from data, machine learning algorithms can perform tasks such as segmentation, classification, anomaly detection, and prediction with increasing accuracy. Despite these advances, many machine learning models operate as “black boxes,” sometimes lacking interpretability, robustness, or generalizability, especially when trained on limited or biased datasets. Furthermore, biomedical image analysis

frequently suffers from scarcity of annotated data due to the high cost, expertise, and time required for manual labeling.

To address these limitations, the integration of domain knowledge with machine learning techniques has become a critical focus. Domain knowledge refers to the expert understanding of biomedical contexts, imaging modalities, biological constraints, and pathological characteristics. When effectively incorporated, this expertise can guide feature extraction to highlight biologically meaningful image patterns, constrain computational models to adhere to known mechanisms, and optimize learning strategies to reduce dependence on exhaustive annotations.

### Significance of Integrating Machine Learning and Domain Knowledge

The fusion of machine learning with domain knowledge enhances biomedical imaging analysis in several key ways:

- **Improved Feature Extraction:** Biomedical images often contain subtle and context-dependent features that standard algorithms may overlook. Domain knowledge can inform the design of feature detectors or filter banks tuned to specific anatomical or pathological characteristics. This results in richer and more discriminative feature representations that improve downstream tasks like classification or segmentation.
- **Robust Computational Modeling:** Incorporating domain expertise enables the development of hybrid models that combine mechanistic insights (e.g., biophysical modeling of tissue properties) with data-driven learning. Such models offer greater interpretability and can better generalize across patient populations or imaging conditions.
- **Annotation-efficient Learning:** Annotated biomedical imaging datasets are often limited by cost and human resource constraints. Domain knowledge can facilitate annotation-efficient learning approaches, such as semi-supervised, weakly supervised, or self-supervised learning. By embedding expert constraints, priors, or heuristic rules, these models reduce reliance on large volumes of labeled data while maintaining or improving performance.

### Challenges in Biomedical Image Analysis

Biomedical imaging analysis faces several domain-specific challenges that underscore the need for integrating domain knowledge with machine learning techniques:

- **High Dimensionality and Variability:** Images contain millions of pixels or voxels, capturing complex tissue heterogeneity, variable contrast, and anatomical differences. This requires advanced feature extraction methods that can preserve salient information while suppressing noise.
- **Limited and Noisy Annotations:** Obtaining high-quality ground truth labels is costly and time-intensive, often requiring expert radiologists, pathologists, or biomedical researchers. Additionally, even expert annotations can be subjective or inconsistent, affecting model training and evaluation.
- **Class Imbalance and Rare Pathologies:** Many biomedical datasets exhibit skewed distributions with prevalent healthy tissue and rare abnormal findings. Machine learning models need to be robust against these imbalances to effectively detect clinically important abnormalities.
- **Inter-patient Variability and Domain Shift:** Biological heterogeneity and differences in imaging protocols across institutions create domain shifts that challenge model generalizability.

In this context, incorporating domain knowledge helps to constrain algorithms with biologically plausible assumptions, improve data representations, and create flexible learning paradigms resilient to annotation scarcity and variability.

## Background and Scope of this Analysis

This comprehensive analysis focuses on the intersection of machine learning and domain expertise within biomedical imaging, exploring how this fusion addresses challenges in feature extraction, computational modeling, and annotation-efficient learning. Feature extraction is critical for capturing relevant image characteristics that reflect underlying tissue structures, pathological changes, or functional information. Computational modeling involves constructing predictive or descriptive frameworks that integrate empirical data with biomedical theories or constraints. Annotation-efficient learning methods aim to reduce the dependency on costly manual annotations by leveraging unlabeled data and domain-driven heuristics.

By examining recent developments across these areas, this study highlights the synergistic benefits of combining sophisticated machine learning algorithms with expert biomedical knowledge. Furthermore, it lays the foundation for quantitatively assessing the impact of such integrative approaches on real-world biomedical imaging applications. While this analysis primarily centers on medical and biological imaging modalities, the principles and methodologies discussed have broader implications across computational biology, bioinformatics, and healthcare technology.

The following sections will first clarify the research objectives and questions guiding this work, followed by a conceptual framework situating the role of domain knowledge in machine learning workflows. Subsequently, a detailed literature review will survey state-of-the-art methods and practices. The methodology section outlines the criteria for data selection, evaluation metrics, and analytical techniques. Quantitative analysis and case studies will then substantiate the theoretical premises with empirical evidence. Finally, the discussion will synthesize the findings and propose future directions for advancing this interdisciplinary field.

## Objectives

The primary objective of this analysis is to systematically investigate the fusion of machine learning methodologies and domain knowledge to enhance biomedical imaging analysis. This investigation will focus on clearly defined goals that address critical challenges and opportunities within feature extraction, computational modeling, and annotation-efficient learning. By establishing measurable objectives, the study aims to guide research efforts toward practical, high-impact outcomes in biomedical imaging applications.

### Specific Objectives

- **Enhance Feature Extraction Methods:** Develop and evaluate feature extraction techniques that effectively incorporate domain knowledge to improve the representation of biomedical images. This includes designing algorithms that can identify relevant anatomical and pathological features with higher discriminative power and robustness against noise and variability.
- **Improve Computational Modeling Accuracy:** Explore hybrid computational models that integrate machine learning algorithms with mechanistic and physiological domain insights. The objective is to achieve improved model interpretability, stability, and predictive accuracy across diverse imaging modalities and biomedical contexts.
- **Investigate Annotation-Efficient Learning Approaches:** Assess and benchmark semi-supervised, weakly supervised, and self-supervised learning methods tailored to biomedical imaging scenarios where labeled data are scarce. These approaches should leverage domain knowledge to minimize annotation requirements while preserving or enhancing model performance.
- **Evaluate Practical Case Scenarios:** Apply the integrated methodologies in real-world biomedical imaging tasks through case studies. Objectives include quantifying improvements in diagnostic accuracy, computational efficiency, and generalizability in clinical and research datasets.

## Measurable Goals

- Quantify feature extraction improvements using metrics such as feature relevance scores, signal-to-noise ratio enhancements, and downstream task classification accuracy.
- Assess computational models by comparing metrics including prediction error rates, model interpretability indices, and robustness to domain shifts.
- Evaluate annotation-efficient learning frameworks by measuring performance gains relative to baseline fully supervised models with varying annotation budgets.
- Demonstrate practical benefits via case study analysis, reporting metrics such as sensitivity, specificity, area under the receiver operating characteristic curve (AUC-ROC), and computational time.

Overall, these objectives anchor the analysis in a performance-driven framework aimed at advancing the state of biomedical image analysis through the synergistic integration of machine learning and domain knowledge.

## Research Questions

To guide this investigation into the integration of machine learning and domain knowledge in biomedical imaging, the following research questions are formulated. These questions align closely with the study's objectives and scope, addressing key aspects such as performance enhancement, methodological effectiveness, and practical challenges.

### **How does the incorporation of domain knowledge impact the accuracy and robustness of machine learning models in biomedical image feature extraction?**

This question explores the extent to which expert insights and biological constraints improve feature relevance, reduce noise sensitivity, and enable better characterization of complex tissues or pathologies.

### **In what ways can annotation-efficient learning methods, such as semi-supervised or weakly supervised learning, be optimized by integrating domain-specific priors to maintain or enhance model performance?**

This probes how domain knowledge can alleviate the scarcity of labeled biomedical image data by guiding model training on sparse annotations or unlabeled samples.

### **What improvements do hybrid computational models combining mechanistic domain knowledge with data-driven machine learning offer in terms of interpretability and generalization across varied biomedical imaging modalities?**

This addresses the balance between leveraging theoretical biomedical understanding and empirical learning to produce models that are both explainable and adaptable.

### **Which specific challenges arise when integrating domain knowledge into machine learning pipelines for biomedical imaging, and what strategies can effectively overcome these obstacles?**

This question investigates domain-specific issues such as heterogeneity of data sources, domain shifts, annotation inconsistency, and computational complexity, aiming to identify best practices.

### **How do integrated machine learning and domain knowledge frameworks perform in real-world biomedical imaging applications compared to traditional machine learning approaches without domain guidance?**

This emphasizes empirical validation through case studies and quantitative metrics to demonstrate practical benefits in clinical or research environments.

## Conceptual Framework

The conceptual framework presented herein serves as a foundational model elucidating the intricate relationships between **machine learning**, **domain knowledge**, **feature extraction**, **computational modeling**, and **annotation-efficient learning** within the context of biomedical imaging analysis. This framework is designed to guide both theoretical understanding and practical implementation by highlighting the flow of information, interactions, and dependencies among these key components.

## Key Components and Relationships

Biomedical imaging data are inherently complex, characterized by high dimensionality and variability. To extract meaningful information, this raw data undergoes a multi-stage analytical process informed by both machine learning methodologies and expert domain knowledge. Central to this process are three interconnected pillars: feature extraction, computational modeling, and annotation-efficient learning. The conceptual framework positions these pillars within a cohesive system as follows:

- **Machine Learning:** Serves as the core engine for data-driven pattern recognition and predictive analysis. Algorithms ranging from classical classifiers to deep neural networks adaptively learn representations and decision boundaries from data.
- **Domain Knowledge:** Encompasses expert insight derived from biomedical sciences, imaging physics, pathology, and clinical contexts. This knowledge informs the design, selection, and tuning of algorithms, ensuring biological and clinical relevance.
- **Feature Extraction:** Functions as the interface between raw biomedical images and subsequent computational analysis. Incorporating domain knowledge in feature extraction enhances the identification of salient anatomical, functional, or pathological markers, thereby producing discriminative and interpretable features.
- **Computational Modeling:** Builds upon extracted features to construct frameworks that integrate mechanistic insights with statistical learning. These models enable robust predictions, facilitate hypothesis testing, and support personalized medicine through explainability and adaptability.
- **Annotation-Efficient Learning:** Addresses limitations posed by scarce and expensive annotations in biomedical imaging. By leveraging domain-guided priors, heuristic constraints, and unlabeled data, these methods enhance learning efficiency and generalization without the exclusive reliance on extensive labeled datasets.

## Visual Representation of the Framework

The framework can be conceptually visualized as an interconnected flowchart:

- Biomedical Imaging Data (input) → **Feature Extraction** (augmented by Domain Knowledge)
- Extracted Features feed into **Computational Modeling**, which is simultaneously informed by Domain Knowledge for model constraints and interpretability.
- **Annotation-Efficient Learning** operates across the modeling pipeline, optimizing training strategies by integrating domain-driven priors and semi-/weakly supervised paradigms, enabling effective learning from limited annotations.
- Machine Learning algorithms form the computational backbone linking feature extraction, modeling, and annotation-efficient strategies.
- The output comprises interpretable, robust predictions and insights applicable to diagnosis, prognosis, and biological understanding.



## Interdependencies and Expected Interactions

The following interactions are central to the framework:

- **Domain Knowledge ↔ Feature Extraction:** Expert knowledge refines feature definition, ensuring that extracted patterns correspond to meaningful biological phenomena rather than artifact or noise.
- **Domain Knowledge ↔ Computational Modeling:** Integrating physiological and pathological understanding constrains models to biologically plausible solutions, enhancing explainability and reducing overfitting.
- **Machine Learning ↔ Annotation-Efficient Learning:** Machine learning algorithms are adapted to leverage unlabeled or weakly labeled data effectively, minimizing manual annotation burden while maintaining accuracy.
- **Feature Extraction ↔ Computational Modeling:** High-quality features facilitate more accurate and generalizable models, while insights from modeling may feedback to refine feature selection and extraction processes.
- **Annotation-Efficient Learning ↔ Domain Knowledge:** Domain expertise guides the development of priors and constraints pivotal for training with limited annotations, such as structural continuity, tissue-specific characteristics, or known pathology distribution.

## Guidance for Research Methodology and Analysis

This conceptual framework directly informs the methodology employed in this analysis:

- **Feature Extraction Strategies:** Methods are evaluated based on their capacity to integrate expert-defined criteria, such as texture measures, morphological descriptors, or functional imaging biomarkers, ensuring the biological validity of extracted features.
- **Development of Computational Models:** Research focuses on hybrid model designs combining mechanistic domain knowledge (e.g., tissue biomechanics, physiological modeling) with advanced machine learning architectures (e.g., convolutional neural networks, probabilistic graphical models).
- **Implementation of Annotation-Efficient Learning:** Investigation targets semi-supervised and weakly supervised algorithms that embed domain-informed constraints, thereby reducing annotation dependency without compromising predictive performance.
- **Quantitative and Qualitative Analysis:** Metrics and evaluation protocols are selected to capture how well the fusion of domain knowledge and machine learning enhances robustness, interpretability, and efficiency, reflecting the synergistic relationships depicted in the framework.
- **Case Study Selection:** Biomedical imaging applications chosen for empirical study exemplify diverse imaging modalities, pathologies, and annotation challenges, aligning with the framework's comprehensive scope.

## Summary

In essence, the conceptual framework situates machine learning and domain expertise not as isolated components but as deeply intertwined forces driving biomedical image analysis. It emphasizes the enhancement of feature extraction and computational modeling through domain-informed principles and the critical role of annotation-efficient learning to address real-world constraints in biomedical datasets. This integrated perspective provides a structured lens through which the research questions, methodology, and analytical strategies are developed,

ensuring that each step benefits from the symbiosis of data-driven algorithms and expert knowledge for advancing biomedical imaging outcomes.

## LITERATURE REVIEW

The intersection of machine learning (ML) and domain knowledge has become a cornerstone in advancing biomedical image analysis over the past decade. Traditional image processing often relied heavily on handcrafted features derived from expert understanding of anatomy, physiology, and pathology. While effective for specific tasks, these methods struggled with the scale, complexity, and variability inherent in modern biomedical datasets. The advent of data-driven machine learning, particularly deep learning, provided powerful tools for learning complex patterns directly from data, often surpassing traditional methods in tasks like image classification and segmentation (LeCun et al., 2015; Litjens et al., 2017). However, purely data-driven models can be data-hungry, sensitive to variations, and often lack interpretability, a critical requirement in clinical settings.

Consequently, researchers have increasingly focused on strategies to synergistically combine the pattern recognition capabilities of ML with the invaluable insights provided by domain experts. This fusion aims to develop models that are not only accurate but also more robust, interpretable, and efficient, particularly in scenarios where labeled data is scarce – a common challenge in biomedical imaging due to the cost and expertise required for annotation (Zhou, 2021). This literature review surveys key contributions from the past ten years (roughly 2014-2024) exploring this integration across three core areas: feature extraction, computational modeling, and annotation-efficient learning, along with relevant case studies.

### Integration of Machine Learning and Domain Knowledge in Biomedical Imaging

The fundamental premise of integrating domain knowledge into ML for biomedical imaging is that expert understanding can guide or constrain the learning process, making it more efficient and biologically relevant (Kononenko, 2018). Early approaches focused on using domain expertise to select or design input features for classical ML algorithms, a process known as feature engineering (Dougherty, 2016). For instance, radiomic features, such as texture, shape, and intensity statistics extracted from regions of interest identified by experts, were used as inputs for classifiers to predict treatment response or prognosis (Aerts et al., 2014; Lambin et al., 2017). This direct integration of expert-defined quantitative descriptors with ML demonstrated the value of combining domain-specific measurements with learning algorithms.

With the rise of deep learning, the focus shifted towards incorporating domain knowledge directly into model architectures or training processes (Zhou et al., 2019). One way this is achieved is through designing network layers or modules that mirror known biological structures or processes. For example, incorporating convolution kernels inspired by Gabor filters or wavelets, traditionally used in image processing informed by visual neuroscience (Larkin & Smith, 2018), can inject domain-specific prior structures into deep learning pipelines. Another approach involves using domain constraints as regularization terms during training. For segmentation tasks, spatial constraints derived from anatomical knowledge, such as connectivity or shape priors, can be added to the loss function to penalize biologically implausible outputs (Chen et al., 2016; Oktay et al., 2018).

Domain knowledge can also inform the initialization of network weights or the selection of appropriate network architectures. Transfer learning, a form of domain adaptation, leverages knowledge learned from large datasets (often natural images) to initialize models for biomedical tasks (Shin et al., 2016; Raghu et al., 2019). While successful, this often requires fine-tuning, and the initial weights may not be optimally suited for the specific characteristics of medical images. Integrating domain knowledge can involve using pre-trained models from related medical imaging tasks or designing architectures that exploit known image properties, such as the multi-scale nature of anatomical structures (Ronneberger et al., 2015).

Furthermore, domain knowledge can be used in post-processing steps to refine model outputs. Expert rules or anatomical atlases can correct segmentation errors or filter false positives from detection results, ensuring the final output aligns with clinical expectations (Litjens et al., 2017). This hybrid approach, combining data-driven

models with knowledge-based post-processing, offers a pragmatic way to integrate expertise. Reviews by Litjens et al. (2017) and Zhou et al. (2021) provide comprehensive overviews of various strategies employed to bridge the gap between ML and domain expertise in medical image analysis. A key challenge remains the formalization and representation of complex, often qualitative, domain knowledge in a way that is amenable to algorithmic integration (Kononenko, 2018).

### **Domain-Informed Feature Extraction**

Feature extraction is a crucial step that transforms raw image data into a more manageable and informative representation. In biomedical imaging, effective feature extraction must capture subtle visual cues related to underlying biological or pathological processes. Domain knowledge plays a vital role in guiding this process, moving beyond generic image descriptors to focus on biologically relevant patterns.

Traditionally, domain experts designed handcrafted features based on their understanding of the imaging modality and the target pathology. These include intensity histograms, texture features (e.g., Haralick features, Gabor filters), shape descriptors, and local binary patterns (LBP) (Castellano et al., 2013; Gillies et al., 2016). For example, in mammography, features related to mass shape (e.g., spiculation, margin smoothness) and texture (e.g., heterogeneity) are known indicators of malignancy, and algorithms were developed to quantify these specific properties based on radiologists' insights. Radiomics, as mentioned earlier, is a systematic extraction of such quantitative features from medical images, often guided by clinical expertise on what characteristics are relevant (Lambin et al., 2017).

With deep learning, feature extraction is often implicitly learned through the network's convolutional layers. However, domain knowledge can still influence this process. Convolutional Neural Networks (CNNs) can be designed with specific receptive field sizes or layer structures that mimic known hierarchies in visual perception or anatomical scales (Zhou et al., 2019). For instance, using multi-scale filters or incorporating attention mechanisms can help the network focus on features at different resolutions that are known to be important for a specific task, guided by domain understanding (Wang et al., 2018; Schlemper et al., 2019).

Another approach involves using domain knowledge to define "semantic features" or high-level concepts that a model should identify (Chen et al., 2020). For instance, in diabetic retinopathy screening, domain knowledge identifies microaneurysms, hemorrhages, and exudates as key features. While deep learning can detect these implicitly, explicitly training models to identify these intermediate features or constraining feature learning to emphasize these structures can improve interpretability and alignment with clinical understanding (Gulshan et al., 2016; Dai et al., 2019).

Furthermore, anatomical knowledge can be used to guide feature extraction within specific regions of interest (ROIs) or across different anatomical structures. This might involve using image registration to align images to an atlas and extracting features within predefined anatomical regions (Iglesias et al., 2015), or incorporating attention mechanisms that prioritize features from clinically relevant areas (Schlemper et al., 2019). Graph-based approaches can represent relationships between different extracted features or image regions, where the graph structure is informed by anatomical connectivity or spatial proximity (Zhang et al., 2018). For example, modeling the relationship between different brain regions based on known functional or structural connectivity using Graph Neural Networks (GNNs) and extracting features on this graph can be a powerful domain-informed approach (Parisot et al., 2017). Overall, the literature shows a trend towards hybrid approaches, where deep learning extracts complex features, but domain knowledge is used to guide, constrain, or interpret these learned features for better clinical relevance and performance (Zhou et al., 2021).

### **Computational Modeling with Domain Constraints**

Computational modeling in biomedical imaging goes beyond simple classification or segmentation to building predictive or descriptive frameworks that often incorporate some level of understanding of the underlying biology or physics. Integrating domain constraints into computational models can lead to more robust, generalizable, and interpretable outcomes.



One significant area is the development of physics-informed models. These models integrate physical principles governing image formation (e.g., MRI physics, CT reconstruction) or biological processes (e.g., diffusion models, biomechanical models) into the ML framework (Adler & Öktem, 2017; Meng et al., 2020). For example, incorporating the known forward model of MRI signal acquisition into a neural network can improve reconstruction quality and robustness, especially when data is limited (Aggarwal et al., 2018). Similarly, modeling tissue deformation based on biomechanical principles can constrain segmentation or registration algorithms, ensuring anatomically plausible transformations (Christodoulou et al., 2020).

Probabilistic graphical models (PGMs) offer a flexible framework to integrate domain knowledge through defining relationships between variables and encoding prior beliefs (Koller & Friedman, 2009). In biomedical imaging, PGMs can model anatomical variability, disease progression, or the relationship between imaging features and clinical outcomes (Criminisi et al., 2013). Hybrid models combining deep learning for feature extraction with PGMs for structured prediction or inference can leverage the strengths of both approaches. For instance, a deep network could extract local image features, which are then used as observations in a Conditional Random Field (CRF) or Markov Random Field (MRF) where pairwise potentials encode spatial smoothness constraints derived from anatomical priors (Chen et al., 2016).

Domain knowledge is also crucial in building models that capture disease progression or patient-specific responses (Zhu et al., 2019). Dynamic models, often informed by biological pathways or physiological models, can be combined with time-series imaging data using ML techniques to predict future states or classify disease subtypes (Altman et al., 2020). For instance, modeling tumor growth based on biological growth curves and imaging data can be used for prognosis prediction or treatment response assessment (Hassib & Shalaby, 2019).

Furthermore, domain constraints can enhance model interpretability. By building models whose components correspond to meaningful biological concepts (e.g., disentangling factors like age, disease status, and imaging artifacts), researchers can gain insights into the underlying relationships (Piao et al., 2019). For example, disentangled representation learning models that use domain labels or priors to separate latent factors can produce embeddings where specific dimensions correlate with clinical variables, making the model's decision process more transparent (Kohlbrenner et al., 2020). Integrating causal reasoning, informed by domain knowledge about disease mechanisms, into ML models is another frontier aimed at improving interpretability and generalizability beyond observational data (Schulam & Saria, 2017; Zhang et al., 2021). This allows models to potentially answer "what-if" questions, which is highly valuable in clinical decision support.

### **Annotation-Efficient Learning Strategies Leveraging Domain Knowledge**

A persistent bottleneck in applying supervised machine learning to biomedical imaging is the scarcity of large, high-quality labeled datasets. Annotating medical images is expensive, time-consuming, and requires highly specialized expertise, leading to small datasets with limited variability and potential annotation inconsistencies (Zhou, 2021). Annotation-efficient learning strategies aim to mitigate this challenge by leveraging unlabeled or weakly labeled data, and domain knowledge is instrumental in making these approaches effective in the biomedical context.

Semi-supervised learning (SSL) utilizes a small amount of labeled data along with a large amount of unlabeled data (Van Engelen & Hoos, 2020). Domain knowledge can enhance SSL by guiding the selection of unlabeled data or by providing consistency constraints. For instance, anatomical knowledge can suggest that neighboring pixels or voxels within the same tissue region should have consistent labels (spatial consistency), or that image transformations that preserve anatomy should also preserve labels (transformation consistency) (Laine & Aila, 2017). These domain-informed consistency criteria can be integrated into SSL loss functions to regularize the learning process on unlabeled data.

Weakly supervised learning (WSL) trains models using coarse-grained or indirect labels, such as image-level diagnoses, bounding boxes, or scribbles, instead of precise pixel-wise annotations (Zhou, 2018). Domain knowledge is critical in WSL to bridge the gap between the weak labels and the desired fine-grained task (e.g.,

segmentation). For example, anatomical atlases can serve as sources of weak labels or constraints, guiding a model to segment structures based on registration to the atlas rather than pixel-wise ground truth (Iglesias et al., 2015). In image classification tasks, domain knowledge can identify "hotspots" within the image that are most indicative of the weak label (e.g., a suspicious lesion in a chest X-ray), helping the model localize the pathology even without bounding box labels (Zhou et al., 2016). Pathological knowledge about the typical appearance and location of lesions is invaluable for generating attention maps or saliency maps that align with clinical relevance.

Self-supervised learning (SSL) trains models using automatically generated "pseudo-labels" derived from the data itself, often through pretext tasks (Liu et al., 2021). While generic pretext tasks like image rotation or jigsaw puzzles can be used, domain knowledge enables the design of more relevant pretext tasks for biomedical images. For instance, predicting the relative position of anatomical slices in a volume, restoring masked anatomical regions, or predicting image properties derived from physics (e.g., T1/T2 values in MRI) can serve as domain-informed pretext tasks that encourage the model to learn features relevant to the biomedical domain (Chen et al., 2019; Zhou et al., 2020). Pre-training on large archives of unlabeled medical images using such pretext tasks can provide a powerful initialization for downstream tasks with limited labels.

Transfer learning, as mentioned before, uses models pre-trained on large source datasets. While often applied using natural image datasets, pre-training on related medical datasets (e.g., training a lung nodule detection model on a large chest CT dataset before fine-tuning it on a smaller dataset for a different lung disease) is a more direct application of domain knowledge (Shin et al., 2016). Furthermore, multi-task learning, where a model is trained simultaneously on multiple related tasks (e.g., segmenting different organs), leverages shared domain knowledge across tasks to improve performance, especially when some tasks have more labels than others (Zhang et al., 2017). Domain knowledge helps in defining which tasks are related and how their learning can be jointly optimized.

### Relevant Case Studies and Applications

The integration of ML and domain knowledge has yielded significant results across various biomedical imaging applications. A prominent area is medical image segmentation, where accurate delineation of organs, tissues, and pathologies is crucial for diagnosis and treatment planning. Domain knowledge in the form of anatomical atlases has been successfully used for atlas-based segmentation, often combined with learning-based registration or refinement (Iglesias et al., 2015). Deep learning models incorporating anatomical constraints or trained with weak labels derived from atlases have demonstrated high performance with reduced annotation burden (Zhou et al., 2019). For instance, segmentation of brain structures in MRI (Zhang et al., 2018), organs in CT scans (Zhou et al., 2017), and tumors in various modalities have benefited from domain-informed approaches.

In disease detection and classification, integrating domain knowledge helps improve model interpretability and robustness. Radiomics features combined with ML classifiers have been used for cancer diagnosis and prognosis in lung, breast, and prostate cancers (Aerts et al., 2014; Gillies et al., 2016). Deep learning models guided by attention mechanisms that highlight clinically relevant regions, identified based on expert knowledge, have improved the detection of pathologies like diabetic retinopathy in retinal images (Gulshan et al., 2016) and interstitial lung disease patterns in CT (Anthimopoulos et al., 2016). Domain expertise also informs the selection of imaging sequences or views most relevant for specific diagnoses.

Disease progression modeling is another area benefiting from domain integration. By combining imaging data with clinical information and biological models of disease pathways, ML models can predict patient outcomes or identify progression trajectories (Zhu et al., 2019). For neurodegenerative diseases like Alzheimer's, models integrating structural and functional MRI features with knowledge of disease spread patterns have shown promise in early prediction (Altman et al., 2020; Suk et al., 2016). In cardiovascular imaging, integrating blood flow dynamics (physics-informed modeling) with ML from cardiac MRI can improve the assessment of heart function (Meng et al., 2020).

Case studies in digital pathology have demonstrated the power of combining domain expertise (pathologist insights on cellular morphology, tissue architecture) with deep learning for tasks like cancer grading, immune

cell profiling, and spatial transcriptomics analysis (Wang et al., 2019; Kather et al., 2019). Domain knowledge guides the identification of key morphological features, the design of algorithms sensitive to tissue heterogeneity, and the interpretation of complex spatial patterns. Annotation-efficient methods are particularly relevant here, as annotating large histopathology slides is extremely labor-intensive. WSL using slide-level diagnoses or sparse annotations has been effectively applied, guided by pathologist-defined criteria for identifying regions of interest (Zhou et al., 2017).

Furthermore, the integration extends to imaging reconstruction and enhancement. Physics-informed neural networks have been developed for faster and more accurate MRI reconstruction (Aggarwal et al., 2018) or denoising CT images (Kang et al., 2017), leveraging knowledge about the underlying signal generation and noise properties. These applications highlight how embedding domain knowledge can lead to models that are not only performant but also adhere to known physical laws, improving trustworthiness and clinical utility.

### Critical Analysis and Research Gaps

The literature clearly demonstrates the significant benefits of integrating machine learning with domain knowledge in biomedical imaging over the past decade. This fusion leads to models that are more accurate, robust, interpretable, and efficient in terms of annotation requirements compared to purely data-driven or purely knowledge-based approaches. Domain expertise provides crucial context, helps prioritize relevant information, constrains solutions to be biologically plausible, and guides learning in data-scarce environments. Annotation-efficient learning methods, particularly WSL and SSL, are significantly empowered by domain-specific priors and constraints, offering a practical path forward for leveraging vast amounts of unlabeled data.

Despite these advances, several challenges and research gaps remain. A fundamental difficulty lies in the formalization and representation of domain knowledge itself. Expert knowledge is often heuristic, context-dependent, and qualitative, making it challenging to translate into algorithmic constraints or quantifiable features (Kononenko, 2018; Zhou, 2021). Developing flexible frameworks that can effectively ingest and utilize diverse forms of domain knowledge (e.g., text reports, ontologies, expert rules, biological pathways) alongside imaging data is an ongoing area of research.

Another gap is in assessing the impact of domain knowledge systematically. While many studies claim improved performance, quantifying the specific contribution of the incorporated domain knowledge versus algorithmic advances or increased data size can be challenging. Standardized benchmarks and evaluation protocols are needed to rigorously compare different integration strategies (Litjens et al., 2017). Furthermore, the generalizability of domain-informed models across different imaging centers, scanners, and patient populations remains a critical concern, as domain knowledge relevant to one context may not directly apply to another (domain shift problem). Research is needed on developing adaptive integration strategies that can handle variability in imaging characteristics while preserving the core biological insights (Wang et al., 2022).

Interpretability remains a key driver for integrating domain knowledge, especially in clinical applications. While incorporating domain constraints can make models more aligned with biological understanding, the internal workings of complex deep learning models can still be opaque. Research is needed on developing inherently interpretable models that explicitly incorporate domain knowledge in their architecture and decision-making processes, rather than just post-hoc explanation methods (Zhou et al., 2019; Kohlbrenner et al., 2020).

Finally, while annotation-efficient learning is a vital area, the optimal strategies for leveraging domain knowledge vary significantly depending on the specific task, imaging modality, and type of available weak supervision. Research is needed to develop unified frameworks that can flexibly incorporate different types of domain knowledge and weak labels to maximize learning efficiency across diverse biomedical imaging problems (Zhou, 2021). Exploring causal inference methods within annotation-efficient learning frameworks, guided by domain knowledge about disease mechanisms, could further improve robustness and reduce reliance on purely correlational patterns learned from limited data (Zhang et al., 2021).

## RESEARCH METHODOLOGY

This section outlines the research design and methodological framework employed to analyze the fusion of machine learning (ML) and domain knowledge in biomedical imaging, with a specific focus on feature extraction, computational modeling, and annotation-efficient learning. Given the nature of this study as a comprehensive analysis building upon existing literature and conceptual frameworks, the methodology focuses on the systematic identification, synthesis, and evaluation of approaches documented in recent research. The overall approach is a structured literature-based analysis, complemented by a framework for evaluating practical implementations through quantitative metrics and case studies, as detailed in subsequent sections.

### Research Design

The research design is primarily analytical and evaluative. It involves a systematic review of the literature published over the past decade to identify key methodologies, techniques, and applications that integrate ML and domain knowledge in biomedical imaging. This systematic review forms the basis for identifying recurring themes, innovative approaches, and documented performance improvements across the three focal areas: feature extraction, computational modeling, and annotation-efficient learning. The analysis then proceeds to synthesize findings from selected studies, comparing different integration strategies based on reported outcomes, and critically evaluating their strengths, limitations, and applicability. The design also incorporates a framework for analyzing quantitative results and case studies from the literature or publicly available benchmarks that exemplify successful implementations of these integrated approaches.

### The research flow is structured as follows:

1. Systematic identification of relevant studies through database searches using keywords related to machine learning, domain knowledge, biomedical imaging, feature extraction, computational modeling, and annotation-efficient learning.
2. Filtering of studies based on publication date (last 10 years) and relevance to the core themes.
3. Extraction of key information from selected studies, including the specific problem addressed, imaging modality, type of domain knowledge incorporated, ML algorithms used, method of integration, dataset characteristics, evaluation metrics, and reported results.
4. Categorization and synthesis of findings according to the three main areas of focus.
5. Development of a framework for quantitative evaluation based on reported metrics in the literature.
6. Selection and analysis of representative case studies demonstrating the practical impact of the integrated approaches.
7. Critical discussion of the findings, challenges, and future directions.

This design allows for a comprehensive overview of the state-of-the-art and provides a structured basis for evaluating the efficacy of integrated ML and domain knowledge approaches.

### Data Sources

As this analysis is primarily literature-based, the "data sources" refer to the research publications themselves. However, for discussing the methodologies applied in the field and for analyzing case studies, it is necessary to describe the types of biomedical imaging data commonly used. These typically include:

### Medical Imaging Data:

Modalities: MRI (Magnetic Resonance Imaging), CT (Computed Tomography), PET (Positron Emission Tomography), Ultrasound, X-ray, Mammography, Digital Pathology (Whole Slide Images).

Anatomical Regions: Brain, lung, heart, abdomen, breast, prostate, retina, skin, etc.



Tasks: Segmentation (organs, tumors, lesions), classification (disease detection, subtype identification), registration, image reconstruction, disease progression prediction.

### **Biological Imaging Data:**

Modalities: Fluorescence Microscopy, Electron Microscopy, Histology.

Tasks: Cell segmentation and counting, organelle detection, analysis of cellular morphology, tissue structure analysis.

**Publicly Available Datasets:** Databases such as The Cancer Imaging Archive (TCIA), Medical Image Computing and Computer Assisted Intervention (MICCAI) challenges datasets, Kaggle competitions data, and other institutional data-sharing initiatives. These serve as crucial resources for validating and comparing different methods.

**Proprietary/Institutional Datasets:** Data collected within specific research institutions or clinical settings, often used in individual studies. Access to detailed descriptions of these datasets from the literature is essential for understanding the context of reported results.

**Simulated Data:** Some studies utilize synthetic data generated based on known physical models or biological processes, particularly for evaluating methods under controlled conditions or when real data is scarce.

Information regarding these data sources (modality, size, annotation level, characteristics) is extracted from the reviewed literature to contextualize the reported methodologies and results.

### **Preprocessing Techniques**

Preprocessing is a crucial step in biomedical image analysis, aimed at normalizing image data, reducing noise, correcting artifacts, and enhancing features relevant for downstream analysis. The choice of preprocessing techniques is often heavily influenced by the imaging modality and the specific task, reflecting implicit or explicit domain knowledge. Common preprocessing steps reviewed include:

- **Intensity Normalization/Standardization:** Adjusting pixel/voxel intensity ranges to ensure consistency across different scans or subjects (e.g., Z-score normalization, histogram matching). Domain knowledge helps in selecting appropriate reference tissues or intensity ranges.
- **Resampling and Registration:** Aligning images from different time points, modalities, or subjects to a common space or resolution. This often involves rigid, affine, or non-rigid transformations, guided by anatomical landmarks or atlas information derived from domain knowledge.
- **Noise Reduction:** Applying filters (e.g., Gaussian, Median, Non-local Means) or more advanced techniques to suppress random variations while preserving relevant image structures. Domain knowledge guides filter selection based on noise characteristics of the modality.
- **Artifact Correction:** Addressing specific imaging artifacts such as bias field inhomogeneity in MRI, metal artifacts in CT, or motion artifacts. Techniques range from retrospective algorithms to ML-based methods, often designed with knowledge of artifact physics.
- **Region of Interest (ROI) Extraction:** Cropping or masking images to focus on specific anatomical regions relevant to the task, often based on anatomical atlases or preliminary segmentation guided by domain expertise.
- **Image Enhancement:** Applying techniques to improve contrast or highlight specific features (e.g., histogram equalization, contrast-limited adaptive histogram equalization - CLAHE), potentially guided by domain knowledge about the visual appearance of relevant structures.



- **Data Augmentation:** Applying random transformations (rotation, scaling, elastic deformation, intensity changes) to increase dataset size and variability, particularly important for training ML models. Domain knowledge ensures that transformations preserve the semantic meaning and biological plausibility of the images.

The review assesses how domain knowledge informs the selection and application of these techniques to optimize data quality and relevance for subsequent ML analysis.

### Machine Learning Algorithms Employed

A wide array of ML algorithms are used in biomedical imaging, broadly categorized into traditional methods and deep learning approaches. This analysis examines the types of algorithms employed and how their application is influenced by domain knowledge:

#### Traditional ML Algorithms:

- Support Vector Machines (SVM), Random Forests, Gradient Boosting Machines (GBM) are often used with handcrafted or radiomic features.
- Clustering algorithms (e.g., K-Means, Hierarchical Clustering) for image segmentation or pattern discovery.
- Principal Component Analysis (PCA) or other dimensionality reduction techniques.

#### Deep Learning Algorithms:

- Convolutional Neural Networks (CNNs) and their variants (e.g., U-Net for segmentation, ResNet, VGG, Inception for classification) are predominant for image processing tasks.
- Recurrent Neural Networks (RNNs) or LSTMs for sequential data like dynamic imaging series.
- Generative Adversarial Networks (GANs) for data augmentation, synthesis, or image translation tasks.
- Graph Neural Networks (GNNs) for analyzing relationships between image regions or features based on anatomical connectivity.
- Attention Mechanisms to focus model learning on relevant image areas.
- Transformer networks, increasingly used for medical image analysis.

**Probabilistic Graphical Models (PGMs):** Markov Random Fields (MRFs), Conditional Random Fields (CRFs) used for structured prediction tasks like segmentation, often combined with deep learning outputs.

The methodology investigates how domain knowledge guides the selection of appropriate architectures, hyperparameters, and loss functions for these algorithms, particularly in the context of feature extraction, modeling, and annotation efficiency.

### Incorporation of Domain Knowledge

Integrating domain knowledge is central to the methodologies reviewed. This integration occurs at various stages of the ML pipeline:

- **Feature Engineering:** Manually designing features (e.g., radiomics, shape descriptors, texture analysis) based on expert understanding of relevant visual markers for specific pathologies or structures.

- **Data Annotation and Curation:** Domain experts provide labels, bounding boxes, segmentations, or even rules for generating weak labels, guiding the training data creation.
- **Model Architecture Design:**
  - Designing network structures that reflect anatomical hierarchies or known processing pathways (e.g., U-Net's skip connections for multi-scale feature integration).
  - Incorporating domain-specific layers or modules (e.g., layers mimicking physical processes, attention mechanisms guided by clinically relevant regions).
- **Loss Function Design:** Adding regularization terms derived from domain knowledge to penalize biologically implausible outputs (e.g., smoothness constraints for segmentation, anatomical shape priors, consistency constraints for unlabeled data).
- **Initialization and Transfer Learning:** Using weights pre-trained on large medical image datasets or related tasks as a form of domain transfer, rather than relying solely on initialization from natural image datasets.
- **Physics-Informed Modeling:** Embedding known physical laws or models related to image acquisition or biological processes directly into the ML model structure or loss function.
- **Constraint Satisfaction:** Enforcing constraints derived from domain knowledge during training or inference (e.g., volume constraints for organ segmentation, spatial relationships between structures).
- **Weak Supervision Signal Generation:** Using atlases, reports, or heuristic rules provided by experts to generate weak labels for training annotation-efficient models.
- **Post-processing:** Applying domain-informed rules or algorithms to refine the raw output of ML models, correcting inconsistencies or filtering implausible results.

The analysis compares these various integration strategies based on their impact on model performance, interpretability, and annotation efficiency as reported in the literature.

## Validation Methods

Rigorous validation is essential to assess the performance and generalizability of the proposed methods. The review examines common validation strategies used in the literature:

- **Dataset Splitting:** Using standard splits into training, validation, and test sets. The methodology notes whether splits are random, patient-wise (to avoid data leakage), or multi-institutional (to assess generalization across domains).
- **Cross-Validation:** Techniques like k-fold cross-validation to ensure robustness of results on limited datasets.
- **External Validation:** Testing models on completely independent datasets from different institutions or populations to evaluate generalizability and robustness to domain shift.
- **Comparison Baselines:** Comparing integrated methods against:
  - Purely data-driven ML models (e.g., deep learning without explicit domain constraints).
  - Traditional image analysis methods based solely on handcrafted features or rules.

- Human expert performance (when ground truth is based on consensus or established clinical practice).
- **Qualitative Evaluation:** Visual inspection of model outputs by domain experts (e.g., radiologists, pathologists) to assess clinical plausibility and identify failure modes.
- **Ablation Studies:** Analyzing the impact of individual components of the integrated framework (e.g., removing a specific domain constraint or feature type) to quantify its contribution.

### Tools for Quantitative Evaluation

Quantitative evaluation relies on specific metrics and computational tools. The analysis references metrics commonly used in biomedical image analysis, categorized by task:

- **Classification:** Accuracy, Sensitivity (Recall), Specificity, Precision (Positive Predictive Value), F1-score, Area Under the Receiver Operating Characteristic Curve (AUC-ROC), Area Under the Precision-Recall Curve (AUC-PR).
- **Segmentation:** Dice Similarity Coefficient (DSC), Jaccard Index (IoU), Sensitivity, Specificity, Average Symmetric Surface Distance (ASSD), Hausdorff Distance.
- **Detection/Localization:** Free-Response Receiver Operating Characteristic (FROC) curve, Average Precision (AP).
- **Regression/Prediction:** Mean Absolute Error (MAE), Mean Squared Error (MSE), R-squared.
- **Feature Extraction:** Feature relevance scores, separability metrics, correlation with clinical outcomes.
- **Annotation Efficiency:** Performance metrics evaluated as a function of the amount or quality of labeled data used for training.

Common software libraries and frameworks used for implementing and evaluating these methods include:

- Machine Learning Libraries: TensorFlow, PyTorch, scikit-learn, Keras.
- Medical Image Processing Libraries: SimpleITK, ITK, NiPy, nibabel, VTK, OpenCV (for general image processing).
- Specific domain-informed libraries or frameworks developed for particular tasks or modalities, as identified in the literature.

### Reproducibility

Ensuring the reproducibility of research findings is paramount. For this analysis, which synthesizes findings from the literature, reproducibility pertains to the clarity and detail provided in reporting the methodology and the ability for other researchers to understand and potentially replicate the reviewed methods given access to the same data and tools (where publicly available). Steps taken or assessed for reproducibility in the reviewed literature typically include:

- Detailed description of data sources, including access information if public.
- Clear specification of preprocessing steps and parameters.
- 9 Explicit definition of ML model architectures, hyperparameters, and training procedures (optimizers, learning rates, epochs).

- Description of how domain knowledge is formally incorporated into the framework.
- Details on validation protocols and metrics used.
- Availability of code (e.g., on GitHub) and model weights (less common for biomedical imaging but increasing).
- Use of containerization (e.g., Docker) to manage dependencies (an emerging practice).

In synthesizing the literature, this analysis aims to report the methodologies with sufficient detail drawn from the source publications to allow readers to grasp the implementation specifics and assess the reproducibility of the reported results within the context of the original studies.

## ANALYSIS OF DATA

This section presents a detailed quantitative and qualitative analysis of the findings pertaining to the fusion of machine learning (ML) and domain knowledge within biomedical imaging. Drawing upon the structured review of recent literature and building upon the methodologies described previously, this analysis synthesizes reported outcomes to evaluate the effectiveness and limitations of integrating domain expertise across feature extraction, computational modeling, and annotation-efficient learning strategies. While this document does not present novel experimental results, it interprets and compiles evidence from the field to highlight key trends and demonstrated improvements, supported by illustrative data representations common in the literature.

### Quantitative Evaluation and Metrics

The effectiveness of integrating domain knowledge with machine learning in biomedical imaging is primarily assessed through quantitative evaluation using a variety of performance metrics. These metrics provide objective measures of how well algorithms perform specific tasks such as classification, segmentation, detection, or regression, enabling comparison between different approaches. The choice of metric is task-dependent and reflects the specific clinical or biological goal.

For binary classification tasks, common metrics include:

- **Accuracy:** The proportion of correctly classified instances (true positives + true negatives) out of the total number of instances.
- **Sensitivity (Recall):** The proportion of actual positive instances that are correctly identified. This is crucial for detecting diseases or abnormalities. 
$$\text{Sensitivity} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}}$$
- **Specificity:** The proportion of actual negative instances that are correctly identified. This is important for correctly ruling out disease. 
$$\text{Specificity} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives}}$$
- **Precision (Positive Predictive Value):** The proportion of predicted positive instances that are actually positive. Relevant when the cost of false positives is high. 
$$\text{Precision} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}}$$
- **F1-score:** The harmonic mean of Sensitivity and Precision, providing a balance between the two.
- **Area Under the Receiver Operating Characteristic Curve (AUC-ROC):** Measures the classifier's ability to distinguish between positive and negative classes across various threshold settings. An AUC of 1.0 indicates a perfect classifier, while 0.5 indicates random chance. A higher AUC signifies better performance.

- **Area Under the Precision-Recall Curve (AUC-PR):** Especially informative for datasets with significant class imbalance, focusing on the trade-off between precision and recall.

For image segmentation tasks, metrics quantify the overlap and boundary agreement between the predicted segmentation and the ground truth:

- **Dice Similarity Coefficient (DSC):** Measures the overlap between two segmentation masks. 
$$\text{DSC} = \frac{2 |A \cap B|}{|A| + |B|}$$
 where A and B are the predicted and ground truth masks, respectively. A DSC of 1.0 indicates perfect overlap.
- **Jaccard Index (IoU - Intersection over Union):** Another measure of overlap, related to DSC. 
$$\text{IoU} = \frac{|A \cap B|}{|A \cup B|}$$
- **Sensitivity and Specificity (for segmentation):** Can be applied pixel-wise or voxel-wise to measure true positive/negative rates for foreground/background classes.
- **Surface Distance Metrics:** Quantify the agreement of the boundaries, such as Average Symmetric Surface Distance (ASSD) and Hausdorff Distance (HD). These are sensitive to boundary errors.

Other tasks utilize specific metrics, such as Free-Response Receiver Operating Characteristic (FROC) curves for object detection, and Mean Absolute Error (MAE) or Root Mean Squared Error (RMSE) for regression or prediction tasks.

Quantitative analysis involves comparing these metrics for:

- ML models trained without explicit domain knowledge versus those incorporating domain knowledge.
- Different strategies for integrating domain knowledge.
- Annotation-efficient learning methods (SSL, WSL, Self-supervised) leveraging domain knowledge versus fully supervised learning with varying amounts of data.
- Comparing model performance against human expert variability or established clinical benchmarks.

The literature consistently demonstrates that incorporating domain knowledge leads to statistically significant improvements in these metrics across various biomedical imaging tasks, often enabling models to achieve performance levels closer to or exceeding those of highly-trained human experts under specific conditions.

## Analysis of Results: Fusion of ML and Domain Knowledge

### Feature Extraction

Studies focusing on domain-informed feature extraction report improvements in feature discriminability and interpretability. Radiomic features, designed based on expert knowledge of tumor texture, shape, and intensity, combined with traditional ML classifiers (e.g., SVM, Random Forest), have shown prognostic value comparable to or better than clinical factors alone in various cancers (Aerts et al., 2014; Lambin et al., 2017). For example, studies in lung cancer prognostication using CT images demonstrate that specific texture features (derived from understanding tissue heterogeneity) are strongly correlated with survival outcomes. Integrating these handcrafted, domain-defined features improved model performance compared to using generic image features alone.

In deep learning, incorporating domain knowledge into feature learning often involves architectural designs or training strategies. Models using attention mechanisms guided by anatomical priors or clinically relevant regions (identified by experts) have shown improved localization accuracy and classification performance. For instance, in detecting diabetic retinopathy lesions, models incorporating attention maps learned from expert annotations or



saliency guided by known lesion appearances achieved higher sensitivity for detecting subtle microaneurysms compared to standard CNNs (Gulshan et al., 2016). Ablation studies typically show a drop in performance when the domain-informed components (e.g., specific feature descriptors, attention layers) are removed, quantifying their contribution.

Quantitative results often show higher feature relevance scores (e.g., mutual information with target variable) for domain-informed features and improved classification or segmentation performance metrics (higher accuracy, AUC, DSC) when these features are used.

### Computational Modeling

Integrating domain constraints into computational models results in models that are not only accurate but also more robust and biologically plausible. Physics-informed neural networks for image reconstruction (e.g., MRI) demonstrate superior robustness to undersampling artifacts and achieve higher reconstruction fidelity (lower RMSE) by incorporating the known signal acquisition physics into the network architecture or loss function compared to purely data-driven reconstruction methods (Aggarwal et al., 2018).

Hybrid models combining deep learning with probabilistic graphical models or anatomical constraints have significantly improved segmentation accuracy and topological correctness. For instance, segmenting complex, deformable structures like the heart ventricles or brain tumors often benefits from anatomical priors (e.g., shape templates, spatial relationships between structures) encoded as constraints in the loss function or as part of a PGM framework that refines deep learning outputs. Studies using U-Net architectures augmented with CRF layers or trained with shape-regularized loss functions report higher DSC and lower surface distance errors, while also producing more topologically correct segmentations compared to standard U-Net (Chen et al., 2016; Oktay et al., 2018). The resulting models exhibit improved generalization across datasets with different levels of noise or variation, a key aspect of robustness.

Beyond accuracy metrics, qualitative assessment by domain experts is crucial for these models. Clinicians evaluate whether segmentations are anatomically correct or whether predictions align with physiological understanding. Interpretability is also a key outcome; models designed with components mapping to biological concepts (e.g., disentangled representation learning with clinical labels) facilitate understanding which factors contribute to a decision, moving beyond black-box predictions (Piao et al., 2019; Kohlbrenner et al., 2020).

### Annotation-Efficient Learning

Quantitative analysis of annotation-efficient learning methods leveraging domain knowledge consistently shows that they can achieve performance metrics comparable to or approaching fully supervised methods while using significantly less labeled data. This addresses a major bottleneck in biomedical imaging.

Semi-supervised learning methods incorporating domain-informed consistency constraints (e.g., spatial smoothness, transformation invariance respecting anatomy) demonstrate higher accuracy and DSC when trained with a small labeled set and a large unlabeled set compared to training a supervised model solely on the small labeled set. For example, segmentation tasks on large medical image archives using SSL with structural consistency priors often show only a marginal decrease in DSC compared to models trained with full supervision on the entire dataset, but require only 1-10% of labels (Laine & Aila, 2017; Zhou et al., 2021).

Weakly supervised learning, using image-level labels or bounding boxes augmented by domain knowledge (e.g., typical lesion location, size constraints from atlases), enables tasks like precise segmentation or localization without requiring pixel-wise masks. Studies using CNNs with Class Activation Maps (CAMs) or attention mechanisms guided by domain heuristics or atlases, trained only with image-level labels, achieve promising segmentation DSC scores (e.g., 0.7-0.8) for easily identifiable structures, which is significantly higher than random chance and often sufficient for screening purposes, despite not reaching the ~0.9+ DSC typically achieved by fully supervised methods with dense annotations (Zhou et al., 2016; Zhou, 2018). The trade-off is often between the precision of the annotation (pixel vs. image level) and the achievable performance ceiling.

Self-supervised learning, using domain-informed pretext tasks (e.g., predicting anatomical slice position, reconstructing anatomical regions), has shown great promise for pre-training models on massive unlabeled medical image archives. Models pre-trained this way and then fine-tuned on small downstream task datasets achieve significantly higher AUC or DSC compared to models initialized randomly or with weights from natural image datasets (Chen et al., 2019; Zhou et al., 2020). The quantitative gain varies depending on the relevance of the pretext task to the downstream task, demonstrating the importance of domain knowledge in designing effective pretext tasks.

## Tables of Illustrative Results

The following tables provide illustrative examples of the types of quantitative performance comparisons frequently reported in the literature. These values are representative of trends observed across numerous studies in various biomedical imaging applications and are not results from a specific, single experiment conducted for this document. They serve to demonstrate the typical impact of integrating domain knowledge and employing annotation-efficient strategies compared to baseline approaches.

Table 1: Illustrative Comparative Classification Performance (e.g., Disease Detection from Image Scans)

Method	Dataset Size (Labeled Samples)	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC-ROC
Pure Data-Driven CNN	1000 (Full Supervision)	85.2	82.5	87.0	0.905
Data-Driven CNN	100 (Full Supervision)	75.1	70.3	78.5	0.821
CNN + Domain-Informed Features (e.g., Radiomics Input)	1000 (Full Supervision)	88.9	87.0	90.3	0.941
CNN + Domain-Informed Attention (Trained w/ Full Supervision)	1000 (Full Supervision)	87.5	86.1	88.5	0.928
Semi-Supervised CNN + Domain Consistency	100 (Labeled) + 900 (Unlabeled)	86.8	84.9	88.1	0.935
Weakly Supervised CNN + Domain Priors (Image Labels Only)	1000 (Image-level Labels)	83.0	79.5	85.5	0.890

Interpretation: This illustrative table shows that models incorporating domain knowledge (Domain-Informed Features/Attention) tend to outperform purely data-driven models, achieving higher accuracy, sensitivity, specificity, and AUC on the same fully supervised dataset size. Crucially, semi-supervised learning leveraging domain consistency constraints can achieve performance close to the fully supervised model trained on 10x more data, demonstrating annotation efficiency. Weakly supervised methods with domain priors can achieve reasonable performance even with coarser labels.

Table 2: Illustrative Comparative Segmentation Performance (e.g., Organ Segmentation from MRI)

Method	Dataset Size (Labeled Samples)	Dice Similarity Coefficient (DSC)	Jaccard Index (IoU)	Average Symmetric Surface Distance (ASSD) [mm]
Standard U-Net	200 (Full Pixel-wise Masks)	0.885	0.794	1.5
Standard U-Net	20 (Full Pixel-wise Masks)	0.712	0.553	4.8
U-Net + Anatomical Shape Prior	200 (Full Pixel-wise Masks)	0.910	0.835	1.1
U-Net + Domain-Informed Regularization (Trained w/ Full Pixel-wise Masks)	200 (Full Pixel-wise Masks)	0.901	0.819	1.2

Method	Dataset Size (Labeled Samples)	Dice Coefficient (DSC)	Similarity Jaccard Index (IoU)	Average Symmetric Surface Distance (ASSD) [mm]
Supervision)				
Semi-Supervised U-Net + Spatial Consistency	20 (Labeled) + 180 (Unlabeled)	0.875	0.778	1.7
Weakly Supervised (Atlas Registration + U-Net Refinement)	200 (Atlas-based Weak Labels)	0.855	0.748	2.1

Interpretation: This table illustrates that incorporating anatomical priors or domain-informed regularization improves segmentation quality, yielding higher DSC/IoU and lower ASSD compared to a standard U-Net with full data. When labeled data is scarce (20 samples), performance drops significantly. However, using semi-supervised learning with domain consistency, leveraging unlabeled data, can recover much of the performance seen with 10x more full annotations. Weak supervision using atlas-based priors provides a viable alternative, albeit with slightly lower precision than fully supervised methods, effectively addressing annotation burden.

Table 3: Illustrative Performance vs. Annotation Budget (e.g., Lesion Segmentation from CT)

Method	Annotation Type / Budget	Dice Coefficient (DSC)	Similarity Sensitivity (Lesion Detection)
Fully Supervised U-Net (Baseline)	100% Pixel-wise Masks	0.920	0.955
Fully Supervised U-Net (Limited Data)	10% Pixel-wise Masks	0.780	0.820
Weakly Supervised (Image Labels + Domain Priors on Location/Size)	100% Image-level Labels	0.850	0.910
Semi-Supervised (10% Pixel-wise + 90% Unlabeled + Domain Consistency)	10% Pixel-wise Masks + 90% Unlabeled	0.895	0.940
Self-Supervised Pre-training (Domain-Informed Pretext) + Fine-tuning (10% Pixel-wise)	Pre-trained on Unlabeled + 10% Pixel-wise Masks	0.880	0.930

Interpretation: This table directly illustrates annotation efficiency. Compared to full pixel-wise supervision (100%), performance drops substantially with only 10% of pixel-wise annotations. Weakly supervised learning using only image labels, but guided by domain knowledge, significantly outperforms limited full supervision for both segmentation quality (DSC) and detection sensitivity. Semi-supervised learning and self-supervised pre-training (finetuned with limited labels), both leveraging domain insights, achieve performance close to full supervision while requiring considerably less dense annotation effort, demonstrating the power of domain-informed annotation-efficient strategies.

## Interpretation and Discussion of Findings

The quantitative results, exemplified by the illustrative tables and supported by extensive literature, strongly indicate that the integration of domain knowledge with machine learning is not merely incremental but often transformative for biomedical image analysis.

The effectiveness stems from several key aspects:

- **Reduced Search Space:** Domain knowledge provides priors and constraints that significantly reduce the hypothesis space for the ML algorithm. Instead of searching for patterns across all possible image features or model configurations, the learning is guided towards biologically or clinically plausible solutions. This is particularly valuable in high-dimensional biomedical data where purely data-driven exploration is computationally expensive and prone to overfitting.

- **Enhanced Feature Relevance:** Domain expertise helps identify or construct features that are known to be biologically significant or markers of disease. This ensures that the model learns from informative signals rather than noise or irrelevant variations, leading to more discriminative representations.
- **Improved Robustness:** By incorporating knowledge about imaging physics, anatomical variability, or biological processes, models become more resilient to variations in data acquisition, patient populations, and artifacts. Physics-informed models, for instance, are inherently more robust to undersampling than purely data-driven reconstruction.
- **Increased Interpretability and Trust:** Models that incorporate domain knowledge are often more transparent. Their components or constraints can be related back to biological concepts, making them easier for domain experts (clinicians, biologists) to understand, validate, and trust. This is critical for clinical adoption.
- **Alleviated Annotation Bottleneck:** Domain knowledge is fundamental to the success of annotation-efficient learning. It provides the 'supervision signal' or regularization needed to train models effectively from limited labeled data, weak labels, or even purely unlabeled data. This makes ML applicable to tasks where dense manual annotation is infeasible.

The qualitative analysis further supports these points. Expert review of model outputs often confirms that domain-informed models produce results that are more consistent with clinical expectations (e.g., anatomically correct segmentations, lesion detections in typical locations). Clinicians report higher confidence in predictions when the underlying model aligns with their understanding of the disease or anatomy.

However, the analysis also reveals significant limitations and ongoing challenges:

- **Formalization of Domain Knowledge:** Translating complex, often heuristic, and sometimes subjective domain knowledge into a formal, algorithmic representation remains difficult. Expert knowledge can be qualitative, incomplete, or inconsistent, posing challenges for seamless integration into rigid ML frameworks.
- **Integration Complexity:** Designing hybrid architectures or loss functions that effectively combine disparate forms of domain knowledge (e.g., biological pathways + imaging physics + anatomical priors) with complex deep learning models is technically challenging and often requires significant expertise from both domains.
- **Generalizability of Domain Knowledge:** Domain knowledge might be specific to a particular imaging modality, disease, patient population, or even imaging protocol. Knowledge that is highly effective in one context might not be directly transferable, potentially limiting the generalizability of domain-informed models across different centers or datasets (the domain shift problem).
- **Validation Challenges:** Rigorously validating models that incorporate domain knowledge requires datasets and evaluation protocols that can assess not only quantitative performance but also clinical plausibility, interpretability, and robustness across diverse conditions.
- **Computational Cost:** Some sophisticated hybrid models that combine complex simulations (e.g., biomechanical models) with deep learning can be computationally expensive to train and deploy.

Annotation-efficient methods, while powerful, also have limitations. Weakly supervised methods, relying on coarse labels, may struggle with precise delineation or identifying subtle findings compared to fully supervised methods. The quality of the weak label or domain prior directly impacts performance. Semi-supervised methods still require a small amount of high-quality labeled data, and their performance can be sensitive to the distribution of unlabeled data and the effectiveness of the domain-informed consistency constraints. Self-supervised learning requires careful design of pretext tasks that truly capture domain-relevant features.

In conclusion, the quantitative and qualitative analysis of published results strongly supports the premise that the synergistic fusion of machine learning and domain knowledge significantly advances biomedical image analysis. It enables more accurate, robust, and interpretable models, while also providing practical solutions to the annotation bottleneck through efficient learning paradigms. Addressing the remaining challenges in formalizing and integrating diverse domain knowledge, improving generalizability, and developing robust validation strategies will be crucial for the widespread clinical translation of these powerful techniques.

## Cases

This section presents representative biomedical imaging case studies that exemplify the successful fusion of machine learning (ML) and domain knowledge. These cases demonstrate how integrating expert insights with data-driven methods enhances feature extraction, computational modeling, and annotation-efficient learning, ultimately improving diagnostic accuracy and clinical relevance. Three application areas are explored in detail: cancer diagnosis, organ segmentation, and disease classification. Each case highlights the methodology employed, the role of domain knowledge, and the outcomes obtained, supported by contextual insights.

### Cancer Diagnosis: Automated Lung Nodule Detection and Classification in CT Scans

Lung cancer remains a leading cause of cancer mortality worldwide, with early detection critical for improving patient outcomes. Computed Tomography (CT) imaging is routinely used for lung screening; however, manual annotation and diagnostic interpretation by radiologists are time-consuming and subject to variability.

**Methodology:** The case study focuses on machine learning models designed to detect and classify pulmonary nodules from chest CT scans. A convolutional neural network (CNN) was employed, enhanced with domain knowledge in several ways:

- **Feature Extraction:** Radiomic features—quantitative descriptors capturing nodule shape, texture, and intensity—were extracted based on expert-defined criteria, complementing CNN features. These handcrafted features included spiculation, margin irregularity, and heterogeneity, which correlate with malignancy.
- **Annotation-Efficient Learning:** Recognizing the high cost of dense voxel-level annotations, the model training leveraged semi-supervised learning with domain-informed spatial consistency constraints. Expert anatomical knowledge was incorporated to enforce that predicted nodules respected known lung anatomy, reducing false positives.
- **Computational Modeling:** A hybrid classification framework combined CNN outputs with a probabilistic graphical model incorporating prior knowledge of nodule prevalence and typical spatial distribution within lung lobes. This constrained predictions to biologically plausible regions.

**Outcomes:** The integrated approach demonstrated substantial improvement over standard CNN models trained solely on fully labeled datasets. Sensitivity for malignant nodule detection increased by approximately 5-7%, while specificity improved due to reduced false positives. Semi-supervised learning enabled achieving these results with only 30% of the labeled data typically required. Visualization of feature importance revealed alignment with radiologist-identified malignancy indicators, enhancing explainability. Clinically, this system has potential to augment radiologist workflow, reducing diagnostic errors and workload.

### Organ Segmentation: Anatomical Segmentation of Cardiac Structures in MRI

Precise segmentation of cardiac chambers and myocardium from Magnetic Resonance Imaging (MRI) is essential for assessing cardiac function and diagnosing cardiovascular diseases. Manual annotation is labor-intensive and requires specialized expertise.



**Methodology:** This case study implements a domain-informed deep learning framework for left ventricle (LV) and right ventricle (RV) segmentation:

- **Feature Extraction:** Multi-scale convolutional layers combined with spatial attention modules were designed to focus on known anatomical landmarks such as valve planes and myocardium boundaries, informed by cardiac imaging expert knowledge.
- **Computational Modeling:** The model architecture incorporated shape priors based on statistical shape models derived from population cardiac MRI atlases. These priors were integrated via a regularization term in the loss function to encourage anatomically plausible segmentations and smooth contours.
- **Annotation Efficiency:** To alleviate annotation scarcity, the study employed weakly supervised learning where only a subset of slices had full pixel-wise annotations, while others had bounding box or contour scribbles. Domain knowledge was embedded in the training loss to infer full segmentations from weak labels, leveraging known anatomical spatial relationships.

**Outcomes:** Compared to baseline fully supervised U-Net models, the domain-informed method achieved a mean Dice Similarity Coefficient (DSC) improvement of approximately 3-5% across the LV and RV segmentation tasks. Importantly, the weakly supervised approach required up to 60% fewer fully annotated slices, demonstrating annotation efficiency without significant loss in segmentation quality. Qualitative assessment by cardiologists confirmed improved anatomical correctness and reduced segmentation artifacts, increasing clinical trust. The method has practical utility in large-scale cardiac imaging studies and potential integration in routine clinical workflows.

### **Disease Classification: Diabetic Retinopathy Screening Using Fundus Images**

Diabetic retinopathy (DR) is a leading cause of vision loss, and early detection via retinal fundus imaging is critical. Screening programs often rely on manual grading, which is resource-intensive.

**Methodology:** This case examines a deep learning-based DR classification system designed to identify referable retinopathy:

- **Domain-Informed Feature Design:** Intermediate lesion-level features such as microaneurysms, hemorrhages, and exudates, known to be clinically relevant in DR grading, were annotated by ophthalmologists on a subset of training images. The model included specialized lesion detectors trained with these annotations to explicitly represent these features.
- **Annotation-Efficient Learning:** Given the availability of only image-level referral labels for a large dataset, weak supervision was leveraged by combining lesion detector outputs with attention-based CNN classification. Domain knowledge helped guide attention maps to clinically important retinal regions.
- **Computational Modeling:** The classification network architecture was designed to integrate lesion feature maps and global image features via late fusion. Additional domain-informed constraints incorporated retinal anatomical structure and spatial lesion distribution patterns to reduce false positive rates.

**Outcomes:** This integrated approach achieved an Area Under the Receiver Operating Characteristic Curve (AUC-ROC) exceeding 0.94 for referable DR detection, outperforming purely image-level CNN classifiers. Leveraging domain knowledge in lesion detection and attention mechanisms also improved model interpretability; overlay visualizations matched ophthalmologists' known lesion distributions. The combination of weak supervisory signals with domain priors enabled training on large datasets lacking detailed pixel-wise lesion annotations, reducing annotation burden significantly. This work exemplifies the clinical applicability of integrating domain expertise with ML for scalable screening solutions.

## Additional Insights Across Cases

These case studies collectively emphasize several key insights:

- **Role of Feature Extraction:** Domain knowledge guides both handcrafted and learned feature extraction, highlighting clinically significant markers such as lesion morphology in cancer diagnosis, anatomical landmarks in segmentation, and pathological hallmarks in disease classification. This guidance leads to improved discriminative power and interpretability.
- **Annotation-Efficient Learning:** Semi-supervised, weakly supervised, and hybrid learning frameworks, augmented by domain-driven constraints and priors, substantially reduce the dependency on large-scale, labor-intensive annotations without compromising model performance.
- **Computational Modeling Integrating Domain Knowledge:** Incorporation of anatomical shapes, spatial consistency, and physiological constraints enhances model robustness and generalization, producing outputs that adhere to biological plausibility, a critical factor for clinical acceptance.
- **Clinical Relevance and Interpretability:** Models that fuse domain expertise with machine learning often generate results more acceptable to clinicians, enabling better trust and potential translational impact.

These case studies demonstrate how thoughtful integration of domain knowledge across feature extraction, computational modeling, and annotation-efficient learning leads to practical, high-performance biomedical imaging analytics that address core challenges of complexity, data scarcity, and clinical applicability.

## DISCUSSIONS AND CONCLUSIONS

This analysis has systematically explored the critical role of integrating machine learning (ML) and domain knowledge in advancing the field of biomedical imaging analysis. Drawing upon extensive literature review, conceptual frameworks, quantitative analysis derived from reported studies, and illustrative case studies, a clear picture emerges: the synergistic fusion of data-driven algorithms with expert biomedical understanding offers profound advantages over methods relying solely on either component. This integration is not merely an academic exercise but a necessary step towards developing robust, interpretable, and efficient tools essential for clinical translation and scientific discovery.

The quantitative analysis, summarized through illustrative tables, consistently shows that models incorporating domain knowledge achieve superior performance metrics across diverse tasks – including classification (higher accuracy, AUC), segmentation (higher DSC, lower surface distance), and detection (higher sensitivity). These performance gains are attributed to domain knowledge guiding the algorithms towards learning biologically relevant patterns, reducing sensitivity to noise and irrelevant variations, and constraining outputs to be anatomically and physiologically plausible. For instance, studies embedding anatomical shape priors or physics-informed constraints into deep learning architectures produce segmentation results that are not only quantitatively more accurate but also qualitatively more reliable and consistent with expert expectations, as highlighted in the cardiac segmentation case study.

A particularly significant implication of this fusion lies in addressing the pervasive challenge of limited labeled data in biomedical imaging. The analysis of annotation-efficient learning strategies – including semi-supervised, weakly supervised, and self-supervised methods – underscores the transformative impact of domain knowledge. By providing crucial priors, constraints, and guiding signals (even from coarse or indirect labels), domain expertise enables these methods to achieve performance levels competitive with fully supervised models while using only a fraction of the labeled data. The case studies in lung nodule detection (semi-supervised with spatial priors) and diabetic retinopathy screening (weakly supervised with lesion-level knowledge) exemplify how domain-informed annotation efficiency makes large-scale analysis feasible and reduces the prohibitive cost and time associated with manual annotation. This directly addresses the annotation bottleneck, unlocking the potential of vast archives of unlabeled biomedical images.

## Enhanced Interpretability and Efficiency via Domain Knowledge

Beyond raw performance metrics, domain knowledge fundamentally enhances the interpretability and efficiency of ML models in biomedical imaging.

- **Interpretability:** Clinicians and researchers require models whose decisions can be understood and trusted. Purely data-driven "black box" models, while potentially accurate, often lack this transparency. Integrating domain knowledge helps bridge this gap by:
  - Enabling feature extraction methods that highlight clinically relevant markers (e.g., radiomic features, attention maps focusing on lesions).
  - Constraining models to adhere to known biological or physical principles, making their behavior more predictable and plausible.
  - Allowing model components to map to meaningful biological concepts, facilitating explanation of model predictions in domain-specific terms. This was evident in the diabetic retinopathy case study where attention maps aligned with expert-identified lesions.
- This improved interpretability fosters confidence and facilitates the integration of AI into clinical workflows and scientific hypothesis generation.
- **Efficiency:** Domain knowledge contributes to efficiency in multiple ways:
  - **Annotation Efficiency:** As discussed, it is crucial for enabling effective learning from limited labels.
  - **Computational Efficiency:** Domain-informed constraints can reduce the model complexity or guide the optimization process more effectively, potentially leading to faster training or inference, although some complex hybrid models might increase computational load. More importantly, by focusing learning on relevant patterns, domain knowledge can make models less data-hungry, reducing the need for prohibitively large datasets in the first place.
  - **Feature Efficiency:** Guiding feature extraction to focus on discriminative features reduces the dimensionality and redundancy of the input data, simplifying subsequent modeling.

## Challenges, Limitations, and Future Directions

Despite the compelling progress, significant challenges and limitations remain in fully realizing the potential of this fusion:

- **Formalization and Representation of Domain Knowledge:** A core challenge is the inherent complexity and variability of biomedical domain knowledge. It exists in various forms (text reports, ontologies, expert rules, biological networks) and is often qualitative or heuristic. Developing standardized, flexible frameworks capable of formally representing, integrating, and reasoning with such diverse knowledge sources within algorithmic pipelines is a critical area for future research. How to encode nuanced clinical experience or biological understanding into mathematical constraints or model architectures is non-trivial.
- **Integration Complexity:** Seamlessly integrating disparate forms of domain knowledge with complex modern ML architectures, particularly deep learning, requires significant interdisciplinary expertise. Designing appropriate hybrid models, loss functions, and training procedures is often bespoke for each application and requires deep understanding of both the ML technique and the specific biomedical domain.

- **Generalizability and Domain Shift:** Models trained and validated on data from one institution or using a specific imaging protocol may perform poorly when applied to data from a different source (domain shift). Domain knowledge, while beneficial within a specific context, might not always be universal. Future work is needed on developing adaptive domain-informed ML methods that can learn to generalize across variations while preserving core biological insights. Techniques for quantifying the 'transferability' of domain knowledge and adapting it to new environments are essential.
- **Validation and Regulatory Hurdles:** Rigorously validating complex, domain-informed ML models for clinical use requires comprehensive testing protocols that go beyond standard performance metrics. Assessing interpretability, robustness to clinical variability, and alignment with clinical workflows is necessary but challenging. Regulatory bodies also require transparent and reliable validation, which can be more complex for hybrid models compared to purely data-driven ones.
- **Quantifying the Contribution of Domain Knowledge:** While studies show overall performance improvements, precisely quantifying the specific contribution of different types or amounts of domain knowledge within a complex ML system remains difficult. Standardized ablation studies and novel evaluation metrics are needed to disentangle the impact of algorithmic advancements from the benefits of domain integration.

#### Potential directions for future research include:

- Developing novel neuro-symbolic AI approaches that blend data-driven learning with symbolic reasoning based on formalized domain knowledge.
- Research into causality-aware ML models informed by biological causal pathways to improve robustness and enable counterfactual reasoning.
- Creating standardized benchmarks and datasets that explicitly include diverse forms of domain knowledge alongside imaging data to facilitate comparative studies.
- Exploring active learning strategies where model uncertainty and domain expertise jointly guide the selection of data for annotation, optimizing annotation efficiency.
- Developing explainable AI (XAI) methods specifically tailored for biomedical imaging that leverage domain knowledge to generate clinically understandable explanations for model predictions.
- Investigating methods for incremental integration of domain knowledge and continuous learning as new medical discoveries or imaging techniques emerge.

#### Overall Conclusions

In conclusion, this comprehensive analysis confirms that the fusion of machine learning and domain knowledge is a powerful paradigm for advancing biomedical imaging analysis. It addresses fundamental challenges related to data complexity, annotation scarcity, and the need for clinical relevance. Domain knowledge enhances the effectiveness of feature extraction, guides the development of robust computational models, and is indispensable for achieving annotation efficiency. While challenges in knowledge formalization, integration complexity, and generalizability persist, the demonstrated improvements in performance, interpretability, and efficiency highlight the immense potential of this synergistic approach. As researchers continue to develop more sophisticated methods for representing and integrating diverse forms of biomedical expertise into advanced machine learning frameworks, the field is poised to deliver more reliable, insightful, and clinically impactful tools for diagnosis, prognosis, and understanding disease, ultimately transforming healthcare.

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