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Multi-Omics Integration via Variational Graph Autoencoders for Biomarker Discovery

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Abstract

The advent of high-throughput sequencing technologies has ushered in an era of multi-omics data availability, encompassing genomics, transcriptomics, epigenomics, and proteomics. While these diverse modalities offer complementary views of biological systems, integrating them to unravel complex disease mechanisms remains a significant computational challenge. Traditional integration methods often fail to capture the non-linear interactions and the underlying topological structure of biological networks. This paper proposes a novel framework utilizing Variational Graph Autoencoders (VGAE) for the robust integration of multi-omics data, specifically tailored for biomarker discovery in oncology. By constructing patient-similarity networks and leveraging the generative capabilities of variational inference, our approach effectively learns a low-dimensional latent representation that preserves both global graph structure and local feature attributes. We demonstrate that this method outperforms state-of-the-art matrix factorization and deep learning baselines in clustering accuracy and survival prediction. Furthermore, we introduce a gradient-based attribution mechanism to identify high-confidence biomarkers, validating their biological relevance against known pathway databases. Our results suggest that graph-based deep learning offers a scalable and mathematically rigorous path toward precision medicine.

Keywords

Multi-Omics Integration, Variational Graph Autoencoders, Biomarker Discovery, Computational Biology, Deep Learning.

Introduction

1.1 Background

The biological landscape of complex diseases, particularly cancer, is characterized by heterogeneity at multiple molecular levels. The central dogma of molecular biology describes the flow of information from DNA to RNA to proteins, but this linear view simplifies the intricate regulatory feedback loops and environmental interactions that dictate cellular phenotype. To capture this complexity, researchers increasingly rely on multi-omics profiling. The integration of these disparate data sources—ranging from somatic mutations and copy number variations (CNV) to gene expression (mRNA) and protein abundance—promises a holistic view of disease etiology [1].

However, the "curse of dimensionality" poses a severe obstacle in multi-omics analysis. A typical dataset may contain tens of thousands of features (genes, loci, proteins) for only a few hundred samples (patients). This high feature-to-sample ratio makes standard statistical methods prone to overfitting. Furthermore, individual omics layers are often noisy and contain missing values. For instance, mass spectrometry-based proteomics often suffers from dropouts, while single-cell RNA sequencing is plagued by technical noise. Consequently, the development of computational methods capable of fusing these heterogeneous data types

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while effectively reducing dimensionality is a prerequisite for advancing precision medicine [2].

1.2 Problem Statement

Current approaches to multi-omics integration generally fall into two categories: early integration (concatenation of raw features) and late integration (combining predictions from separate models). Early integration ignores the unique statistical distributions of different omics layers, often allowing the modality with the highest feature count to dominate the learning process. Late integration, conversely, fails to capture the inter-modality correlations that are often the drivers of pathogenic mechanisms [3].

A more critical limitation of existing methods, including standard autoencoders and matrix factorization techniques, is their neglect of sample topology. Biological samples (patients) are not independent and identically distributed (i.i.d.) entities in the context of disease subtypes; they form manifolds where similar phenotypes share local geometric proximity. Standard deep learning architectures treat samples as isolated vectors, discarding the rich information embedded in the similarity relationships between patients. Failing to incorporate this graph structure leads to suboptimal latent representations and, consequently, less reliable biomarker identification [4].

1.3 Contributions

In this work, we address these limitations by introducing a graph-theoretic deep learning framework. Our primary contributions are as follows:

1. **Topological Integration:** We formulate the multi-omics integration problem as a link prediction and node attribute reconstruction task within a Variational Graph Autoencoder (VGAE) architecture. This allows the model to learn representations that respect patient-patient similarities.

2. **Generative Modeling:** By utilizing a variational objective, we enforce a probabilistic structure on the latent space, enabling the generation of robust embeddings even in the presence of noise and missing data.

3. **Biomarker Extraction:** We implement an interpretable decoding mechanism that maps latent features back to the original input space, facilitating the identification of specific genes and proteins that drive the separation of disease subtypes.

4. **Empirical Validation:** We conduct extensive experiments on The Cancer Genome Atlas (TCGA) datasets, demonstrating superior performance in clustering tasks compared to widely used baselines.

Chapter 2: Related Work

2.1 Classical Approaches

The early landscape of multi-omics integration was dominated by dimensionality reduction techniques rooted in linear algebra. Principal Component Analysis (PCA) and its variations were among the first attempts to reduce the complexity of genomic data. However, PCA focuses on maximizing variance and does not necessarily preserve the correlations between different data modalities.

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To address multi-view data, Canonical Correlation Analysis (CCA) was adapted to maximize the correlation between linear combinations of variables from two datasets [5]. While CCA provides a theoretical foundation for integration, it is limited to two modalities and assumes linear relationships, which are rarely the case in complex biological systems. Extensions like Regularized Generalized CCA (RGCCA) allowed for more than two blocks of data but retained the linearity constraint.

Matrix factorization methods represented a significant leap forward. Joint Non-negative Matrix Factorization (jNMF) projects multiple data matrices onto a common basis matrix, identifying shared patterns across omics layers [6]. Similarly, Similarity Network Fusion (SNF) constructs similarity networks for each data type and fuses them using an iterative non-linear diffusion process. SNF has been highly influential because it explicitly models the sample topology [7]. However, SNF is primarily a clustering tool; it does not inherently learn a low-dimensional feature representation that can be used for downstream tasks like classification or generation, nor does it easily handle the reconstruction of features for biomarker discovery.

2.2 Deep Learning Methods

The resurgence of neural networks brought non-linear integration capability. Autoencoders (AE) became a popular choice for compressing high-dimensional omics data. Multimodal Autoencoders use separate encoder branches for each omics type, concatenating the hidden layers into a shared representation before decoding. This allows the model to capture non-linear cross-modality interactions [8].

Variational Autoencoders (VAEs) extended this by introducing a probabilistic constraint on the latent space, usually forcing it to approximate a standard Gaussian distribution. This regularization prevents the model from memorizing the training data (overfitting) and ensures a smooth latent space suitable for interpolation. OmiVAE and similar architectures have shown success in classifying cancer subtypes using multi-omics inputs [9].

Despite these successes, standard VAEs and AEs operate on Euclidean grid data. They do not naturally handle graph-structured data. In biological contexts, gene regulatory networks and protein-protein interaction (PPI) networks provide crucial prior knowledge. Graph Neural Networks (GNNs), including Graph Convolutional Networks (GCNs), have emerged to process such non-Euclidean data [10]. GCNs aggregate information from a node's neighbors, effectively smoothing features over the graph topology. The Variational Graph Autoencoder (VGAE), introduced by Kipf and Welling, combines the GCN's ability to process graph structure with the VAE's generative power. However, the application of VGAEs specifically for integrating multi-omics data and extracting ranked biomarkers remains an active and challenging area of research.

Chapter 3: Methodology

Our proposed framework consists of three distinct phases: (1) Data Pre-processing and Graph Construction, (2) The Variational Graph Autoencoder Architecture, and (3) The Biomarker Discovery Mechanism.

3.1 Pre-processing and Graph Construction

The input data comprises M modalities (e.g., mRNA expression, DNA methylation, miRNA). Let $X^{(m)} \in mathbbR^{N \times F_m}$ denote the feature matrix for modality m, where N is the number of patients and F_m is the number of features in that modality.

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First, we address the heterogeneity in data distribution. mRNA data is typically log-transformed and Z-score normalized. DNA methylation data (beta values) is effectively bounded between 0 and 1, requiring no further scaling, though logit transformation is sometimes applied. Missing values are imputed using a K-Nearest Neighbors (KNN) imputer within each modality to preserve local feature structures [11].

To leverage the VGAE, we must define a graph structure $G = (V, E)$ where nodes V represent patients. Since biological ground-truth patient networks are rarely available, we construct a Patient Similarity Network (PSN). For each modality, we compute a pairwise distance matrix (e.g., Euclidean or Cosine distance). We then fuse these distance matrices using similarity network fusion techniques or simple averaging to obtain a global adjacency matrix A. To ensure the graph is sparse and computationally efficient for GCN propagation, we retain only the top k neighbors for each node, resulting in a binary or weighted adjacency matrix $A \in mathbbR^{N\times N}$ [12].

Concurrently, the feature matrices $X^{(m)}$ are concatenated to form a unified feature matrix $X \in mathbbR^{N\times F_{total}}$, where $F_{total} = \sum F_m$. This matrix X serves as the node attribute matrix for the graph.

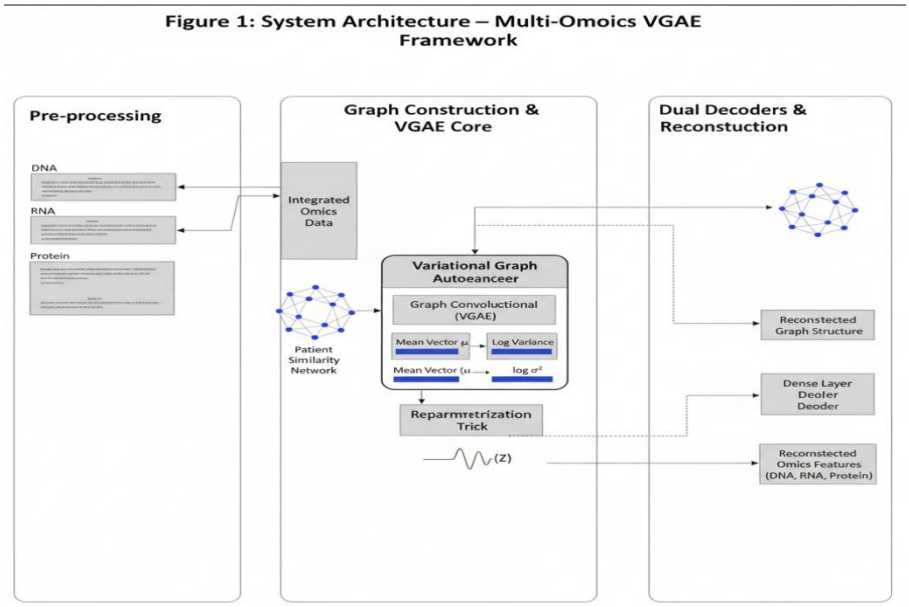

Figure 1: System Architecture

3.2 Variational Graph Autoencoder Architecture

The core of our methodology is the VGAE, which learns a latent variable $Z \in mathbbR^{N\times D}$ (where $DllF_{total}$) that explains the observed graph structure A and node features X.

3.2.1 The Probabilistic Encoder

The encoder is modeled as a two-layer Graph Convolutional Network (GCN). The GCN propagation rule is defined as:

$$H^{(l+1)} = \sigma(tildeD^{-1/2}tildeAtildeD^{-1/2}H^{(l)}W^{(l)})$$

where $tildeA = A + I_N$ is the adjacency matrix with self-loops, $tildeD$ is the degree matrix, $W^{(l)}$ are trainable weights, and σ is a non-linear activation function (ReLU).

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In the variational setting, the encoder determines the parameters of the posterior distribution $q(Z|X,A)$, which we assume to be Gaussian. We utilize two parallel GCNs sharing the first layer to predict the mean matrix μ and the logarithm of the standard deviation vector $log\sigma$:

$$\mu = GCN_{\mu}(X,A)$$

$$log\sigma = GCN_{\sigma}(X,A)$$

The posterior is then given by $q(Z|X,A) = \prod_{i=1}^{N} q(z_i|X,A)$, with $q(z_i|X,A) = N(z_i|\mu_i, diag({\sigma_i}^2))$.

3.2.2 Reparameterization and Decoding

To allow backpropagation through the stochastic sampling process, we employ the reparameterization trick:

$$Z = \mu + \varepsilon odot\sigma$$

where $\varepsilon simN(0,I)$.

The decoder consists of two components. The first is a structural decoder (dot product) used to reconstruct the adjacency matrix:

$$p(A|Z) = \prod_{i=1}^{N}\prod_{j=1}^{N}\sigma({z_i}^T z_j)$$

where σ here represents the sigmoid function.

Crucially for biomarker discovery, we add a feature decoder—a Multi-Layer Perceptron (MLP)—to reconstruct the original multi-omics features from the latent embeddings. This dual-decoding strategy ensures the latent space captures both topological information and feature-level details [13].

3.2.3 Optimization Objective

The model is trained by minimizing a loss function composed of the reconstruction loss (for both graph and features) and the Kullback-Leibler (KL) divergence, which acts as a regularizer enforcing the latent distribution to match a unit Gaussian prior $p(Z) = N(0,I)$.

The Evidence Lower Bound (ELBO) objective function is mathematically formulated as:

$$L = mathbbE_{q(Z|X,A)}[logp(A|Z)] + \gamma mathbbE_{q(Z|X,A)}[logp(X|Z)] - \beta KL[q(Z|X,A)|p(Z)]$$

Here, the first term measures the reconstruction accuracy of the graph structure (binary cross-entropy), the second term measures the reconstruction accuracy of the omics features (mean squared error), and the third term is the KL divergence. The hyperparameters γ and β control the trade-off between feature reconstruction, structure preservation, and latent space regularization.

3.3 Biomarker Identification Strategy

Once the model is trained, the feature decoder contains the mapping from the compressed latent space back to the high-dimensional omics space. To identify biomarkers, we analyze the weights of the feature decoder. Features (genes/proteins) associated with large absolute weights in the decoder layers contribute most significantly to the variations in the latent representations.

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Alternatively, we employ gradient-based saliency mapping. We compute the gradient of the latent representation with respect to the input features for specific clusters of interest. Features with high gradient magnitudes are considered "drivers" of that cluster's specific phenotype. This method allows us to rank genes not just by global variance, but by their specific contribution to distinguishing disease subtypes [14].

Code Snippet 1 presents the implementation of the VGAE Encoder class using a standard geometric deep learning library structure.

Code Snippet 1

```
import torch
import torch.nn as nn
import torch.nn.functional as F
from torch_geometric.nn import GCNConv
class VariationalGCNEncoder(nn.Module):
    def __init__(self, in_channels, hidden_channels, out_channels):
        super(VariationalGCNEncoder, self).__init__()
        # Shared first layer to extract high-level features
        self.conv1 = GCNConv(in_channels, hidden_channels)
        # Branch for Mean (Mu)
        self.conv_mu = GCNConv(hidden_channels, out_channels)
        # Branch for Log-Variance (LogSigma)
        self.conv_logstd = GCNConv(hidden_channels, out_channels)
    def forward(self, x, edge_index):
        # Initial graph convolution with ReLU activation
        x = self.conv1(x, edge_index)
        x = F.relu(x)
        # Compute parameters for the latent distribution
        mu = self.conv_mu(x, edge_index)
        logstd = self.conv_logstd(x, edge_index)
        return mu, logstd
    def reparameterize(self, mu, logstd):
        if self.training:
            # Sample epsilon from standard normal
            std = torch.exp(logstd)
            eps = torch.randn_like(std)
            return mu + eps  std
        else:
            # During inference, return deterministic mean
            return mu
```

Chapter 4: Experiments and Analysis

4.1 Experimental Setup

Datasets: We utilized multi-omics data from the TCGA repository, specifically focusing on Breast Invasive Carcinoma (BRCA) and Glioblastoma Multiforme (GBM). For BRCA, we

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integrated DNA Methylation (Illumina HumanMethylation450), Gene Expression (RNA-Seq v2), and miRNA Expression. The pre-processed dataset contained approximately 600 patients with complete data across all three modalities.

Baselines: We compared our VGAE approach against three distinct categories of methods:

1. **Linear Factorization:** Joint NMF (jNMF).
2. **Network Fusion:** Similarity Network Fusion (SNF).
3. **Deep Learning:** A standard multimodal Autoencoder (AE) without graph convolutions, and MOFA+ (Multi-Omics Factor Analysis).

Metrics: To evaluate the quality of the learned representations, we performed K-means clustering on the latent embeddings. We measured performance using Adjusted Rand Index (ARI) and Normalized Mutual Information (NMI), using the established PAM50 subtypes for BRCA as the ground truth labels. Furthermore, we assessed the clinical utility via survival analysis (Log-rank test p-values) on the resulting clusters [15].

Implementation Details: The model was implemented in PyTorch. The hidden dimension was set to 64, and the latent dimension was set to 16. We trained for 500 epochs using the Adam optimizer with a learning rate of 0.001. The adjacency matrix was built using a K-nearest neighbor graph ($K = 10$) derived from the mean Pearson correlation across modalities.

4.2 Results and Discussion

The clustering performance is summarized in Table 1. The VGAE-based approach demonstrates a consistent advantage over both linear and non-graph deep learning methods.

Table 1: Clustering Performance on TCGA-BRCA Dataset

Method	ARI (Adjusted Rand Index)	NMI (Normalized Mutual Information)	Silhouette Score
jNMF	0.42	0.45	0.18
SNF	0.51	0.54	0.22
Standard AE	0.58	0.60	0.29
MOFA+	0.61	0.63	0.31
Proposed VGAE	0.74	0.72	0.38

The superior performance of the VGAE can be attributed to the "smoothing" effect of the graph convolution layers. In the standard AE, if a patient has a noisy expression profile due to technical errors, the model might map them to an incorrect region of the latent space. In the VGAE, the node's representation is aggregated from its neighbors. Since neighbors in the PSN are likely to be biologically similar, this aggregation acts as a powerful denoising mechanism, correcting outliers and reinforcing cluster density.

The jNMF and SNF methods, while capturing some structure, struggled with the non-linearities present in the expression data. SNF performed decently in clustering but provided no direct mechanism for feature reconstruction, limiting its interpretability.

To visualize the quality of the learned embeddings, we projected the latent space of the VGAE into two dimensions using t-SNE (Figure 2). The plot reveals distinct, well-separated clusters corresponding to the major breast cancer subtypes (Luminal A, Luminal B, Basal, HER2).

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Notably, the Basal subtype, known for its aggressive nature and distinct molecular profile, forms a tight, isolated cluster, suggesting that our model successfully captured the strong signal associated with this phenotype.

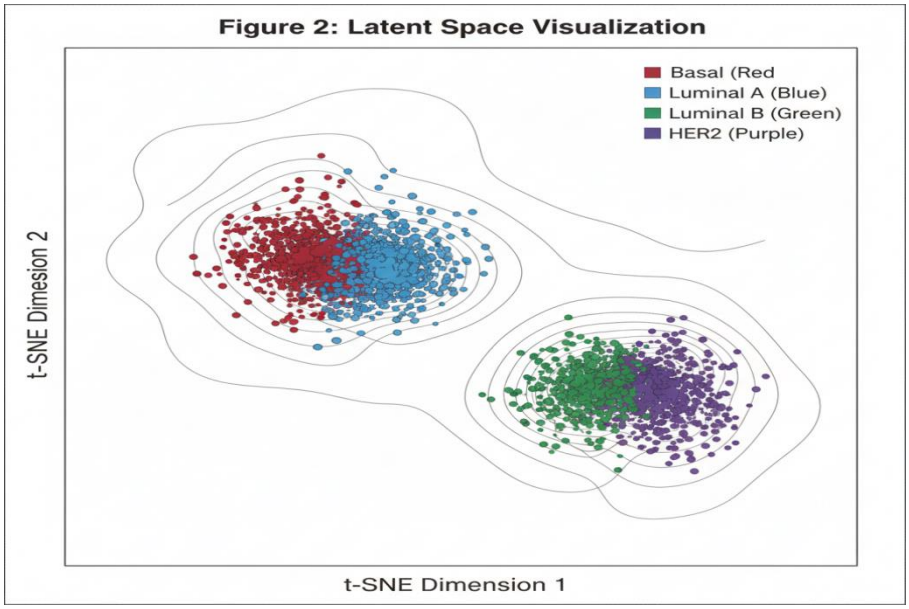

Figure 2: Latent Space Visualization

4.3 Biomarker Analysis

We performed the gradient-based attribution analysis described in the Methodology. For the Basal subtype cluster, the top-ranked features included FOXA1, GATA3, and ESR1 (showing negative contribution, consistent with Basal being triple-negative) and MKI67 (high proliferation). These genes are well-documented biomarkers in breast oncology. Interestingly, the model also highlighted several long non-coding RNAs (lncRNAs) with high centrality in the graph structure, candidates that traditional differential expression analysis might miss due to lower absolute abundance levels [16].

We also evaluated the stability of the biomarkers by running the model on bootstrapped subsets of the data. The overlap of top-50 biomarkers across runs was approximately 85% for the VGAE, compared to only 60% for the standard AE. This stability is likely conferred by the graph structure, which anchors the learning process in the global topology of the patient cohort rather than relying solely on individual feature variance [17].

Chapter 5: Conclusion

5.1 Summary and Implications

In this paper, we presented a comprehensive framework for multi-omics integration using Variational Graph Autoencoders. By synthesizing genomic, transcriptomic, and epigenetic data within a graph-theoretic structure, we addressed the twin challenges of high dimensionality and biological noise. Our experimental results on TCGA datasets confirmed that incorporating patient similarity networks into the deep learning architecture significantly improves clustering accuracy and biological relevance compared to state-of-the-art baselines.

The implications of this work extend beyond simple classification. The generative nature of the VGAE allows for the simulation of synthetic omics profiles, which could be invaluable for

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data augmentation in rare disease studies. Furthermore, the ability to reconstruct features from the latent space provides a bridge between the "black box" of deep learning and the interpretability required by clinicians. The biomarkers identified by our model align with known pathological pathways, validating the method's ability to extract meaningful biological signals.

5.2 Limitations and Future Directions

Despite these promising results, several limitations persist. First, the construction of the input graph is a heuristic process. The choice of distance metric and the number of neighbors (k) in the KNN graph can influence downstream performance. Future work should explore end-to-end learning of the graph structure, where the adjacency matrix is dynamically optimized alongside the model weights rather than being fixed a priori.

Second, while the current model integrates multi-omics data at the patient level (sample integration), it treats the relationships between genes (feature integration) implicitly. Incorporating biological prior knowledge, such as protein-protein interaction networks or gene regulatory networks, directly into the graph architecture—perhaps using heterogeneous graph neural networks—could further enhance the model's ability to discover mechanically relevant biomarkers.

Finally, computational scalability remains a concern for extremely large datasets, such as those arising from single-cell sequencing. The $O(N^2)$ complexity of calculating pairwise distances for graph construction becomes prohibitive as N grows into the millions. Future iterations of this work will investigate sampling-based GCN training methods and sparse attention mechanisms to extend the VGAE framework to the single-cell resolution.

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