Supervised Hierarchical Autoencoders for Multi-Omics Integration in Cancer Survival Models

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Abstract

With the increasing amount of high-throughput sequencing data becoming available, the proper integration of differently sized and heterogeneous molecular and clinical groups of variables has become crucial in cancer survival models. Due to the difficulty of multi-omics integration, the Cox Proportional-Hazards (Cox PH) model using clinical data has remained one of the best-performing methods [Herrmann et al., 2021]. This motivates the need for new models which can successfully perform multi-omics integration in survival models and outperform the Cox PH model. Furthermore, there is a strong need to make multi-omics models more sparse and interpretable to encourage their usage in clinical settings. We developed a novel neural architecture, termed Supervised Hierarchical Autoencoder (SHAE), based on supervised autoencoders and Sparse-Group-Lasso regularization. Our new method performed competitively with the best performing statistical models used for multi-omics survival analysis. Moreover, it outperformed the Cox PH model using clinical data across all 17 cancers from The Cancer Genome Atlas (TCGA) considered in our work. We further showed that surrogate linear models for SHAE trained on a subset of multi-omics groups achieved competitive performance at consistently high sparsity levels, enabling usage within clinics. Alternatively, surrogate models can act as a feature selection step, permitting improved performance in arbitrary downstream survival models. Code for the reproduction of our results is available on Github.

1 Introduction

Accurate prediction of survival times is essential for clinicians and researchers to decide treatment and identify which variables drive survival. The Cox Proportional-Hazards (Cox PH) model [Cox 1972, Breslow 1975] is still the de facto standard model for survival analysis today, despite proposals for various other methods such as random survival forests [Ishwaran et al., 2008], boosting [Hothorn et al., 2010] and neural networks [Ching et al., 2018].

Survival analysis of cancer patients can be particularly challenging due to the heterogeneous nature of the disease, even for patients suffering from the same type of cancer [Polyak et al., 2011] [Fisher et al., 2013, Melo et al., 2013]. With the advent of high throughput sequencing technologies, researchers hoped to leverage the information inherent in biological data such as gene expression, DNA methylation, and others (jointly referred to as multi-omics) to help explain and mitigate this heterogeneity.
However, even using the wealth of newly available biological data in large scale projects such as The Cancer Genome Atlas Program (TCGA) [Tomczak et al., 2015], significant improvements in performance in cancer survival analysis as measured by performance metrics such as Harrell’s concordance [Harrell et al., 1982] or the brier score [Brier et al., 1950] have been elusive [Herrmann et al., 2021] showed that the Cox PH model using clinical data outperformed most other methods, even when these were designed to integrate multi-omics data.

1.1 Multi-omics survival models

There have been various proposals for statistical and neural network-based models that perform multi-omics integration in the context of (cancer) survival analysis. Hornung and Wright [2019] proposed five variations of the random forest algorithm [Breiman, 2001], all of which change the split point selection by taking into account that the input variables belong to different groups (e.g., multi-omics data). BlockForest, their best performing method, statistically significantly outperformed random survival forest in their work [Hornung and Wright, 2019] and was shown to outperform the clinical Cox PH model on TCGA by Herrmann et al. [2021]. Boulesteix et al. [2017] proposed a modified Lasso regularized Cox PH model that scales the Lasso penalty $\lambda$ with a group-specific penalty factor that can be chosen through a priori knowledge or using cross-validation. The authors showed that their new model termed ipfLasso performed better than the standard Lasso regularized Cox PH model in simulations and on TCGA. Klau et al. [2018] introduced a sequential Lasso regularized Cox PH approach based on offsetting, priorityLasso, which considers input groups one at a time in order and uses the previous model prediction as an unregularized offset for the next model. PriorityLasso outperformed Lasso regularized Cox PH and offers clinicians the advantage of deciding which variables to preferentially include in the model [Klau et al., 2018].

Cheerla and Gevaert [2019] proposed a novel neural network architecture that integrates gene expression, miRNA, clinical data, and whole slide images to predict cancer survival on 20 TCGA cancers. Their model benefitted (that is, exhibited an increased concordance index) from pan-cancer training relative to training solely on each cancer type for most considered cancers. Kim et al. [2020] proposed an architecture based on a variational autoencoder (VAE) [Kingma and Welling, 2013] on which they applied transfer-learning. They trained their VAE on 20 TCGA cancers and transferred the weights of the first two layers to their survival model, which they then fine-tuned on each of the same ten TCGA cancers on which cox-nnet was benchmarked [Ching et al., 2018]. Their model outperformed both cox-nnet and regularized Cox PH on seven out of ten cancers when trained on gene expression data only. Huang et al. [2019] modeled TCGA breast cancer survival by integrating miRNA, mRNA, copy number variation, and mutation data. They proposed an architecture that takes the mRNA-seq eigengene matrix and the miRNA-seq eigengene matrix; both passed through a hidden layer individually (i.e., miRNA does not interact with mRNA). Afterward, a final layer predicts the relative risk from the output of the hidden layer of miRNA, the hidden layer of mRNA, copy number variation, mutation, and selected clinical variables. Their new model outperformed random survival forest, regularized Cox PH, and deepsurv [Katzman et al., 2018].

1.2 Sparse group Lasso regularized models

An alternative architecture-agnostic method for incorporating knowledge about input feature groups is (Sparse-)Group-Lasso regularization. Sparse-group Lasso [Friedman et al., 2010a; Simon et al., 2013] (SGL) regularization is a convex combination of the Lasso [Tibshirani, 1996] and the group-Lasso. Initially introduced by Friedman et al. [2010a], SGL regularization promotes sparsity both within groups (through the Lasso) and between groups (through the Group-Lasso).

Lemsara et al. [2020] proposed a multi-modal autoencoder, deemed PathME, which leverages SGL between different multi-omics feature groups to perform, in combination with sparse non-negative matrix factorization, clustering of TCGA patients. Xie et al. [2019] used Group-Lasso regularization to propose an architecture similar to Ching et al. [2018] but designed for multi-omics integration. The authors showed that group-Lasso regularization prevented overfitting (relative to Lasso and using no regularization) and statistically significantly outperformed the same architecture with Lasso regularization on three out of 14 considered TCGA cancers.

\footnote{From here on out, we will use concordance index and Harrell’s concordance interchangeably.}
1.3 Autoencoders

Autoencoders have also been widely used for multi-omics integration and cancer survival analysis more broadly. Long et al. [2020] explored multi-modal autoencoders for the integration of multi-omics data in breast cancer survival. They proposed two architectures, each of which has a dedicated autoencoder per modality. The first, termed *CrossAE*, tries to reconstruct both its own input and all other input groups. Afterward, *CrossAE* mean-pools the latent representations and uses the result to predict the relative risk. In their second architecture, *ConcatAE*, each autoencoder only reconstructs its input. Afterward, the model concatenates all latent representations and uses them to predict the relative risk. When comparing different combined multi-omics groups and their different architectures, *ConcatAE* performed the best on TCGA breast cancer when integrating methylation and miRNA and using PCA for dimensionality reduction.

Instead of using autoencoders solely for dimension reduction, their reconstruction loss can also act as a regularizer to be trained jointly with a supervised loss. Le et al. [2018] showed that these models have good theoretical properties and that training such an autoencoder (deemed a supervised autoencoder) performed as well or better than neural networks that optimized only a supervised loss on the respective supervised task. Thus, the reconstruction loss can be treated as a form of regularization, the level of which is a hyper-parameter. Le et al. [2018] found that when \( L_{\text{total}} = L_{\text{reconstruction}} + \alpha L_{\text{supervised}} \), levels of \( \alpha \) around 0.01 were optimal on their datasets. Tan et al. [2020] presented an application of supervised autoencoders on TCGA data. The authors tried to predict binarized clinical endpoints (e.g., overall survival, disease-free survival) from TCGA data using methylation, miRNA, mRNA, and reversed-phase protein arrays (RPPA). They trained one supervised autoencoder for each omics group and fused their latent spaces using mean-pooling, from which they then predicted the endpoints. Using this architecture, they outperformed other machine learning models such as random forests and SVMs.

Our work explored a neural network-based approach to multi-omics integration, which leverages hierarchical supervised autoencoders [Le et al., 2018] combined with sparse group Lasso regularization [Simon et al., 2013] to achieve competitive performance on TCGA. In particular, we showed that neural models could perform as well or better than BlockForest and its variants, even without transfer learning. Furthermore, we studied how training surrogate models on a subset of all multi-omics groups could help transfer multi-omics models to clinical settings by achieving close to state-of-the-art results at very high sparsity. In addition, we partially reframed multi-omics integration as feature selection, showing that fitting arbitrary survival models on a suitable feature set partially closes the performance gap to integrative models.

2 Methods

2.1 Architecture

We developed a novel method, termed *SHAE* (Supervised Hierarchical Autoencoder) for multi-omics integration in cancer survival models, which builds on hierarchical multi-modal autoencoders and Sparse-Group-Lasso regularization (Figure 1). Our models have two levels of autoencoders. On the first level, each input group \( m \in M \) has a separate autoencoder that compresses the features of each group \( X(m_i) \) into a latent space \( \tilde{m}_i \). Since we modeled survival using supervised autoencoders, we also introduced linear layers from each latent space to a predicted relative risk \( \hat{\phi}_i(\tilde{m}_i) \). On the second level, another autoencoder takes the concatenation of all latent spaces \( C = [\tilde{m}_1, ..., \tilde{m}_{|M|}] \) from all first-level autoencoders and compresses them into another latent space \( \tilde{C} \) used for the final prediction of the relative risk for each patient \( \hat{\varphi}(\tilde{C}) \). The hierarchical aspect of our model was partially inspired by Simidjievski et al. [2019], who provided an overview of different possible architectures of VAEs for multi-omics integration.

We also explored a residual variant of *SHAE* (Figure 1). We fed the first modality \( (m_1, \text{clinical data}) \) into our model and skipped it to the final layer in this variant. Using this skipping, we hoped to achieve two goals:

1. The model could still take clinical data into account within the second-level autoencoder, which might help other features, both with the reconstruction and for learning a better latent space for survival prediction.
2. This may aid performance since clinical data (in most datasets) contains valuable survival information.

This residual idea was heavily inspired by the favoring approach of BlockForest [Hornung and Wright 2019] and resnets [He et al. 2016]. We used the mean squared error (MSE) as our reconstruction loss for all autoencoders and the Breslow approximation of the negative partial log-likelihood as the loss for all predicted relative risk values. Let $A$ denote the set of all linear layers in our networks and let $B$ be the linear regularized using SGL (blue edges in Figure 1). We regularized all linear layers $a \in A \backslash B$ with L2 regularization and layer $B$ with SGL. Let $\delta_i$ be the event indicator for patient $i$ where $\delta_i = 1$ if patient $i$ experienced the event during the study and $\delta_i = 0$ otherwise. Further, supposing that $X_i$ is the time of the event, we let $T_i = \min(X_i, S_i)$ where $S_i$ is the time at which patient $i$ was censored. $\xi$ and $\gamma$ are hyper-parameters controlling the strength of the reconstruction regularization $\lambda_1, \lambda_2$ are hyper-parameters controlling the strength of the L2 and SGL regularization respectively and $\alpha$ is a trade-off hyper-parameter between the Lasso ($\alpha = 1$) and the Group Lasso ($\alpha = 0$). $X^{(m_1)}$ denotes the first input modality and $\hat{X}^{(m_1)}$ denotes a reconstruction of the first input modality. Then, the full loss $L_{\text{total}}$ for SHAE becomes:

$$L_{\text{total}}(\hat{\varphi}, \hat{\phi}_1, ..., \hat{\phi}_{|M|}, X, \hat{X}, C, \hat{C}) = L_{\text{cox}}(U, \delta, \hat{\varphi}) + \xi \cdot \text{MSE}(C, \hat{C}) + \sum_{q=1}^{|M|} \left( L_{\text{cox}}(T, \delta, \hat{\phi}_q) + \gamma \cdot \text{MSE}(X^{(m_q)}, \hat{X}^{(m_q)}) \right) + \lambda_1 \sum_{a \in A \backslash B} ||a||_F^2 + \lambda_2 (1 - \alpha) \sum_{m \in \{m_1, ..., m_{|M|}\}} \sqrt{|m|} ||B^{(m)}||_F + \lambda_2 \alpha ||B||_{1,1}$$

Where $||.||_F$ denotes the Frobenius norm, $L_{\text{cox}}$ is the Breslow approximation of the negative partial log-likelihood, and $||.||_{1,1}$ denotes the entrywise matrix L1 norm. MSE denotes the mean-squared error, and $B^{(m)}$ is a submatrix of $B$ with only those columns corresponding to inputs of modality $m$. $U_i = \min(T_i, X_i)$, is the observed time until a patient was either right-censored $C_i$ or experienced the event $T_i$ (death, in this setting). We developed all neural nets using Pytorch [Paszke et al. 2019] and skorch [Tietz et al. 2017]. We defaulted to scaling the supervised loss by multiplying it by the batch size (i.e., $\xi = \gamma = $ batch size) since we found this worked well initially and saved one hyper-parameter. For both SHAE and SHAE residual, we performed standardization of all features before fitting the model. Further, we used batch normalization [Ioffe and Szegedy 2015] and Parametric Rectified Linear Units for non-linear activations [He et al. 2015]. We used the Adam optimizer [Kingma and Ba 2014] for training our models and trained for 25 epochs, with a batch size equal to the size of the dataset (i.e., no batching) and an initial learning rate of $0.01$ (the highest learning rate before the training loss started diverging for most cancers). We tuned the regularization parameters $\lambda_1, \lambda_2 \in \{1e^{-2}, 1e^{-3}, 1e^{-4}\}$ using cross-validation. Since our models employ batch normalization, research suggests that it may be possible to fix the learning rate given the right level of weight decay due to their strong interdependence in the presence of batch normalization, even in adaptive methods like Adam [Hoffer et al. 2018] and Van Laarhoven [2017]. Thus, we tuned only the regularization parameters and not the learning rate. All latent space sizes were set to 64, and all encoders (and, by symmetry, decoders) were set to have one hidden layer with 128 nodes. While all of these architectural hyper-parameters were trainable in our implementation, we did not tune these in order not to complicate the hyper-parameter search space.

We included both SHAE and SHAE residual in our benchmarks, where the clinical input variable group was skipped for SHAE residual.

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2 Instead of down-weighting the supervised loss, as Le et al. [2018] did, we upweighted the reconstruction loss.
Figure 1: Architecture diagram of SHAE. Grey edges denote L2 regularization, blue edges SGL regularization. Let $X^{(m)}_i$ denote the part of $X$ which corresponds to the $i$-th input variable group, $\hat{X}^{(m)}_i$ a reconstruction of the same. $\hat{m}_i$ is the latent space of an autoencoder taking $X^{(m)}_i$ as its input and $C = [\hat{m}_1, ..., \hat{m}_{|M|}]$ is a concatenation of all first level latent spaces. $\hat{\phi}_1, ..., \hat{\phi}_m$ as well as $\hat{\phi}$ are predicted log-partial hazards based on their respective inputs. $\hat{C}$ is the latent space of the second-level autoencoder that takes $C$ as its input.

2.2 Reference models

For reference models, we used the best performing model from the benchmark study of [Herrmann et al. 2021]. BlockForest (BF), as well as RandomBlock favoring (RBF). Favoring refers to the model always considering a particular block of variables in the split-point selection (most often clinical variables). RBF and BF were implemented using the blockForest package. For RBF, we favored clinical variables.

We also included a random survival forest method (RSF) and a Lasso Regularized Cox PH (Lasso) as two benchmark methods that did not use the group structure information present in the multi-omics variables. Lastly, we included a Ridge regularized Cox PH using only the clinical variables (Clin. Cox PH). We opted for a Ridge regularized model since this allowed us to prevent convergence issues often seen with one-hot encoded categorical clinical variables. RSF was implemented using ranger [Wright and Ziegler, 2017] while Lasso and Cox PH were both implemented using glmnet [Friedman et al., 2010b, Simon et al., 2011]. Lasso and Cox PH were set to standardize their input matrices, while no further preprocessing was performed for RSF, BF and RBF.

2.3 Datasets

We benchmarked all models on the TCGA dataset. We followed the approach of [Herrmann et al. 2021] in selecting cancers with at least 100 samples (after preprocessing in our case) and an average event ratio $\geq 5\%$ to ensure there were enough patients and enough events to calculate meaningful concordance values. Further, we used GISTIC 2.0 for copy number variation (CNV) data [Mermel et al. 2011] and the number of non-silent MC3 mutation calls per gene per patient [Elliott et al. 2018], the former of which is taken from Xenabrowser [Goldman et al., 2020], with mutation coming

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$^3$RandomBlock is an alternative version of BlockForest. Hornung and Wright [2019] showed that it outperformed BF when clinical variables were favored with multi-omics data on TCGA.
Table 1: Summary information of all 17 considered TCGA datasets used in our study. TCGA cancer abbreviations used for space, please refer to https://gdc.cancer.gov/resources-tcga-users/tcga-code-tables/tcga-study-abbreviations for a full overview. Tabel format adapted from [Herrmann et al., 2021].

| Cancer | n   | p   | Event ratio | clinical | mRNA | CNV | methylation | miRNA | mutation | RPPA |
|--------|-----|-----|-------------|----------|------|-----|-------------|-------|----------|------|
| BLCA   | 325 | 84380 | 0.44        | 9        | 20225 | 24776 | 22124       | 740   | 16317    | 189  |
| BRCA   | 765 | 80668 | 0.13        | 9        | 20227 | 24776 | 19371       | 737   | 15358    | 190  |
| COAD   | 284 | 82221 | 0.22        | 16       | 17507 | 24776 | 21424       | 740   | 17569    | 191  |
| ESCA   | 118 | 75752 | 0.36        | 17       | 19076 | 24776 | 21941       | 737   | 9012     | 193  |
| HNSC   | 201 | 79286 | 0.60        | 16       | 20169 | 24776 | 21647       | 735   | 11752    | 191  |
| KIRC   | 309 | 74652 | 0.28        | 14       | 20230 | 24776 | 19456       | 735   | 9252     | 189  |
| KIRP   | 199 | 76294 | 0.15        | 5        | 20178 | 24776 | 21921       | 738   | 8486     | 190  |
| LGG    | 395 | 78254 | 0.22        | 15       | 20209 | 24776 | 21564       | 740   | 10760    | 190  |
| LUAD   | 338 | 82999 | 0.40        | 11       | 20165 | 24776 | 21059       | 739   | 16060    | 189  |
| PAAD   | 100 | 76654 | 0.58        | 26       | 19932 | 24776 | 21586       | 732   | 9412     | 190  |
| SARC   | 190 | 76068 | 0.36        | 45       | 20206 | 24776 | 21524       | 733   | 9412     | 190  |
| SKCM   | 238 | 85254 | 0.52        | 3        | 20179 | 24776 | 21635       | 741   | 17731    | 190  |
| STAD   | 304 | 76247 | 0.51        | 7        | 20165 | 24776 | 21059       | 739   | 16060    | 189  |
| UCEC   | 392 | 84130 | 0.16        | 11       | 20165 | 24776 | 21059       | 739   | 16060    | 189  |
| OV     | 238 | 85254 | 0.52        | 3        | 20179 | 24776 | 21635       | 741   | 17731    | 190  |
| LIHC   | 157 | 76247 | 0.51        | 7        | 20165 | 24776 | 21059       | 739   | 16060    | 189  |
| LUSC   | 280 | 82125 | 0.41        | 20       | 20232 | 24776 | 20659       | 739   | 16060    | 189  |

In addition, we considered miRNA, mRNA, DNA methylation, RPPA, and clinical data, all of which are also taken directly from the PANCANATLAS. We log-transformed both mRNA and miRNA expression. Otherwise, no further preprocessing of the datasets was performed.

For comparability, we used the same clinical variables as Herrmann et al. [2021], with the caveat that we dropped clinical variables missing for more than five patients. Categorical clinical variables were one-hot encoded. We excluded molecular variables if they were missing for more than one patient to preserve as many patients as possible. Table 1 shows an overview of all TCGA datasets which were used in our study.

2.4 Performance metric

Similar to other works [Cheerla and Gevaert, 2019, Kim et al., 2020, Tong et al., 2020], we used Harrell’s concordance [Harrell et al., 1982] to measure the performance of our models, where \( \hat{\phi}_i \) is an estimated score for patient \( i \) (where higher estimated score implies higher estimated risk), \( U_i = \min(T_i, C_i) \) is the time until a patient was either censored (\( C_i \)) or experienced the event (\( T_i \)). We have \( \delta = 0 \) for censored patients and \( \delta = 1 \) otherwise. Equivalently, Harrell’s concordance is the ratio of concordant pairs and all comparable pairs.

\[
\text{Concordance}(U, \delta, \hat{\phi}) = \frac{\sum_{i=1}^{n} \sum_{j=1}^{n} \mathbb{1}(T_i > T_j) \mathbb{1}(\hat{\phi}_i < \hat{\phi}_j) \delta_j}{\sum_{i=1}^{n} \sum_{j=1}^{n} \mathbb{1}(T_i > T_j) \delta_j}
\] (2)

2.5 Validation

We tuned all models using nested cross-validation with five inner folds or out-of-bag error (for random forest-based methods) to choose the best parameters to refit on the outer fold. We used the \texttt{glmnet} internal \texttt{cv.glmnet} function to optimize the regularization parameter for Cox PH and Lasso. BF and RBF were tuned using the \texttt{blockForest::blockforest} function. For RSF, we tuned the \texttt{mtry} parameter using the \texttt{tuneRanger::tuneMtryFast} function. For SHAE and SHAE residual, we tuned only the regularization parameters \( \lambda_1, \lambda_2 \in \{1e^{-2}, 1e^{-3}, 1e^{-4}\} \), while setting the other parameters to the defaults detailed in Section 2.1.

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4Mutation calls were calculated from the PANCANATLAS MAF file using \texttt{Maftools} [Mayakonda et al., 2018].
For all cancers in our dataset, we performed outer five-fold cross-validation, twice repeated, giving us a total of ten outer splits per cancer. For statistical significance testing, we tested for an overall difference between models by adopting the same approach as Hornung and Wright [2019]. We calculated the mean concordance per model per cancer (17 in total) and treated these mean values as independent between datasets. We then ran a one-sided paired t-test with a null hypothesis of non-inferiority of each benchmark model relative to SHAE and SHAE residual. The alternative hypothesis was that our model performed better than the respective benchmark method. We thus performed a total of ten tests (SHAE and SHAE residual compared to each of the five reference models), for which we corrected using Bonferroni-Holm [Holm, 1979]. We report both the raw p-values and p-values after correction.

2.6 Surrogate models

For enhanced clinical applicability, we chose to fit global surrogate Lasso models on the predictions of SHAE and SHAE residual. We fitted the models using python-glmnet [Friedman et al., 2010b] on clinical and gene expression data only and predicted the outputs of the full multi-omics SHAE and SHAE residual models. We did not penalize the clinical variables, as they are generally known to contain much prognostic information. We then compared the performance of these surrogate models to the reference models fitted on only clinical and gene expression data to investigate whether the surrogate model learned multi-omics specific information (which might show up in terms of increased test concordance) even though it did not have access to them in training directly.

Our approach in predicting the relative risk estimated by SHAE (residual) is somewhat reminiscent of pseudo-value methods in survival analysis, which replace right-censored survival data with jackknife pseudo-observations, thus enabling a change in model class to perform regression instead of survival analysis [Zhao and Feng, 2020; Klein and Andersen, 2005]. However, note that our approach does not have any statistical guarantees (as far as we know) that some of the other pseudo-value techniques do. We also emphasize that care must be taken when interpreting the pseudo hazard ratios obtainable by analyzing the coefficients of the surrogate models. In effect, these cannot be directly interpreted as hazard ratios but rather as a prediction of the hazard ratio which would have been predicted by SHAE (residual).

Alternatively, we can also frame the surrogate models as a feature selection technique, discovering the main features learned to be essential by our multi-omics methods. We can then refit a survival model such as an RSF, or a Ridge regularized Cox PH model on the feature set selected by the surrogate models. While this can also be powerful, we note that it does not allow for a transfer of multi-omics information (as the downstream survival model must be fit on the original survival data, thus not enabling a transfer from the SHAE (residual) predictions).

3 Results

3.1 Performance on TCGA

Overall, both SHAE and SHAE residual clinical (residual SHAE) statistically significantly outperformed both RSF and Lasso after multiple testing correction (Table 2). The comparison to the other baseline models was more subtle, as none of the other p-values was statistically significant after correction. Still, both of our proposed models outperformed BF and Cox PH in terms of overall concordance (Figure 2A) and in terms of rank across datasets (Figure 2B). There were no strong differences between the concordance of our models and that of RBF as all of them perform roughly equally (Figure 2A). RBF had the lowest (that is, best) rank across datasets however (Figure 2B).

For computation times, both SHAE and residual SHAE ran much faster than RBF and BF (Figure S1), with both SHAE models being around a factor of four times faster than RBF across datasets. Thus, SHAE achieved comparable performance to RBF in considerably faster computation times. Of course, RSF, Lasso and Cox PH all ran much faster than any of the multi-omics models, although this came at the price of decreased concordance.

Timing benchmarks were performed on the Euler cluster of ETH Zurich using eight CPU cores with 4096 MHz, using tictoc [Izrailev, 2021] in R and timeit.default_timer in Python. Note that we did not use a GPU for the benchmarks.
Figure 2: Performance of all models on TCGA. A: Overall test concordance across across the 17 TCGA cancers. B: Mean test concordance rank per cancer across the 17 TCGA cancers (lower is better).

Table 2: P-values of testing non-inferiority of each reference method (rounded to four digits).

| model            | comparison model | p-value (before correction) | p-value (after correction) |
|------------------|------------------|-----------------------------|---------------------------|
| SHAE (ours)      | BF               | 0.0978                      | 0.3912                    |
| SHAE (ours)      | Cox PH           | 0.0265                      | 0.1456                    |
| SHAE (ours)      | Lasso            | 0.0007                      | 0.0048                    |
| SHAE (ours)      | RB favoring      | 0.6403                      | 1.0000                    |
| SHAE (ours)      | RSF              | 0.0002                      | 0.0023                    |
| SHAE residual (ours) | BF           | 0.1089                      | 0.3912                    |
| SHAE residual (ours) | Cox PH       | 0.0243                      | 0.1456                    |
| SHAE residual (ours) | Lasso        | 0.0006                      | 0.0048                    |
| SHAE residual (ours) | RB favoring   | 0.6725                      | 1.0000                    |
| SHAE residual (ours) | RSF           | 0.0003                      | 0.0024                    |

3.2 Surrogate model performance

The performance of our Lasso surrogate models of SHAE (residual) exceeded that of any other model trained on clinical and gene expression (Figure S3A) except BF. All multi-omics models and surrogate models beat Lasso, RSF and Cox PH when trained on clinical and gene expression only (Figure S3A). We note that the good performance of the surrogate models was not merely due to the favoring of clinical variables, as a Lasso model fitted on clinical and gene expression, which did not penalize clinical variables underperformed both of our surrogates (Figure S2).

While the training $R^2$ of our surrogate models was generally quite good (Figure S3), the test $R^2$ was much more mixed (Figure S4). This suggests that while the models effectively reproduced the predictions of SHAE on the training set, they struggled to do so on the test set for certain cancers. Most cancers (for example, ESCA and OV) where the models achieved a median test $R^2$ of below 0.5 had a sample size of below 200 suggests that this issue might be at least partially due to the low sample size. We saw overall high test $R^2$ values for cancers such as bladder or breast, both of which contained over 300 patients (Figure S4). Interestingly, low test $R^2$ of the surrogates did not necessarily correspond to lower performance relative to the full multi-omics SHAE (residual) models (Figure S5).

Despite their competitive performance, our surrogate models were highly sparse, with a median of 35 and 37 variables selected across all cancers for the SHAE surrogate and the SHAE residual surrogate, respectively (Figure 3B). The sparsity structure of the surrogate models by cancer and splits revealed that the models were relatively stable in the number of features selected across splits (Figure 4 and Figure S6). In addition, the surrogate models were able not to use any gene expression features when it presumably could have hurt performance (e.g., on ESCA; Figure S4). The Lasso model trained
Figure 3: Performance of the Lasso surrogate models for multi-omics SHAE (residual). A: Test concordance of all models trained on clinical and gene expression only. Cox PH trained on clinical only, surrogate models trained on the predictions of full multi-omics SHAE (residual). B: Number of non-zero coefficients of the surrogate models and Lasso.

on clinical and gene expression data tended to have major differences in the number of non-zero coefficients across splits (Figure S7).

When leveraging surrogate models purely for feature selection, survival models trained on the same feature set as one of the surrogate models achieved improved performance relative to fitting them on all clinical and gene expression features (Figure S8). However, the models refit with the feature set recovered by the SHAE residual surrogate could not achieve the same performance as the surrogates (Figure S9).

4 Discussion

First and foremost, we showed that SHAE could be leveraged to achieve competitive performance on the TCGA dataset as measured by the concordance index. Our benchmark is especially interesting since there has not been a conclusive comparison of neural models for multi-omics integration to state-of-the-art statistical methods such as BF. Most other work either focused on statistical methods only [Herrmann et al., 2021] or used simple statistical methods such as the Lasso [Huang et al., 2019].

While our work was not a neutral benchmark study and thus likely contains some bias, we believe it validates SHAE as a solid alternative to BF and its variants. There were certain cancers such as Esophageal carcinoma (ESCA) where SHAE outperformed RBF while on other cancers (e.g., Brain Lower Grade Glioma (LGG)), RBF dominated SHAE (Figure S10). Ensemble methods or a mixture of experts approach could leverage this diversity of performance across cancers to produce even better results. Neural networks such as SHAE were also shown to provide additional benefits relative to RBF, such as faster computation times (Figure S2). In addition, SHAE performed approximately as well as RBF overall, even without having to be told that clinical information was important. This suggests that SHAE might be a good alternative, especially when researchers are unsure whether clinical data contains considerable prognostic information.

More broadly, our results were consistent with those of [Herrmann et al., 2021]. We saw BF outperform Clin. Cox PH by a small margin. At the same time, both RSF and Lasso failed to beat the clinical-only model. One difference in our work is that we only kept clinical variables if no more than five patients were missing them. Since our objective was to compare SHAE to other multi-omics methods such as BF, this limitation seemed acceptable since all multi-omics models should be affected roughly uniformly by having access to fewer clinical variables.

We found that the difference in performance between SHAE and SHAE residual was much smaller than that between BF and RBF. Across all cancers, the two SHAE models had practically the same performance in terms of mean and median concordance (Figure 3A). Future work is thus needed to
establish the effect of and ideal way (if any) of forcing autoencoders to include a particular variable group, potentially yielding a similar performance boost to that seen in BF based models.

We also showed that Lasso surrogate models for SHAE (residual) could maintain good surrogate performance (in terms of train $R^2$) even when trained on only a subset of available modalities (specifically clinical and gene expression) (Figure S3). Although the test $R^2$ was more nuanced and very cancer-specific (Figure S4), we nevertheless validated that training surrogate models of full multi-omics models can outperform most multi-omics models trained from scratch on the same subset of input groups (Figure 3A). We found that survival models trained on the same feature set as the surrogates could not entirely match their performance (Figure S9). This might imply that the surrogates benefitted from some of the multi-omics information present in the SHAE (residual) predictions.

The only model that our best surrogate model could not outperform was BF. BF performed better when trained on clinical and gene expression only as opposed to all multi-omics data (for clinical and gene expression only, BF had 0.014 higher mean and median concordance), which matches the study of Hornung and Wright [2019]. Possible reasons for this include high redundancy of information in additional added blocks beyond clinical and gene expression [Hornung and Wright, 2019]. Nevertheless, all other multi-omics models (RBF, SHAE and SHAE residual) performed better with multi-omics data.

The surrogate models produced highly sparse models overall (Figure 3B). Especially considering clinical variables were left unpenalized (and thus always selected), the surrogate models did not use many additional variables relative to Clin. Cox PH, yet were able to outperform it consistently (Figure 3A and Figure S9).

Furthermore, since all that needs to be communicated for the application of regression models such as our surrogates are the coefficients and intercept (if any), they are much more robust and easier to deploy relative to complicated black-box models [Klau et al., 2018] [Boulesteix et al., 2017]. Of course, sufficient care must be taken when deploying surrogate models in clinics, both due to mismatches in sequencing protocol (although this is the case for all methods) and potential difficulties in analyzing surrogate coefficients. Alternatively, clinicians or researchers can refit regularized Cox PH models at the same sparsity level using the feature set recovered by the surrogates. Although this does not quite recover the same performance, it nevertheless outperformed Clin. Cox PH at high sparsity levels (Figure S9).

There are many promising avenues of future work connected with our approach in this study which we did not pursue further. First and foremost, it would have been interesting to disentangle the effects of SGL, the supervised autoencoder, and the hierarchical autoencoder architecture on model
performance. This may yield additional insights as to which architectures should be preferentially explored in future work. Another avenue concerns the favoring of the clinical variables: We examined the residual approach, in which we both fed clinical data into our autoencoder and skipped it to the end, where it was fed directly into the linear layer connected to the final prediction. One straightforward extension would explore differentially regularizing the latent space from the autoencoder and the skipped clinical data, e.g., using different penalty factors, similar to ipfLasso [Boulesteix et al., 2017].

Lastly, our work has some limitations. First and foremost, we chose a fixed initial learning rate and number of epochs for our models that may have caused overfitting, even though we did not choose these hyper-parameters based on test performance. Therefore, more experiments should be conducted to validate the robustness of SHAE to its different hyper-parameters as well as modern techniques for learning rate scheduling such as cosine annealing [Loshchilov and Hutter, 2016]. Another limitation is that we only benchmarked on TCGA; even though this is a common strategy among researchers, future work should run a comparable benchmark, including statistical methods and neural networks on another large-scale multi-omics survival dataset. In addition, our exploration of surrogate models should be taken with a grain of salt. Despite their good performance, our approach does not have any statistical guarantees that we are aware of.

5 Conclusion

Our work demonstrated that supervised hierarchical autoencoders with sparse-group Lasso regularization are effective for multi-omics integration in cancer survival models. They performed on-par with the best statistical method in a recent large-scale benchmarking study [Herrmann et al., 2021, BlockForest, and one of its variants, RandomBlock favoring. We benchmarked all methods on 17 datasets of TCGA, following the dataset selection strategy of [Herrmann et al., 2021].

The main contribution of our work was the architecture of our model, which to our knowledge, was the first to apply supervised hierarchical autoencoders to multi-omics integration in cancer survival. We further showed that by training global surrogate models using only clinical and gene expression, we could outperform all models except BF trained on clinical and gene expression only by transferring some of the multi-omics information learned by SHAE. Since our surrogate models also proved to be very sparse, they can enable high performance in clinical settings while only using few variables from one additional modality (namely gene expression).

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