Graph Neural Network-Based Integration of Long-Read Immune Genotyping and Skeletal Muscle Transcriptomics for Precision Nutrition and Personalized Exercise Response Prediction

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Abstract

The convergence of long-read sequencing technologies, high-resolution immune genotyping, and skeletal muscle transcriptomics offers an unprecedented opportunity to model the complex biological interactions that govern individual responses to nutrition and exercise. This paper proposes a graph neural network (GNN)-based integrative framework that fuses polymorphic immune gene profiles, such as human leukocyte antigen and killer-cell immunoglobulin-like receptor alleles, with transcriptomic signatures from skeletal muscle biopsies. By representing biological entities and their functional relationships as a heterogeneous graph, the GNN architecture captures nonlinear dependencies among genetic variation, gene expression, and environmental stimuli, enabling the prediction of personalized outcomes in dietary intervention and exercise regimens. We examine the system-level design trade-offs involved in building such a multimodal pipeline, including data heterogeneity, graph construction strategies, scalability constraints, and model interpretability. Deployment considerations addressing computational infrastructure, real-time inference, and integration with wearable sensor streams are discussed. The governance landscape is analyzed with respect to data privacy, algorithmic fairness across diverse populations, and regulatory oversight for clinical translation. Cross-domain comparisons with similar integrative approaches in drug discovery and multi-omics oncology illustrate structural parallels and unique challenges. Forward-looking perspectives emphasize the need for federated learning architectures, robust causal inference methods, and longitudinal validation frameworks. The proposed GNN-based paradigm moves beyond single-modality biomarker analysis toward a systems-level understanding of human variability, with profound implications for precision health, sports science, and public nutrition policy.

Keywords

Graph neural networks, long-read sequencing, immune genotyping, transcriptomics, precision nutrition, exercise response, personalized medicine, systems architecture.

1. Introduction

Personalized nutrition and exercise prescription have long been constrained by an incomplete understanding of the inter-individual variability that arises from genetic, epigenetic, and

environmental factors. Recent advances in long-read sequencing technologies have enabled the comprehensive typing of highly polymorphic immune genes, notably those in the human leukocyte antigen and killer-cell immunoglobulin-like receptor clusters, which play critical roles in inflammation, immune surveillance, and tissue remodeling [1]. Simultaneously, skeletal muscle transcriptomics provides a dynamic snapshot of gene expression responses to acute and chronic exercise stimuli, revealing pathways involved in metabolism, hypertrophy, and repair [2]. However, these data modalities are typically analyzed in isolation, yielding fragmented insights that fail to capture the synergistic interactions between immune genotype and muscle phenotype. A systems-level integration is required to move from population-level averages to truly personalized recommendations.

Graph neural networks have emerged as a powerful class of deep learning models for relational data, capable of learning representations from graph-structured biological knowledge [3]. Unlike traditional machine learning methods that assume independent and identically distributed samples, GNNs explicitly model dependencies between entities, such as genes, proteins, and regulatory elements, and can propagate information across heterogeneous node and edge types. This architectural property makes GNNs well suited for fusing long-read immune genotyping data with skeletal muscle transcriptomics, as the underlying biological processes are inherently network-based. In this paper, we propose a GNN-based integration framework that embeds immune gene variants and transcriptomic profiles into a common latent space, enabling the prediction of individual responses to dietary interventions and exercise protocols. The framework is designed to address the structural trade-offs associated with data integration, including resolution mismatches between genomic and transcriptomic scales, sparsity of rare alleles, and the need for interpretable predictions in clinical and consumer settings.

2. Background and Related Work

Long-read sequencing technologies, such as those from Pacific Biosciences and Oxford Nanopore, have revolutionized the characterization of complex genomic regions that are refractory to short-read alignment [4]. These platforms produce reads exceeding ten kilobases, allowing phased haplotyping and the resolution of highly homologous gene families. The comprehensive typing of immune genes, which exhibit extreme polymorphism and copy number variation, has been facilitated by scalable bioinformatics pipelines that leverage graph-based alignment and pangenome references [5]. The ability to accurately genotype human leukocyte antigen and killer-cell immunoglobulin-like receptor alleles at single-molecule resolution opens new avenues for studying immune-mediated adaptations to exercise and diet [6]. For example, certain human leukocyte antigen haplotypes have been associated with altered inflammatory cytokine profiles following resistance training, while killer-cell immunoglobulin-like receptor diversity influences natural killer cell activity in response to macronutrient composition [7].

Parallel advances in skeletal muscle transcriptomics have identified thousands of exercise-responsive genes, including those involved in oxidative phosphorylation, autophagy, and extracellular matrix remodeling [8]. Diet-induced weight loss further modulates the expression of genes related to lipid metabolism and insulin signaling, often in an allele-specific manner [9]. However, the integration of immune genotyping with muscle transcriptomics remains largely unexplored. Traditional multivariate regression approaches struggle to capture the high-dimensional, non-linear interactions between thousands of genetic variants and tens of thousands of transcriptomic features. Moreover, the tissue-specific

expression of immune genes within skeletal muscle, particularly in resident immune cells, adds another layer of complexity [10]. Graph neural networks offer a natural solution because they can model both local and global dependencies in a biologically informed graph, where nodes represent genes, alleles, or transcripts, and edges encode regulatory, co-expression, or physical interaction relationships.

In the broader landscape of multi-omics integration, GNNs have been applied to predict drug response, disease subtypes, and protein function [11]. For instance, heterogeneous graph architectures that combine genomic mutation data with gene expression networks have outperformed standard feedforward models in cancer prognosis [12]. Nevertheless, the application of GNNs to the specific domain of precision nutrition and exercise response is nascent. The present work extends these concepts by incorporating long-read immune genotyping, which introduces unique graph construction challenges due to the multi-allelic nature of immune loci and the need to represent haplotype-level information [13]. Furthermore, the dynamic nature of transcriptomic responses to exercise and diet requires temporal graph models that can accommodate time-series data from repeated measurements.

3. System Architecture and Data Integration Framework

The proposed integration framework consists of three primary modules: data acquisition and preprocessing, graph construction, and GNN-based prediction. Data acquisition involves the collection of long-read sequencing reads from peripheral blood or buccal samples for immune genotyping, alongside skeletal muscle biopsy specimens collected before and after a standardized exercise bout or dietary intervention. Skeletal muscle transcriptomic data are generated via RNA sequencing, with alignment and quantification tools producing gene-level expression counts. Immune genotyping pipelines, such as those described in the literature, produce allele calls for each classical and non-classical human leukocyte antigen gene as well as for killer-cell immunoglobulin-like receptor haplotypes, often including copy number estimates [13]. Both data types are aligned to a common reference genome and harmonized using standardized ontologies.

Graph construction is the critical architectural step. The heterogeneous graph is composed of three node types: immune allele nodes, gene expression nodes, and sample nodes. Immune allele nodes are derived from the genotyping results, with each allele represented as a distinct node that carries features such as allele frequency, functional annotation (e.g., peptide-binding specificity), and linkage disequilibrium score. Gene expression nodes correspond to individual transcripts measured in muscle tissue, and their features include normalized expression levels, variance across the cohort, and pathway membership. Sample nodes represent individual participants and are connected to both allele and expression nodes based on the presence of specific alleles and the measured expression values. Edges between allele and gene expression nodes encode prior biological knowledge, such as transcription factor binding sites, protein-protein interactions, or expression quantitative trait loci reported in muscle tissue. Edges between gene expression nodes encode co-expression networks derived from the same cohort or from external databases. Sample nodes are linked to all their associated genetic and transcriptomic nodes, forming a star-like structure that is enriched with cross-modality edges.

This graph structure inherently captures the multimodal dependencies necessary for personalized prediction. However, several trade-offs emerge. Increasing the number of node types and edges improves expressivity but raises computational costs and risks overfitting, particularly given the limited sample sizes typical of exercise intervention studies. A sparser

graph that only includes edges with strong prior evidence may generalize better but could miss novel interactions. Additionally, the choice of edge weighting schemes, such as using correlation coefficients or mutual information, influences the message-passing dynamics of the GNN. We advocate for a design that prioritizes interpretability by incorporating attention mechanisms that highlight the most influential connections for a given prediction.

4. Graph Neural Network Design for Multimodal Biological Data

The GNN architecture selected for this integration task is a heterogeneous graph transformer, which extends the standard transformer attention mechanism to operate over multiple node and edge types. Each node type is associated with its own linear projection layers, and attention scores are computed separately for each relation type before being aggregated. This design allows the model to learn distinct propagation rules for allele-to-gene, gene-to-gene, and sample-to-node interactions. The output embeddings for sample nodes are then passed through a multi-layer perceptron to produce predictions for continuous outcomes, such as changes in muscle mass, maximal oxygen uptake, or postprandial glucose response, as well as categorical outcomes like injury risk or metabolic syndrome classification.

Message passing occurs over several layers, enabling the model to aggregate information from higher-order neighbors. For example, a sample node that carries a rare killer-cell immunoglobulin-like receptor allele can receive information not only from that allele’s direct connections but also from co-expressed genes that are linked to the same allele through prior knowledge edges. This ability to propagate information across multiple hops is crucial for capturing indirect regulatory effects, such as a variant that modulates a transcription factor, which in turn affects dozens of downstream genes. Nevertheless, deep graph networks suffer from oversmoothing, where node representations become indistinguishable after many layers. Residual connections, layer normalization, and gating mechanisms are employed to mitigate this issue.

Training the GNN requires careful handling of data imbalance and confounding variables. Immune alleles with low population frequency are often underrepresented in training sets, leading to poor generalization for rare variants. Synthetic oversampling techniques or graph augmentation strategies, such as random edge dropout and feature masking, can improve robustness. Furthermore, the model must be trained to distinguish causal effects from spurious correlations introduced by population stratification. Incorporating propensity score weighting or counterfactual reasoning into the loss function is an area of active research. The final predictive outputs are accompanied by uncertainty estimates, obtained through Monte Carlo dropout or ensemble methods, which are essential for high-stakes health recommendations.

5. Deployment and Infrastructure Considerations

Translating the GNN-based framework from a research prototype to a deployable system for precision nutrition and exercise guidance presents substantial infrastructure challenges. Real-world deployment scenarios include integration with direct-to-consumer genomic services, clinical decision support platforms, and mobile health applications that collect wearable data. The computational demands of training a heterogeneous GNN on large-scale multi-omics data are significant, often requiring GPU clusters with substantial memory to store the graph adjacency matrix and node features. However, inference can be optimized for resource-constrained environments by distilling the GNN into a smaller surrogate model or by precomputing sample embeddings for known genotype-expression combinations.

Latency requirements differ by use case. For longitudinal monitoring, where predictions are updated weekly, batch inference is acceptable. For real-time feedback during a training session, low-latency inference is needed, which may require on-device deployment of a compressed model. Federated learning becomes attractive when data cannot be centralized due to privacy regulations, as is common with genomic data. In a federated setting, each institution trains a local GNN on its own cohort and shares only model updates with a central server, preserving data confidentiality while benefiting from collective learning.

Data storage and retrieval must handle the high-volume nature of long-read sequencing files, which can exceed 100 gigabytes per sample. Efficient indexing of variant calls and expression matrices using columnar storage formats, such as Apache Parquet, can reduce query times. Moreover, the integration of streaming data from wearables, such as heart rate and accelerometry, requires a pipeline for temporal alignment and feature extraction. The overall system must be designed with a modular microservice architecture that separates data ingestion, graph construction, model inference, and result visualization, enabling independent scaling of each component.

6. Governance, Fairness, and Ethical Implications

The deployment of a GNN-based personalized nutrition and exercise prediction system raises profound governance questions. Data privacy is paramount because both immune genotyping and skeletal muscle transcriptomics contain individually identifiable information. The Health Insurance Portability and Accountability Act in the United States and the General Data Protection Regulation in Europe impose strict requirements on the storage and sharing of such data. Informed consent procedures must clearly communicate the scope of data use, the potential for incidental findings (e.g., disease predispositions), and the right to withdraw. De-identification techniques, such as differential privacy added during graph construction or model training, can provide mathematical guarantees against re-identification attacks.

Algorithmic fairness is another critical dimension. The allele frequencies of immune genes vary substantially across ancestral populations, and transcriptomic responses to exercise differ by sex, age, and baseline fitness level. If the training cohort predominantly comprises individuals of European descent, the resulting predictions may be systematically biased against underrepresented groups, leading to suboptimal recommendations or even harm. Fairness-aware GNN training methods, including adversarial debiasing and reweighting of samples from minority groups, should be incorporated. Auditing frameworks must be developed to evaluate the model's performance across demographic strata before deployment.

Regulatory oversight for such predictive tools is still evolving. The U.S. Food and Drug Administration has classified some digital health products as medical devices, and any system that provides actionable dietary or exercise recommendations could fall under this umbrella. Validation trials demonstrating improved outcomes compared to standard care will be necessary for approval. Additionally, the potential for over-reliance on algorithmic recommendations, particularly among vulnerable populations such as athletes or individuals with eating disorders, necessitates built-in safeguards and human-in-the-loop review.

7. Cross-Domain Comparisons and Forward-Looking Perspectives

The architectural principles underlying the GNN-based integration framework are not unique to nutrition and exercise science. Similar heterogeneous graph approaches have been developed for drug-target interaction prediction, where nodes represent drugs, proteins, and diseases, and edges encode known affinities and side effects [14]. In oncology, GNNs have

been used to combine somatic mutation data with gene expression and histological images for cancer subtyping [15]. The key difference in the present domain is the temporally dynamic nature of the outcome variables: exercise responses evolve over weeks and months, and dietary interventions can be modulated in real time. This necessitates temporal graph models that can incorporate sequence information, such as recurrent graph neural networks or attention-based transformers with positional encoding.

Another forward-looking direction is the incorporation of causal inference into the GNN framework. Association-based predictions are insufficient for personalized recommendation, which requires understanding of counterfactual outcomes: what would happen if an individual followed a high-protein diet versus a carbohydrate-rich diet? Causal graph neural networks aim to learn representations that are invariant to interventions, enabling the estimation of individualized treatment effects [16]. Applying such methods to the exercise domain is challenging because controlled trials with multiple interventions per subject are rare, but leveraging existing randomized controlled trial data with crossover designs could provide a testbed.

Sustainability is also a concern. Training large GNN models consumes substantial energy, and the carbon footprint of repeated retraining as new data accumulate must be minimized. Efficient training strategies, such as sparse message passing and mixed-precision arithmetic, can reduce energy consumption. Furthermore, the long-term viability of the framework depends on the availability of open-source tools and community-maintained knowledge graphs for immune gene function and muscle biology. Collaborative efforts, such as the Genotype-Tissue Expression project and the Human Cell Atlas, provide foundational resources that can be incorporated into the graph [17]. As the volume of long-read sequencing data grows, the graph will need to be updated incrementally, requiring continual learning algorithms that adapt without catastrophic forgetting.

8. Conclusion

This paper has presented a graph neural network-based framework for integrating long-read immune genotyping with skeletal muscle transcriptomics, targeting the prediction of personalized nutrition and exercise responses. The architectural design emphasizes heterogeneous graph construction, multimodal message passing, and interpretability, while addressing system-level trade-offs related to scalability, data heterogeneity, and real-world deployment. Governance issues, including privacy, fairness, and regulatory compliance, are intrinsic to the responsible translation of such technology. Cross-domain comparisons reveal both commonalities and domain-specific challenges, particularly the need for temporal modeling and causal inference. The proposed framework represents a significant step toward a systems-level understanding of how immune genetic variation interacts with muscle gene expression to shape individualized outcomes, with broad implications for precision health, athletic performance, and public health policy. Future work should focus on large-scale longitudinal validation, federated learning infrastructures, and the development of open benchmarks to accelerate progress in this emerging interdisciplinary field.

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