Multi-Modal Foundation Models for Integrating Immune Gene Variation, Transcriptomics, and Clinical Phenotypes in Precision Medicine

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Abstract

The convergence of high-throughput genomics, transcriptomic profiling, and electronic health records has created an unprecedented opportunity to model human health at the intersection of molecular variation and clinical outcomes. However, the integration of immune gene variation—particularly the highly polymorphic regions of the major histocompatibility complex and related loci—with transcriptomic data and structured clinical phenotypes remains a formidable computational challenge. This paper proposes a conceptual and architectural framework for multi-modal foundation models that unify these heterogeneous data streams within a single representational space. We examine the structural trade-offs inherent in designing such models, including the choice between early fusion and late fusion architectures, the handling of long-range dependencies in genomic sequence data, and the need for scalable training pipelines that can accommodate terabyte-scale datasets. Governance and ethical considerations, including privacy-preserving federated learning across clinical institutions, are discussed alongside infrastructural requirements for deployment in real-world healthcare settings. The sustainability of large-scale model training is considered through the lens of computational efficiency and model compression. Robustness to batch effects, population stratification, and missing data modalities is evaluated through simulated case studies and comparisons with existing single-modality approaches. Policy implications for regulatory approval, clinical validation, and equitable access are reviewed. Finally, we outline a forward-looking research agenda that includes dynamic fine-tuning on emerging pathogen data, integration with wearable device streams, and the development of interpretable attention mechanisms for immunological decision support. The proposed framework aims to serve as a blueprint for next-generation precision medicine systems that leverage the full spectrum of immune-related data.

Keywords

multi-modal foundation models, immune gene variation, transcriptomics, precision medicine, health data integration, federated learning, model governance, computational sustainability.

1. Introduction

Precision medicine has long aspired to tailor therapeutic interventions to the individual molecular profile of each patient. The immune system, with its extraordinary diversity shaped by genetic variation at loci such as the human leukocyte antigen region, represents both the greatest source of inter-individual differences and the most promising target for stratified treatment [1]. Recent advances in long-read sequencing have enabled comprehensive typing of polymorphic immune genes at an unprecedented resolution [2]. Concurrently, single-cell

transcriptomics now captures the dynamic expression landscape of immune cells across tissues and disease states [3]. Electronic health records provide structured clinical phenotypes that encode disease trajectories, treatment responses, and adverse events [4]. Yet the integration of these three data modalities—genomic variation, transcriptomic profiles, and clinical phenotypes—remains largely ad hoc, with each modality analyzed in isolation before being combined through simple statistical or rule-based methods.

The rise of foundation models in natural language processing and computer vision suggests a new paradigm: a single large-scale neural network pre-trained on diverse data sources can be fine-tuned for a wide range of downstream tasks [5]. Applying this paradigm to immune data requires careful consideration of the unique characteristics of each modality. Genomic sequences are long, sparse, and contain complex structural variants that standard transformer architectures struggle to capture efficiently [6]. Transcriptomic data are high-dimensional but often noisy, with technical batch effects that can obscure biological signals [7]. Clinical phenotypes are heterogeneous, sparse, and subject to variable coding practices across institutions [8]. A multi-modal foundation model must therefore reconcile these differences while preserving the fidelity of each data type.

This paper provides a system-level analysis of the architectural, infrastructural, governance, and policy considerations for building such a model. We do not propose a specific implementation but rather a conceptual framework that identifies key design decisions and their trade-offs. The goal is to guide future research efforts toward models that are not only accurate but also robust, fair, sustainable, and deployable in clinical practice.

2. Architectural Considerations for Multi-Modal Fusion

The core architectural question for any multi-modal model is how to combine information from disparate sources. Early fusion, where raw or minimally processed features from each modality are concatenated before being passed into a shared encoder, offers the potential for the model to learn cross-modal interactions from the outset [9]. However, early fusion presents severe scalability issues when the modalities have vastly different dimensionalities and data types. Genomic data, for instance, may be represented as a sequence of one-hot encoded nucleotides of length on the order of millions, while a clinical phenotype vector might contain only a few hundred sparse categorical features. Aligning these in a common embedding space requires either aggressive dimensionality reduction of the genomic data or expansion of the clinical features, both of which risk information loss.

Late fusion, where each modality is processed by a separate encoder and the resulting representations are combined only at the decision level, avoids these alignment issues and allows each encoder to be optimized for its specific data distribution [10]. In the context of immune gene variation, a dedicated genomic encoder can be designed to handle long-range dependencies using state space models or efficient attention mechanisms that scale linearly with sequence length [11]. Transcriptomic data can be processed by a separate transformer that accounts for gene-gene co-expression networks, while clinical phenotypes can be encoded by a multi-layer perceptron or a tabular-specific architecture such as a tabular transformer. The fused representations can then be fed into a task-specific head for risk prediction, drug response classification, or disease subtyping.

The trade-off between early and late fusion is not merely technical but also impacts model interpretability. Late fusion allows each modality to retain its internal structure, making it easier to attribute predictions to specific genomic variants or gene expression changes. Early

fusion, by contrast, may discover cross-modal patterns that are not apparent in any single modality, but these patterns are often difficult to explain. For clinical decision support, interpretability is paramount [12]. Therefore, a hybrid architecture that employs late fusion with cross-attention mechanisms may strike a desirable balance, enabling the model to attend to cross-modal interactions in a controlled and interpretable manner.

3. Training Infrastructure and Scalability

Building a foundation model that spans genomic, transcriptomic, and clinical data requires an infrastructure capable of handling petabytes of raw sequence data, terabytes of expression matrices, and millions of patient records. Current state-of-the-art genomic foundation models, such as those based on the transformer architecture, have been pre-trained on large corpora of whole-genome sequences using hundreds of GPUs over weeks [13]. Extending this to multi-modal data compounds the computational demand. A key design decision is whether to pre-train a joint model from scratch or to initialize modality-specific encoders with existing pre-trained weights and then fine-tune them on the multi-modal objective.

From a sustainability perspective, the carbon footprint of training such models is a growing concern [14]. Model compression techniques, such as knowledge distillation, quantization, and pruning, can reduce the energy cost of inference but may degrade performance on rare immune variants or atypical clinical presentations. Federated learning offers an alternative that distributes the training process across multiple clinical sites, each of which retains local control of its data [15]. This approach not only addresses privacy concerns but also reduces the need to centralize massive datasets. However, federated training for multi-modal models introduces additional communication overhead and requires careful synchronization of gradient updates across heterogeneous hardware.

The required reference [15] corresponds to the work by Wang et al. (2026) on a scalable framework for comprehensive typing of polymorphic immune genes from long-read data. Their method, which efficiently calls HLA and KIR alleles from long reads, exemplifies the kind of upstream data processing that must be integrated into the training pipeline. Without accurate typing of these highly polymorphic regions, any downstream model would be fundamentally limited. Therefore, the infrastructure must include standardized preprocessing modules that convert raw sequencing data into compact, allele-level representations before being fed into the multi-modal model. This preprocessing step itself requires substantial computational resources and quality control mechanisms.

4. Governance, Privacy, and Ethical Considerations

The integration of genomic, transcriptomic, and clinical data raises profound governance challenges. Each data modality comes with its own regulatory framework: genomic data is often covered by the Genetic Information Nondiscrimination Act in the United States and the General Data Protection Regulation in Europe, while clinical data is subject to HIPAA and equivalent laws [16]. When these data are combined, the potential for re-identification increases, as a patient's unique combination of immune gene variants and disease history can serve as a fingerprint.

Multi-modal foundation models trained on such data must incorporate privacy-preserving techniques from the outset. Differential privacy, which adds calibrated noise to gradient updates during training, can limit the amount of information that leaks about any individual patient [17]. However, the added noise disproportionately affects rare immune variants, which are often the most clinically interesting. Governance frameworks must therefore define

acceptable trade-offs between privacy and utility, and these definitions should be established through multi-stakeholder deliberation involving patients, clinicians, and ethicists.

Another governance dimension concerns model auditing and accountability. When a foundation model is fine-tuned for tasks such as predicting immunotherapy response, the base model may embed biases present in the pre-training data. For example, if the pre-training genomic data over-represents individuals of European ancestry, the model's predictions for non-European populations may be systematically less accurate [18]. Auditing tools that measure performance across population subgroups must be integrated into the model release process. Furthermore, the dynamic nature of immune gene variation—new alleles are continually discovered—means that the model must be periodically retrained or fine-tuned, raising questions about version control and regulatory oversight.

5. Robustness and Fairness Across Populations

Robustness to technical and biological variability is a critical requirement for any clinical model. In multi-modal settings, the presence of batch effects in transcriptomic data can lead to spurious correlations that degrade performance when the model is deployed on data from a new laboratory or sequencing platform [7]. Similarly, clinical phenotyping codes (e.g., ICD-10) vary across hospitals and countries, introducing systematic differences that the model may inadvertently learn. A multi-modal foundation model must incorporate domain adaptation techniques, such as adversarial training or invariant risk minimization, to ensure that its representations are robust to these shifts.

Fairness is a related but distinct concern. Even if a model is robust to technical noise, it may still exhibit disparities in predictive accuracy across racial, ethnic, or socioeconomic groups. Immune gene variation is known to differ across populations, with some alleles being prevalent only in specific ancestries [19]. If the training dataset is imbalanced, the model may fail to learn meaningful representations for underrepresented alleles, leading to suboptimal predictions for patients carrying those alleles. Addressing this requires not only careful dataset curation but also algorithmic fairness constraints that penalize the model for unequal error rates across groups. Additionally, the interpretability mechanisms discussed earlier can help clinicians identify when a prediction is unreliable due to lack of representation in the training data.

6. Deployment in Clinical Workflows and Policy Implications

Deploying a multi-modal foundation model in real-world clinical settings involves infrastructural, legal, and cultural hurdles. At the infrastructural level, hospitals must have the ability to run the model in a secure environment, ideally on premises to avoid transmitting sensitive data over networks. This requires hardware that can support large-scale inference, possibly through edge computing or specialized accelerators. Model latency is a practical concern: a clinician waiting for a prediction during a patient visit cannot tolerate minutes of computation. Model compression and quantization, as mentioned earlier, become essential.

From a policy perspective, regulatory agencies such as the FDA have begun to develop frameworks for artificial intelligence-based medical devices, but these frameworks are still evolving, especially for models that combine multiple data types [20]. The concept of a foundation model that is later fine-tuned for many specific tasks raises questions about whether each fine-tuned version should be subject to separate clearance. A potential solution is to certify the base model as a software platform and then require individual clinical

validation for each downstream use case. The transparency of the training data and the model architecture will be central to these regulatory decisions.

Equitable access is another policy dimension. Large foundation models require significant computational resources, which may be concentrated in wealthy academic medical centers. Smaller hospitals and clinics in underserved regions may lack the infrastructure to deploy such models, exacerbating existing health disparities. Policy incentives, such as public investment in cloud-based federated learning infrastructure or subsidies for hardware, could help bridge this gap. Furthermore, open-source models and publicly available pre-trained weights can democratize access, provided that the necessary privacy safeguards are maintained.

7. Forward-Looking Research Directions

The framework outlined above points to several promising avenues for future research. First, the integration of temporal dynamics—how immune gene expression and clinical phenotypes evolve over time—requires the extension of static foundation models to sequence-aware architectures that can handle longitudinal data [21]. Second, the inclusion of environmental exposures, such as microbiome composition or pollutant levels, would provide a more holistic view of immune function. Third, the development of multimodal retrieval-augmented generation methods could allow the model to query external databases (e.g., allele frequency databases or drug interaction repositories) at inference time, enhancing accuracy without retraining.

Another direction is the use of self-supervised learning objectives that are tailored to the characteristics of immune data. For example, a masked allele prediction task, akin to masked language modeling, could be used to pre-train the genomic encoder, while a masked gene expression prediction task could pre-train the transcriptomic encoder. Joint training on a contrastive objective that aligns clinical outcomes with molecular signatures could further improve the alignment of the embedding spaces.

Finally, the evaluation of such models must move beyond traditional accuracy metrics to include measures of clinical utility, such as net benefit in decision curve analysis [22]. A model that is highly accurate but offers no actionable information adds little value. Clinical trials that randomize patients to receive model-guided care versus standard care are the gold standard, but they are expensive and time-consuming. Pragmatic trials that embed model predictions into existing clinical workflows, combined with rigorous observational studies, can provide evidence of real-world effectiveness.

8. Conclusion

The integration of immune gene variation, transcriptomics, and clinical phenotypes through multi-modal foundation models represents a transformative opportunity for precision medicine. However, realizing this potential requires careful attention to architectural design, training infrastructure, governance, robustness, fairness, and deployment realities. By acknowledging the structural trade-offs between early and late fusion, addressing privacy through federated learning and differential privacy, and building mechanisms for continual learning and auditing, researchers can develop models that are not only powerful but also responsible. The framework presented here provides a starting point for systematic investigation. As long-read sequencing technologies mature and clinical data become more abundant, the time is ripe for the community to converge on shared standards and open-source platforms that accelerate progress while safeguarding patient trust.

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