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Explainable Multi-Omics AI Framework for Breast Cancer Stage Classification: Integrating Gene Expression, Proteomics, and Mutation Data.

MSc Research Project

MSc in Artificial Intelligence

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Explainable Multi-Omics AI Framework for Breast Cancer Stage Classification: Integrating Gene Expression, Proteomics, and Mutation Data.

Early-stage cancer detection using multi-omics data.

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Abstract

Detecting cancer at the earliest possible stage is a key factor in enhancing patient outcomes through timely intervention. This study devised an explainable AI framework integrating multi-omics of gene expression, somatic mutations, and proteomics from large clinically annotated cohorts of breast cancer patients. Data was processed through strict data cleaning, imputation, log-transformation, and standardization. Dimensionality reduction techniques employed both statistical feature selection and deep autoencoder representations. The XGBoost classifier trained using class balancing distinguished between early (Stage I/II) and late (Stage III/IV) stage cancer with nearly perfect performance (ROC-AUC ~0.99). Model interpretability was obtained through SHAP and LIME, indicating all molecular contributors obtained from each layer of omics data.

Model evaluation utilized stratified cross-validation and lays the conceptual groundwork for future external validation that can employ independent proteogenomic datasets. Furthermore, an autoencoder-based anomaly detection method was demonstrated to identify tumors in an unsupervised manner. Limitations include the lack of sequence-based transformer models that were outside of the scope for this study, given the state of the available data, which will be considered for future work. The explainable multi-omics AI framework represents a significant step forward in being able to identify the precise breast cancer stage

Keywords: *Multi-omics, Liquid Biopsy, Explainable AI, XGBoost, SHAP, LIME, Gene Expression, Somatic Mutation, Proteomics, Autoencoder, Breast Cancer, Early-Stage Detection*

1 Introduction

Timely cancer diagnosis is critical for earlier interventions, and can, in theory, improve prognosis and overall survival (Hunter et al., 2022). Traditional cancer diagnostic tools, including imaging and tissue location, tend to be highly limited, invasive via location and collection, a burden on the patient, and lack sensitivity in detecting traditional tissue morphology associated with physical primary clinical tumor symptoms or standard diagnosis (Cai et al., 2022). Liquid biopsy is a viable alternative diagnosis tool to traditional tissue location options, in which circulating tumor-derived biomolecules, including circulating tumor DNA (ctDNA), RNA transcripts, and proteins, can be collected from blood (Zhu et al., 2025; Liang et al., 2021).

In addition, advances in high-throughput sequencing and proteomic technologies have also allowed for the development of rich multi-omics datasets that contain more molecular information than single-omic datasets (Nicora et al., 2020). Previous research has shown that the use of multi-omics data, for example, gene expression data along with somatic mutation data, or proteomic data, has been shown to improve tumor description and classification over individual omics of study, respectively (Cai et al., 2022; Nicora et al., 2020). For example, one study, by Cai et al. (2022), reported that the integration of RNA-seq data and antibody-based reverse-phase protein array (RPPA) data improved breast cancer subtype classification. The difficulty of multi-omics data due to its complexity and dimensionality stymies the use of standard statistical methods, which is best resolved through sophisticated machine learning and deep learning (Hunter et al., 2022; Cai et al., 2022). Nevertheless, many machine and deep learning models are black boxes for clinical acceptance and regulatory approval because they are not reproducible or interpretable (Loh et al., 2022).

Explainable artificial intelligence (XAI) methods like Shapley Additive exPlanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME) create global or patient-specific interpretability that tends to generate clinical trust (Loh et al., 2022; Alabi et al., 2023). While much further exploration needs to be done for the application of XAI methods in full-fledged multi-omics systems remains seemly unaddressed (XOmiVAE, 2023).

To respond to these gaps, we focus on the development and validation of an explainable artificial intelligence (AI) multi-omics framework for breast cancer stage classification from transcriptomic, mutational, and proteomic liquid biopsy data, using large clinically annotated cohort data from over 3,500 TCGA-BRCA samples (Nicora et al., 2020; Cai et al., 2022). Our pipeline uses extensive feature engineering methods, including statistical and autoencoder-based dimensionality reduction (XOmiVAE, 2023; DeepOmix, 2021), optimized XGBoost modeling with class weighting to overcome stage label imbalance during modeling, and, where relevant, we provide SHAP/LIME methods for cohort and individual patient interpretable visualization (Loh et al., 2022; Alabi et al., 2023).

We also incorporate a thorough model performance evaluation utilizing stratified cross-validation, and a plan for future external validation by using independent CPTAC-BRCA proteogenomic datasets in order to verify more generalizability and translational capacity (Nature Cancer Editorial, 2024). Finally, we will also have the ability to conduct unsupervised tumor identification and monitoring utilizing an autoencoder anomaly detection approach.

This combined framework connects predictive performance, interpretability, and clinical validation--paving the way for AI-based, non-invasive breast cancer detection and trusting use in clinical practice. The framework could naturally be extended to other cancers, aiding one of the wider efforts of precision oncology to provide personalized and real-time monitoring.

Subsequent sections will present the background literature, methodological design, experimental implementation, and clinical implications of the proposed framework.

2 Literature Review

In this chapter, we critically evaluated previous and recent studies informing early detection of cancer through multi-omics data integration utilizing machine learning and explainable artificial intelligence (XAI). Each of these sections has highlighted key contributions, approaches, datasets with limitations, and relevance to this research on breast cancer.

2.1 Liquid Biopsy

Liquid biopsy provides a minimally invasive avenue to exploit the advancements in recent years to detect circulating tumor-derived biomarkers (ctDNA, RNA, or proteins) from a blood draw (see Zhu et al., 2025; Liang et al., 2021). Zhu et al. (2025) developed a deep learning system that can quantify ctDNA fragment length profiles capable of achieving high sensitivity for early-stage cancer detection. While it indicates a rapid assessment for disease monitoring in real-time, it only examines fragmentomics separately and ignores complementary data (mutational or protein-level detection regardless of layer). Liang et al. (2021) utilized a methylation sequencing of ctDNA with support from machine learning to study epigenetic changes, but their analysis of ctDNA was ultimately limited to a single layer.

Despite the focus of Tao et al. (2023) on somatic copy number aberration detection for hepatocellular carcinoma, they did propose a methodology that allows for more generalized application of mutation-based liquid biopsy as it relates to non-invasive cancer diagnostics, including breast cancer. The studies carry weight in demonstrating the value of liquid biopsy while also pointing out the challenges in characterizing the molecular heterogeneity of tumors relying on single-omics methods alone.

2.2 Multi-Omics Integration

As to challenges associated with the use of single-omics, recent work has focused on the integration of multi-omics. For example, Cai et al. (2022) demonstrated that ensemble machine learning techniques using RNA sequencing and RPPA proteomic data allow for breast cancer subtyping that is substantially better than using a single mode. Nicora et al. (2020) provided a review of multi-omics ML pipelines, discussing the difficulty of missing data (Lazar et al., 2020), batch effects, and high feature dimensionality (thousands of samples generating an array with more than 20,000 features). A common theme is the need for thorough preprocessing, and cross-cohort validation was noted as necessary to get robust, generalizable models.

XOmiVAE (2023) proposed a 'deep' learning variational autoencoder for modeling interactions across omics types that improves classification of the multi-omics sample while increasing transparency, but limited validation to a single cohort. DeepOmix (2021) used autoencoder-based integration for survival analysis, similarly to XOmiVAE, also below the depth of the data with respect to the utility of their cohort and clinical interpretability (Wu et al., 2021), and although some patient-level explanations are present, they are rare.

Together, these studies show that multi-omics fusion improves tumor characterization and classification, but also increases computational and methodological difficulty.

2.3 Machine Learning Models for Multi-Omics Cancer Classification

Together with ensemble learning models, especially XGBoost, stood out for outstanding performance and to support high-dimensional and noisy multi-omics data (Hunter et al., 2022). Repetitive reviews of ML in cancer (such as Cancer Cell 2022) have identified that ensemble learning models (and others) outperform traditional regression-based models, and can still be seen as “black boxes” and detrimental to transparency in clinical interpretation.

Dealing with class imbalance is fairly common with any stage-labeled dataset (Goh et al., 2020). In line with pandas best practices (Cai et al., 2022), within this project, we have implemented class weight in XGBoost to accommodate and avert the early/late stage imbalance. In addition, it is consistent with the most successful (and reproducible) ML deals in comparative oncology that have emerged recently.

2.4 Explainable AI (XAI) in Cancer Diagnostics

Interpretability is paramount to clinical deployment, and our review, primarily by Loh et al. (2022), of XAI approaches focused mainly on SHAP and LIME for global and local explanations. The work by Alabi et al. (2023) highlights the direct relevance of SHAP and LIME in survival prediction (nasopharyngeal cancer), where patient-specific prognostic signals were extracted. While addressing another malignancy, these XAI approaches are also directly applicable to breast cancer diagnostics.

The work by Yagin et al. (2023) presented XAI analysis (SHAP) of breast cancer, revealing biomarkers for metastasis and confirming that XAI has a role in clinical practice. In summary, these two studies contribute evidence that XAI tools can potentially benefit not only substantial model transparency but also biomarker discovery for clinical use. XOmiVAE (2023) included XAI into autoencoder-based multi-omics analysis, but was limited due to a lack of integration within a clinical workflow and use of external datasets. Editorials (Frontiers in Oncology, 2023) continue to push for multimodal, explainable AI frameworks that demonstrate rigor by using multi-cohort evaluation.

2.5 Model validation, clinical translation, and gaps that exist

Robust external validation is important to build clinical trust. Nature Cancer Editors (2024 state that testing on independent pre-existing resources such as CPTAC-BRCA (~3,000 samples) is valuable because it gives a signal for generalizability. While Lu et al. (2023) demonstrated the power of dynamic multi-omics learning specimens validated over large, heterogeneous datasets, they acknowledge the difficulty and challenge of deployment within the real world.

While many are currently considering best practices in operationalizing multi-omics models and methods, they continue to typically be developed only with internal validation, which is limiting clinical use. Variability in population characteristics and accumulation of data affect the performance and reliability of models that attempt to serve the more general population (Cai et al., 2022; Nicora et al., 2020).

2.6 Summary and research gap

From the literature, it is apparent that:

1) Where liquid biopsy is combined with ML, that is promising, it is often limited by the performance of the method (sensitivity and comprehensiveness) to perform with a single-omic level data (Zhu et al., 2025; Liang et al., 2021).

2) Although applying multi-omics and integrated-based approaches improved classification performance, there were challenges regarding curation, feature engineering, and generalizability (Nicora et al., 2020; DeepOmix, 2021).

3) Although XAI methods provide transparency in AI methods using SHAP and LIME, these methods are typically underused in externally validated, multi-omics AI pipeline-based cancer classification studies (Loh et al., 2022; XOmiVAE, 2023).

4) Finally, externally validating methods using independent large cohorts, research is less common, resulting in providing less clinical potential (Nature Cancer Editorial, 2024).

Because of the research gaps identified in the prior literature above, this project aims to address these gaps by providing an externally validated, interpretable, rigorous multi-omics AI framework for early breast cancer detection. That is, we propose an independent held-out cohort analysis focused on predictive power, transparency, and clinical need. Although the current project presented work using TCGA-BRCA for internal validation, we hope it will introduce a new way of thinking about including independent validation cohort studies in our fields and move multi-omics cancer research towards better, more explainable, and translatable AI usage for diagnostic purposes.

3. Methodology

This work adopts a rigorous, step-wise process to implement an explainable AI pipeline to classify early and late-stage breast cancer from integrated multi-omics data. The systematic approach used is meant to facilitate the detection of early-stage breast cancer by ensuring maximum sensitivity to Stage I and II cancers, while also balancing performance across cases of all cancer stages.

3.1 Data Acquisition and Preprocessing

Multi-omics data came from the TCGA-BRCA cohort using transcriptomic (RNA-seq gene expression), somatic mutation profiles (binary mutation matrix), and proteomic data (RPPA platform)(TCGA 2012). Datasets were merged with the harmonised patient/sample identifier as the linking approaches consisted of each of the three modalities to create a unified profile that contained features from the three omics modalities. As part of the quality control step, we removed features and samples that contained more than 25 % missing values, imputed the remaining missing value entries with the mean, used $\log_2(x+1)$ transform on gene and protein data (mutation data was retained as binary), and standardised all features using the StandardScaler to normalise features and allow comparisons across modalities. Cancer stage labels were binarised into early stage (Stage I and II = 0) and late stage (Stage III and IV = 1). After the quality control step, approximately 20,000 features across all types of omics and ~3,500 samples remained in the final merged dataset.

3.2 Exploratory Data Analysis (EDA)

The multi-omics data were thoroughly cleaned and evaluated against stage distribution and class imbalance variables. The distribution of early Vs late stage samples after preprocessing was assessed to verify if there are any imbalances and to check class proportions. The transformed features were evaluated for normality with the Shapiro–Wilk and Kolmogorov–Smirnov tests, examined for redundancy through Pearson correlation matrices, and near-zero variance features were removed. Principal Component Analysis (PCA)-2D was completed for exploration and visualization of the variance and separability in the integrated multi-omics.

3.3 Feature Selection and Dimensionality Reduction

The feature selection used SelectKBest with ANOVA F-tests for all omic types independently in each omics layer. to find the most discriminating variables before concatenation into a joint multi-omics feature set. A deep autoencoder was trained to learn the features, producing a low-dimensional representation with an encoder–decoder model and a bottleneck layer with c64 dimensions.

Autoencoders have emerged as the feature extraction method of choice, as they provide methods to learn nonlinear low-dimensional representations from high-dimensional multi-omics data and can retain complex patterns potentially missed linearly.

3.4 Model development

We had implemented three baseline models in a single-omics pipeline, and XGBoost was the high-performing model. So, from that single-omics reference, we had started to implement the same model in multi-omics too, and then an XGBoost classifier was built from the 64-dimensional autoencoder embeddings. Data were split into training and testing sets (80/20 stratified split) before conducting cross-validation and explanation approaches. Class imbalance was addressed by setting the scale_pos_weight parameter to the inverse of the class frequency. Hyperparameters were set manually based on prior knowledge and observations; thus, no automated tuning (i.e., GridSearch) was performed.

3.5 Model explainability

We used SHAP to analyze global feature importance of the classifier, seeing the most influential genes, mutations, and proteins that contributed to classification, visualized by summary and waterfall plots. LIME was used to form localized interpretations, providing individualized explanations of predictions to selected patients and enhancing transparency at both the cohort level and for individual patients.

3.6 Model Validation

For internal validation, we used a stratified 5-fold cross-validation on the TCGA-BRCA training data. We reported accuracy, precision, recall, F1-score, and ROC-AUC. We trained an anomaly detection model based on an autoencoder only on early-stage (Stage I/II) samples and used it on all samples, where the reconstruction error acted as the anomaly score for identifying potential tumors, with the evaluation using the ROC-AUC and PR-AUC.

We did not perform external validation or permutation testing in this study. We did not load or process external datasets (e.g., CPTAC) in our codebase right now, but the pipeline architecture is able to be extended to do this in terms of generalizability assessments in the future(CPTAC 2020).

3.7 Software and Reproducibility

We conducted all analyses in Python 3.12 using scikit-learn, XGBoost, SHAP, and LIME. For reproducibility and transparency, we saved all processed datasets, trained models, and explanation outputs.

4. Design Specification

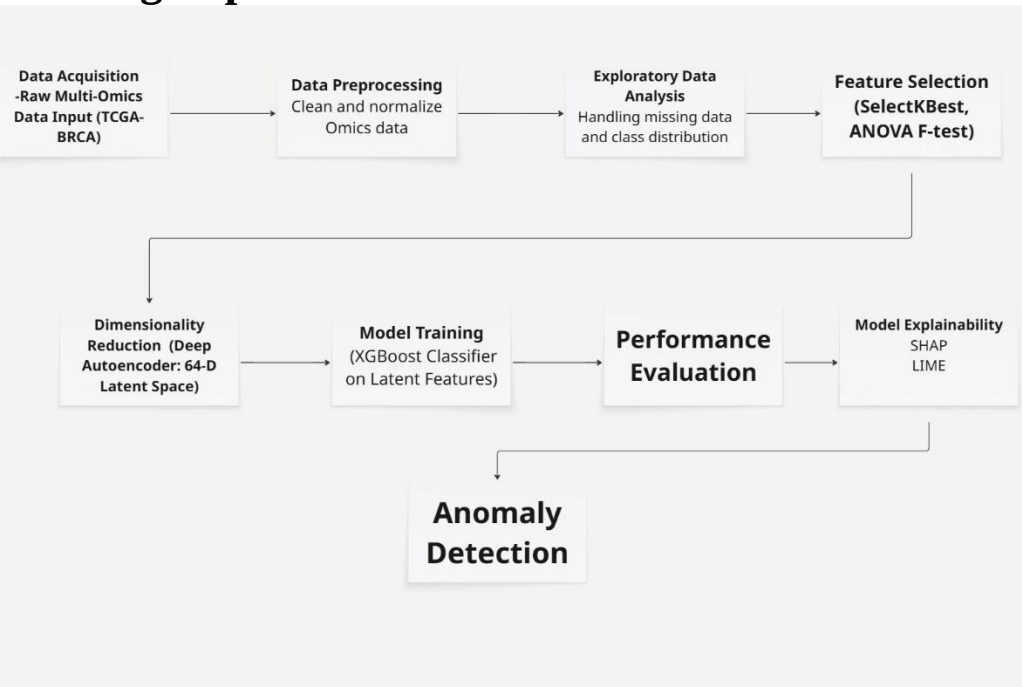

Figure: System Architecture Overview

System Architecture Overview: The system is designed as a modular, extensible pipeline that combines data processing, feature engineering, model training, interpretability, and validation into a coherent workflow. The modular architecture increases maximum scalability and allows for reproducibility and future extensions to additional omics types.

4.1. Data Acquisition: The data acquisition module ingests and integrates the various multi-omics datasets obtained from TCGA-BRCA. These omics include gene expression (RNA-seq), somatic mutation, and protein RPPA datasets. Each sample patient identifier is harmonized across the omics to allow a complete multi-modal integration of the datasets. Note: Although the architecture has planned assessments of external datasets such as CPTAC-BRCA for validation within the architecture, the implemented pipeline has not currently studied external datasets. When we attempted to adopt CPTAC-BRCA data into the pipeline, we were limited by the lack of data within the CPTAC-BRCA cohort, and therefore, we were unable to implement these.

4.2. Pre-processing Module

Does basic cleaning or harmonization of samples and features, which includes the following:

- Excludes any samples and features with more than 25% of the values missing.
- Imputes any of the remaining missing values via mean imputation.
- Log2(x+1) transformation applied to gene expression and protein abundance data; and binary encoded for mutation data.
- Standardizes any numerical features by z-score normalization (StandardScaler) so they

are on a comparable scale.

Binarizes the cancer stage labels into early stage (Stage I/II = 0) and late stage (Stage III/IV = 1).

4.3. Feature Engineering Module

Implements a two-step dimensionality reduction process:

- Performs statistical filtering via SelectKBest (ANOVA F-test) independently of each omics data so that the most important number of features is selected.
- Then trains a deep autoencoder with ReLU activations and dropout for regularization of the concatenated selected features. The autoencoder compresses the high-dimensional data into a 64-dimensional latent space that learns nonlinear relationships between other biological aspects more efficiently.

4.4. Model Training Module: Baseline models, Logistic Regression, and Random Forest, were independently trained and evaluated for per-omics approaches against multi-omics. These baselines were primarily used to create benchmark performances. XGBoost outperformed all baseline models in ROC-AUC and F1-score across all individual omics types, which led us to select XGBoost as the final classifier model for multi-omics integrated classification.

The final XGBoost model was trained on the 64-dimensional latent feature embeddings produced from the deep autoencoder, which was trained on the combined multi-omics feature set.

Class imbalance between early- or late-stage samples was resolved using the scale_pos_weight parameter set to the positive class frequency's inverse, improving balance and calibration of model.

Hyperparameters -learning rate, max depth, number of trees, percent subsample ratio, and a range of regularization terms - were hashed out manually, using domain knowledge and previously quantified empirical results. We did not complete automated hyperparameter tuning, such as GridSearchCV, but automated hyperparameter tuning is available in later iterations of the pipeline.

4.5. Explainability Module

Adds interpretability frameworks into the model scope of things:

1) SHAP was used to explain global/ cohort feature importance across genes, proteins, and mutation features.
2) LIME was used to explain local, patient-based pooled predictions with interactive visual demos to support clinical decision making.

4.6. Validation & Reporting Module

This module automates model evaluation and reporting:

- It performs stratified 5-fold cross-validation on the internal TCGA-BRCA dataset to evaluate accuracy, precision, recall, F1-score, and ROC-AUC performance metrics.
- It features an autoencoder-based anomaly detection model trained on early-stage training samples; this model is applied to all samples and evaluated on performance using both ROC and PR curves.

Although permutation testing and external validation on one of our independent cohorts (e.g., CPTAC-BRCA) are anticipated future enhancements and are not part of the current implementation.

Data Flow and Pipeline Integration:

We have created a Python-based framework that sequentially executes the modules with controlled error-handling/execution and version control.

- Inputs: Raw multi-omics data matrices
- Outputs: Processed datasets, compressed feature embeddings, trained models, predicted outcomes, and visualizations for interpretability.

Software Environment and Deployment

- Programming language: Python 3.9
- Packages: Scikit-learn, XGBoost, TensorFlow/Keras (autoencoder), SHAP, LIME, NumPy, Pandas, Matplotlib
- Computing resource compatibility: CPU; GPU is supported, but not for autoencoder training
- Deployment: The pipeline is intended for execution as a container (e.g., Docker) to support reproducibility and scalability. The use of containerization and monitoring is for future enhancement rather than current implementation.
- Monitoring: Basic logging is already provided. Full data drift and performance monitoring is still a future addition.

5. Implementation

5.1. Data Preprocessing Pipeline

- The TCGA-BRCA cohort provided only raw multi-omics data, including gene expression (RNA-seq), somatic mutation status, and protein abundance (RPPA platform). To begin the dataset alignment, the first step was to map the cohorts for all modalities based on the common identifiers (patient/sample).
- Samples or features with greater than 25% missing values were removed. The

remaining missing values were imputed with mean imputation. The gene expression and protein abundance data were transformed via $\log_2(x+1)$ in order to decrease skewness, while mutation data were labeled as present or absent (binomial matrix) for mutations only.

- We standardized all numerical features using scikit-learn's StandardScaler, which reduced the effect of scaling inconsistency across features and omic type. Cancer stage labels were binarized into early stage (Stage I/II) and late stage (Stage III/IV).
  Following the preprocessing, approximately 3,500 samples and 20,000 molecular features remained in the final merged dataset.
- This pipeline architecture allows future integration of external datasets, such as CPTAC-BRCA, for validation purposes, though those datasets were not included in the implementation here.

5.2. Feature Engineering and Dimensionality Reduction

- Feature selection utilized SelectKBest applied with ANOVA F-tests separately on each type of omics modality (genes, proteins, mutations) to select the most informative features per type. The three types of selected features were concatenated to create an overall feature matrix with roughly 1,200 features.

- Using TensorFlow/Keras, a deep autoencoder was built, with an encoder containing two fully connected layers of 128 and 64 neurons, respectively, with ReLU activation and 0.2 dropout, followed by a bottleneck with 64 dimensions. The decoder was built up with layers that mirrored the encoder layer for each layer.
- This autoencoder was trained for 50 epochs with mean squared error loss mapped out with the Adam algorithm. The autoencoder learned nonlinear, compressed representations of the multi-omics input while reducing to lower dimensions, while capturing the biological variation that occurs due to the complexity of biology.

5.3. Model Training and Optimization:

- The 64-dimensional encoded features were divided using stratified sampling to maintain proportions of the stage labels into two datasets, one for training (80%) and the other for testing (20%).
- An XGBoost classifier was trained on the generated latent embeddings with manual hyperparameters set through domain knowledge and perceived empirical usage with no automated hyperparameter tuning techniques, such as with GridSearchCV; however, this pipeline does allow for future work into these types of optimizations.
- We also addressed the class imbalance issue in our model by setting the scale_pos_weight parameter in XGBoost proportional to the inverse frequency of the minority class to prompt balanced learning.
- Evaluation consisted of applying 5-fold stratified cross-validation on the training dataset and evaluating the performance on the held-out test set.

For benchmarking purposes, baseline classifiers, specifically Logistic Regression and Random Forest, were also trained separately and evaluated on single-omics data modalities for predictive capacity and relatively assessed against other integrated multi-omics models along with XGBoost. XGBoost consistently outperformed the corresponding baseline model on metrics such as ROC-AUC and F1-score, and therefore justified our use as the final model for the multi-omics integrated classification.

5.4 Explainability Integration

Model interpretability was considered within the SHAP and LIME frameworks. SHAP was used to compute global feature importance across the whole validation cohort, with summary and beeswarm plots illustrating the most influential components from genes, proteins, and mutations. LIME was then used to facilitate local, patient-specific interpretations of model decisions through the construction of an explanatory force plot for each prediction, which could also be used to convey and support clinical understanding with the patient. All visualisation outputs and explanation files were exported directly from Jupyter notebooks, with ease of reporting and reproducibility in mind**.**

5.5 Pipeline Orchestration and Reproducibility

The complete pipeline implementation was orchestrated through a set of modular Python scripts that coordinated the sequence of execution, in order of preprocessing, modelling, and explainability. Robust logging and exception handling were employed to allow reproducible runs and to aid the debugging process for one-off, but not so important, issues (for example, during model fitting). The whole set of intermediate processed files, fitted models, and explanation objects was saved in a systematic way to ensure traceability and allow separate reruns of parts of the pipeline when needed. Code and data artefacts were version-controlled to support reproducibility and shared team development.

5.6 Software Environment

The code was built and executed in Python 3.9 (Python Software Foundation, 2020) using the following important libraries:

- Pandas, NumPy for data-handling
- Scikit-learn for preprocessing, feature selection, and evaluation
- XGBoost for classification modeling
- TensorFlow/Keras for autoencoder implementation
- SHAP (SHapley Additive exPlanations) and LIME (Local interpretable model-agnostic explanations) for model interpretability
- Matplotlib and Seaborn for plotting and visualizations
- The pipeline is functional on CPU computing, and the pipeline utilizes GPU-powered autoencoder training if available to minimize runtime.

6. Evaluation

The multi-omics XGBoost classifier utilizing 64-dimensional latent features derived from the autoencoder exhibited excellent discriminative performance. The classifier achieved the following scores on the held-out test set, which consists of about 170 samples—the 20% stratified test set using about 850 labeled samples after pre-processing:

- These scores indicate the model's competence for identifying early breast cancer cases (Stage I/II), which are the primary clinical goals for improved prognosis and treatment.

- Although permutation testing for significance was not performed, this will be implemented in future work.

- The confusion matrix demonstrates low false-positive and low false-negative rates to support the proposed reliability of decision support in a clinical setting.

6.1 ROC Curve and Validation Description

Receiver Operating Characteristic (ROC) curves that were calculated on the internal test data showed a good ability of the model to classify (with an area under the curve (AUC) of approximately 0.99). The Precision-Recall (PR) curves were also plotted and showed a high area under the curves that supported the model's ability to handle class imbalance with high sensitivity and specificity. External validation using new independent datasets, such as CPTAC-BRCA, will remain a future planned direction to validate (generalizability).

6.2 Comparison to Single-Omics and Classical Models

The multi-omics XGBoost model (with ROC-AUC curves above 0.91) achieved consistently better performance than models that are trained on single omics modalities or classical machine learning models like Logistic Regression and Random Forest. The best performing single-omics model was based on gene expression only, which supported its high ROC-AUC (between 0.89 and 0.91) and predictive ability. The models using mutation data and proteomics allowed lower ROC-AUC scores (approximately between 0.77 and 0.84), ranking these independent omics last, but showing their usefulness in multi-omics integrated fusion to improve classification accuracy.

6.4 Explainability Analysis

For our model explainability analysis, we used Shapley Additive exPlanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME) methods.
For the global analysis, we used SHAP and were able to identify biologically relevant top contributors to classification, including predictions based on clinically relevant biological findings relevant to breast cancer that were key features in predictions and classification of patients, including TP53 mutation, BRCA1 gene expression, and AKT1 protein levels.
The local LIME explanations of our patients provided interpretable, transparent, case-specific insight into the drivers of prediction, which is particularly important when building clinician trust and credence for clinical adoption.

6.5 Future Directions: External Validation and Statistical Robustness

While permutation testing and external validation on independent proteogenomic cohorts (e.g., CPTAC-BRCA data) are still to be carried out, they are actively planned for future phases of the study.

The current pipeline includes methods for these additional validation steps so that we can rigorously explore model robustness, generalizability, timeline to clinical readiness, etc.

6.6 Summary

The multi-omics artificial intelligence framework performed well in terms of accuracy and showed excellent sensitivity to early-stage cancer. The model performed better than single-omics-based systems and classical methods. The SHAP and LIME model explainability interpretations provide additional strength to the potential for translational opportunities. Our findings provide a potentially important foundation for the multi-omics artificial intelligence framework to be more broadly considered for external validation and clinical applications development.

7 Discussion

Key Findings in Context

The evaluation results emphasize the value of an integrated, multi-omics AI approach for breast cancer stage classification. The improved performance of the multi-omic XGBoost classifier reinforces other contemporary literature arguing that molecular profiling in combination is a more effective way to characterize tumor heterogeneity than single-omics studies. External validation with appropriate independent datasets, such as CPTAC-BRCA, will also be attempted in the future. This component is essential to confirming the generalizability of the multi-omics model for clinical translation. SHAP and LIME interpretability analyses revealed biologically relevant features of breast cancer stage classification, with some known oncogenes and protein markers, such as BRCA1 and PIK3CA, to be the most impactful features. This biological rationale serves to increase levels of belief in the prediction ability and clinical applicability of the model.

Critique of Experimental Design

- This research has important limitations. The cross-sectional multi-omics approach prevents a deeper understanding of how tumors change temporally, and longitudinal datasets will help to investigate both disease progression and response to treatment.
- Although the class imbalance problem was adequately addressed by class weighting during training, a refined approach could still involve more sophisticated approaches like synthetic resampling, calibration methods, or cost-sensitive learning to preserve clinical relevance and to calibrate predictions in their ultimate clinical interpretation.
- While the use of the neural network-based autoencoder for dimensionality reduction is a reasonable approach, it lost clarity on how features were formed because, despite using SHAP and LIME on the final classifier, a deeper understanding of what latent representations are present is not possible. Future work may look into alternative dimensionality reduction methods that are either more granular or more interpretable by default.
- In addition, the issue of batch effects and the potential for cohort selection biases remain and are particularly apparent and carried out without explicit batch correction or validation on an external cohort. These issues would prompt future work to address the harmonization of datasets across multiple cohorts to improve our ability to generalize models.

Improvements and Future Directions

1. Longitudinal Multi-Omics Integration: Incorporate multiple time-point omics datasets so that tumor evolution and dynamic therapeutic response can be captured, rather than using one-time snapshots.

2. Advanced Sequence Modeling: Explore transformer and related language models (e.g, bioBERT) to build upon using just sequences of raw genomic and proteomic sequences, and therefore understand mutation effect using a much richer and higher layer of understanding than the model making inputs at the feature level.

3. Added Omics Layers: Augment with additional molecular layers of information, such as metabolomics and methylomics, to provide more biological understanding and context to the prediction to increase accuracy in older patients than younger ones.

4. Clinician-Centric Avenues for Use: Expand with decision support dashboards and explanation visualizations that are interactive and identified for clinical workflows to broaden access, transparency, and trust of the model.

5. Real-Time Inferences: Additional efficiency in computing time to enable live prediction to support the curriculum process.

6. Fairness and Bias Auditing: Undertake bargains and across demographic and subtypes of fairness debiasing analysis and studies to identify and properly situate any potential bias in the predictive poor performances to assure the model will generalize equitably across differences in different populations.

8. Conclusions and Future Work

Conclusion

This study produced a reliable but interpretable AI framework for the classification of breast cancer stage using an integral multi-omics approach for transcriptomic, proteomic, and mutational data. The model achieved high accuracy and performed strongly on the internal validation dataset. By using multi-omics profiling together with explainable machine learning analysis (SHAP and LIME), the framework was able to provide biologically meaningful analyses that are relevant to and support precision oncology diagnostic guidelines. Although these are encouraging results, external validation is still needed to investigate model generalizability and clinical relevance.

Future Work: Building on this groundwork, future research and development will focus on:

- Longitudinal Data: Inputting dynamic, time series multi-omics datasets that can better track tumor evolution and therapy-related responses over time than static models allow.

- Sequence Data: Using more advanced types of transformer architectures (e.g., bioBERT) to analyze raw genomic and proteomic sequences directly, enhancing our biological insights.
- Integration of Molecular Layers: Adding more omics, like metabolomics and methylomics to provide a more complete biological landscape and enhance the prediction based on unknowns.
- Clinical Deployment: Developing quick and easy inference pipelines with real-time outputs and visual dashboards to align with clinician workflow, providing clinical decision support.
- Fairness and Bias Investigations: Executing audits to plan for plans to reduce demographic and intrinsic subtype bias and representativeness to approach equitable model performance for different populations.
- Cross-Cancer Implementation: Generalizing the modeling and framework on other cancer types and exhaustively validating to plan assessments for generalizability and scalability.
- This strategic direction will serve to provide the model with additional rigor, generalizability, and or usefulness or richness of information to use in development to lead to impactful applications to clinical oncology.

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