Abstract

One of the central goals of precision health is the understanding and interpretation of high-dimensional biological data to identify genes and markers associated with disease initiation, development and outcomes. Significant effort has been committed to harness gene expression data as real-valued matrices for multiple analyses while accounting for time-to-event modeling by including survival times. Traditional biological analysis has focused separately on non-negative matrix factorization (NMF) of the gene expression data matrix and survival regression with Cox proportional hazards model. In this work, Cox proportional hazards regression is integrated with NMF by imposing survival constraints. This is accomplished by jointly optimizing the Frobenius norm and partial log likelihood for events such as death or relapse. Simulation results based on synthetic data demonstrated the superiority of the proposed methodology, when compared to other NMF algorithms, in finding survival associated gene clusters. In addition, using breast cancer gene expression data, the proposed technique can unravel critical clusters of cancer genes. The discovered gene clusters reflect rich biological implications and can help identify survival-related biomarkers. Towards the goal of precision health and cancer treatments, the proposed algorithm can help understand and interpret high-dimensional heterogeneous genomics data with accurate identification of survival-associated gene clusters.

1 Introduction and Related Work

Identify genes and biomarkers associated with patient survival is of great interest to cancer researchers. This has been facilitated by the advances in biotechnology such as next generation sequencing (NGS)

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as well as the availability of genomics, transcriptomics, proteomics, and other omics data, which constitute an indispensable multi-omics source of biological information.

Survival analysis, also known as “time-to-event” analysis, aims to model patient lifespan and estimate the time to an event of interest (especially a death event) given the observed data \[1\]. It is worth noting that not all subjects of a given population will experience the event of interest (e.g., death) during the study. Cases in which survival times exceeded study duration are labelled as “censored” \[1\]. Survival analysis considers the lifetimes even when the subjects are not experiencing the event of interest (e.g., death). Though analyzing on gene expression matrix by Cox proportional hazards regression \[2\] is the standard way of identifying survival associated genes, it does not aggregate high-dimensional features nor account for the clustering property to identify gene clusters or pathways. Among the numerous techniques used to discover feature contribution to a classification problem, non-negative matrix factorization (NMF) have demonstrated the dual capability of dimensionality reduction and clustering in latent dimension \[3\] which also reflects biological representation \[4, 5\] by introducing non-negative constraint.

Non-negative matrix factorization (NMF), studied since 1999 \[6\], was initially developed for face recognition \[7, 8, 9, 10\], but has since been applied to biological analysis including gene clustering \[11, 12, 13, 14, 15\] and provide new insights about complex latent relationships in high-dimensional biological data \[5\]. It decomposes a non-negative matrix \(X\) into two low-rank matrices: a basis matrix \(W\) representing features, and a coefficient matrix \(H\) representing samples, provides a well-established geometrical and topological perspective to understand the feature space by visualizing the basis matrix. Different from other matrix factorization methods, the imposed non-negative property on \(W\) and \(H\) can lead to interpretable results \[6\].

Applying NMF in biological studies such as unveiling gene interactions and clusters have been exploited since last decade. Liu et al. \[15\] compared PCA with NMF to reduce the dimension of microarray data and showed the superiority of NMF. Zheng et al. \[16\] used NMF technique to identify tumor types. Wang et al. \[17\] and Gao et al. \[18\] performed cancer clustering with NMF algorithms. Using NMF to perform gene expression clustering can be found in \[19, 20, 21, 22, 23, 11, 12\]. For example, Wang et al. \[23\] proposed LS-NMF to link functionally related genes. More recently, Zhu et al. \[13\] suggested that NMF is well-suited to analyze heterogeneous single-cell RNA-Seq data. Jiang et al. \[14\] used NMF to unravel disease-related genes. Jia et al. \[24\] developed discriminant NMF to rank genes. Lai et al. \[4\] performed survival prediction after NMF-based pre-selection of genes.

Though there is evidence that NMF has an inherent clustering property \[3\], fully utilizing the survival data along with the given gene expression matrix and effectively integrating hazards provided by survival information in its update rule has not be systematically study. To address this gap, we aim to find an ideal solution to the NMF along with the associated survival data simultaneously. The derived solution successfully demonstrated the power of retrieving survival associated clusters in both synthetic data and human cancer expressions. As a success endeavor towards the central goal of precision health and cancer treatments, the proposed algorithm CoxNMF can help understand and interpret high-dimensional biological data, as well as unveiling critical gene clusters that associated with survival.

## 2 Formulation of CoxNMF

In this section, we first introduce the proposed algorithm named “CoxNMF”, especially how the objective function was constructed as well as the solution. Then, we based on the developed algorithms, performed experiments on simulated time to event data to show its superiority. After the simulation study, we performed the analysis to real human cancer data and aimed to discover the clusters of genes which may play important roles to survival.

### 2.1 Input and Output Data

In this section, we assume the input gene expression data \(X\) with shape \(P\) by \(N\) to be non-negative, real-valued 2-dimensional matrix, which may contains several zero-valued entries. The rows indicate \(P\) features/genes, and the columns indicate \(N\) samples/patients. The output generated by CoxNMF has two parts: a low-rank \(K\) by \(N\) coefficient matrix \(H\) which learned from NMF and Cox propor-
tional hazards regression, and a low-rank $P$ by $K$ basis matrix $W$, associated with $H$ that minimizes the Frobenius norm $\|X - WH\|_F$.

2.2 Objective Function

Given the target non-negative matrix $X$, two initialized non-negative matrices $W$ and $H$, the objective function of CoxNMF is

\[
\text{Minimize } \|X - WH\|_F^2 - \alpha \ell_{H, \beta}(C, Y) + \xi \|\beta\|_1 \tag{1}
\]

subject to $X_{i,j} \geq 0 \ \forall i \in [0, P], j \in [0, N]$, $W_{i,j} \geq 0 \ \forall i \in [0, P], j \in [0, K]$, and $H_{i,j} \geq 0 \ \forall i \in [0, K], j \in [0, N]$. Where $\alpha, \xi \geq 0$ are two positive weights, $\|\cdot\|_F$ is the Frobenius norm, also known as Euclidean distance [25], $C$ stand for the death events, $Y$ stand for survival times. $\ell_{H, \beta}(C, Y)$ is the log partial likelihood [2]:

\[
\ell_{H, \beta}(C, Y) = \sum_{i \in C, t} \left( \beta^T H_i - \log \left( \sum_{j : Y_j \geq Y_i} \exp(\beta^T H_j) \right) \right).
\]

The log partial likelihood $\ell_{H, \beta}(C, Y)$ is derived based on the partial likelihood $L_i(\beta, H)$ of the death event to be observed occurring for patient $i$ at time $Y_i$:

\[
L_i(\beta, H) = \frac{\lambda(Y_i) H_i}{\sum_{j : Y_j \geq Y_i} \lambda(Y_j) H_j} = \frac{\lambda_0(Y_i) \exp(\beta^T H_i)}{\sum_{j : Y_j \geq Y_i} \lambda_0(Y_j) \exp(\beta^T H_j)} = \frac{\exp(\beta^T H_i)}{\sum_{j : Y_j \geq Y_i} \exp(\beta^T H_j)},
\]

where $\lambda$ is the hazard function, and $\beta$ stand for the covariates associated to the log partial likelihood function.

2.3 CoxNMF Update Rule

Given the target non-negative matrix $X$, two initialized parameter $\beta$ for Cox proportional hazards model, and a certain number of iterations $M$, we propose the CoxNMF alternately iterative update algorithm

\[
W_{i,j}^{(iter+1)} \leftarrow W_{i,j}^{(iter)} \odot \frac{X H_{i,j}^{(iter)} T}{W_{i,j}^{(iter)} H_{i,j}^{(iter)} T},
\]

\[
\beta^{(iter+1)} \leftarrow \beta^{(iter)} + \gamma \beta \frac{\partial \ell_{H^{(iter)}, \beta}(C, Y)}{\partial \beta} + \xi \frac{\|\beta\|_1}{\beta},
\]

\[
H_{i,j}^{(iter+1)} \leftarrow H_{i,j}^{(iter)} + \alpha \max \left( 0, \frac{\partial \ell_{H^{(iter)}, \beta}(C, Y)}{\partial H^{(iter)}} \right) \odot \frac{W_{i,j}^{(iter+1)} T X}{W_{i,j}^{(iter+1)} T W_{i,j}^{(iter+1)} H_{i,j}^{(iter)}}.
\]

Where

\[
\frac{\partial \ell_{H, \beta}(C, Y)}{\partial H} = \\
\begin{bmatrix}
\frac{\partial H_{1,1}}{\partial H_1} & \frac{\partial H_{1,2}}{\partial H_1} & \cdots & \frac{\partial H_{1,n}}{\partial H_1} \\
\frac{\partial H_{2,1}}{\partial H_1} & \frac{\partial H_{2,2}}{\partial H_1} & \cdots & \frac{\partial H_{2,n}}{\partial H_1} \\
\vdots & \ddots & \ddots & \vdots \\
\frac{\partial H_{n,1}}{\partial H_1} & \frac{\partial H_{n,2}}{\partial H_1} & \cdots & \frac{\partial H_{n,n}}{\partial H_1} \\
\frac{\partial H_{1,1}}{\partial H_2} & \frac{\partial H_{1,2}}{\partial H_2} & \cdots & \frac{\partial H_{1,n}}{\partial H_2} \\
\frac{\partial H_{2,1}}{\partial H_2} & \frac{\partial H_{2,2}}{\partial H_2} & \cdots & \frac{\partial H_{2,n}}{\partial H_2} \\
\vdots & \ddots & \ddots & \vdots \\
\frac{\partial H_{n,1}}{\partial H_2} & \frac{\partial H_{n,2}}{\partial H_2} & \cdots & \frac{\partial H_{n,n}}{\partial H_2} \\
\frac{\partial H_{1,1}}{\partial H_n} & \frac{\partial H_{1,2}}{\partial H_n} & \cdots & \frac{\partial H_{1,n}}{\partial H_n} \\
\frac{\partial H_{2,1}}{\partial H_n} & \frac{\partial H_{2,2}}{\partial H_n} & \cdots & \frac{\partial H_{2,n}}{\partial H_n} \\
\vdots & \ddots & \ddots & \vdots \\
\frac{\partial H_{n,1}}{\partial H_n} & \frac{\partial H_{n,2}}{\partial H_n} & \cdots & \frac{\partial H_{n,n}}{\partial H_n}
\end{bmatrix}
\]

\[
= \begin{bmatrix}
C_1 \beta - \sum_{a=1}^n C_s \frac{\lambda(Y_a) \exp(\beta^T H_1)}{\sum_{j : Y_j \geq Y_a} \exp(\beta^T H_j)} \\
\cdots \\
C_n \beta - \sum_{a=1}^n C_s \frac{\lambda(Y_a) \exp(\beta^T H_n)}{\sum_{j : Y_j \geq Y_a} \exp(\beta^T H_j)}
\end{bmatrix},
\]

3
Algorithm 1: CoxNMF

Input : $X, K, Y, C, \alpha, M$.  
Output : $W, H, \beta, \text{CI}$.
Initialization : Initialize $W^{(0)}, H^{(0)}, \beta^{(0)}$, empty list CI.
for $\text{iter} = 0 : M - 1$ do
\[
W^{(\text{iter}+1)} \leftarrow W^{(\text{iter})} \odot \frac{XH^{(\text{iter})}T}{W^{(\text{iter})}H^{(\text{iter})} + \gamma \beta^{(\text{iter})} + \xi ||\beta||^2} \\
\beta^{(\text{iter}+1)} \leftarrow \beta^{(\text{iter})} + \gamma \beta^{(\text{iter})} + \frac{\partial \ell(w^{(\text{iter}), \beta(\text{iter}), C, Y})}{\partial \beta^{(\text{iter})}} + \xi \beta^{(\text{iter})} \\
H^{(\text{iter}+1)} \leftarrow \left(H^{(\text{iter})} + \frac{\partial \ell(w^{(\text{iter}), \beta(\text{iter}), C, Y})}{\partial H^{(\text{iter})}} \right) \odot \frac{W^{(\text{iter}+1)}X(\beta^{(\text{iter}+1)}H^{(\text{iter}+1)})^T}{W^{(\text{iter}+1)}H^{(\text{iter}+1)}} \\
\text{CI}[\text{iter} + 1] = \text{CONCORDANCEINDEX}(\beta^{(\text{iter}+1)}H^{(\text{iter}+1)}, Y, C) \\
\text{end}
\]

\[
\text{imax} = \arg\max_{\text{iter}} \text{CI} \\
W = W^{(\text{imax})} \\
H = H^{(\text{imax})} \\
\beta = \beta^{(\text{imax})} \\
\text{CI} = \text{CI}[\text{imax}] \\
\text{return } W, H, \beta, \text{CI}
\]

2.4 Evaluation Metrics

Silhouette Score for Determining Optimal Number of Latent Dimension $K$

The silhouette score, or mean silhouette coefficient, measures the consistency within clusters of data. The score describes how well each element has been classified [29]. In this study, Euclidean distance was adopted as distance metric. We used silhouette score to determine the optimal values of $K$ as the estimations to $K$ among experiments.

Quantitative Measurements of Optimization Results and Label Accuracy

To tune the hyper-parameters as well as evaluating the performance of optimization results along with survival information, the concordance index (C-Index) was adopted. It is a generalization of the area under the ROC curve (AUC) which introduces the censorship information. It assesses the model discrimination power of the ability to correctly provide a reliable ranking of the survival times based on the individual risk scores and can be computed with the formula

\[
\text{C-Index} = \frac{\sum_{i,j} \mathbb{1}(Y_j < Y_i) \mathbb{1}(r_j < r_i) - C_i}{\sum_{i,j} \mathbb{1}(Y_j < Y_i) C_i},
\]

where $r_j$ is the risk score of a subject $j$. $\mathbb{1}(Y_j < Y_i)$ is the indicator function: $\mathbb{1}(Y_j < Y_i) = \begin{cases} 1 & \text{if } Y_j < Y_i \\ 0 & \text{otherwise} \end{cases}$. Similar to the AUC, C-Index = 1 corresponds to the best model prediction, and C-Index = 0.5 represents a random prediction.

To quantify whether models can identify the survival-associated gene clusters correctly, we adopted four measurements to evaluate the results, namely, accuracy, F-1 score, precision, and recall. The F-1 score is formulated as $F-1 = 2(\text{precision} \times \text{recall})/(\text{precision} + \text{recall})$.

3 Experiments

Our method was first validated on three different sizes of synthetic data to show its efficacy, and then applied on a human breast cancer dataset. In simulation study, CoxNMF was compared with two baseline NMF with updating rules Coordinate Descent (CD) solver and Mutiplicative Update
With were styled in bold text.

The ground truth data matrix \( X \) was then constructed as \( X = WH + E \). The matrix \( E \) suggests an artificial noise introduced into the system followed exponential distribution \( \varepsilon e^{-\varepsilon w} \) with \( \varepsilon \in \{0, 0.05, 0.1\} \). As in reality \( K \) remains unknown, the first step is required to determine the optimal hyper-parameter \( K \) according to the silhouette score. We performed experiments with all combinations of \( K \in \{7, 9, 11\} \) and searching \( K \in \{5, 7, 9, 11, 13\} \). All experiments ran 5 times each with different random seeds for the initialization and optimizations. From Table I we found almost all algorithms can found the optimal \( K = K \) based on highest silhouette score especially

Table 1: Silhouette score for different combinations of \( \varepsilon, K \) and \( K \) reported by four models in the simulation. Performances reported in mean \( \pm \) standard deviation. Highest mean values among \( K \) were styled in bold text.
the proposed CoxNMF. This step helped us to determine number of the latent dimension $K$ in the simulation study.

After row normalization on the resulting basis matrix $W_p = W_p/\|W_p\|$ for each row $p$, we applied the Cox proportional hazards regression parameter weighted on the normalized basis matrix: $W_p = \beta^T \odot W_p$, (i.e., the $\beta$ parameter will multiply each row $p$ of $W$ element-wisely), and sort the columns and rows of $W$ and $H$, as well as $\beta$ according to $\beta$ in ascending order, respectively. Note that the elements of $W$ can be negative. In this case, a positive value in $W$ suggests an association with worse prognosis and vice versa. Then a hierarchical agglomerative clustering measured in Euclidean distance with Ward linkage [31] was performed on $W$ to determine the optimal $K$ according to the highest silhouette score and clusters $L_j, j \in \{1, 2, \cdots, K\}$.

| $\varepsilon$ | $K = 7$ | $K = 9$ | $K = 11$ |
|---------------|---------|---------|---------|
| Accuracy      | 0.7714 ± 0.06 | 0.8226 ± 0.05 | 0.8545 ± 0.05 |
| C-Index       | 0.7714 ± 0.06 | 0.8226 ± 0.05 | 0.8545 ± 0.05 |
| F-1 score     | 0.7744 ± 0.07 | 0.8737 ± 0.07 | 0.9346 ± 0.07 |
| Precision     | 0.7744 ± 0.07 | 0.8737 ± 0.07 | 0.9346 ± 0.07 |
| Recall        | 0.8857 ± 0.13 | 0.9060 ± 0.13 | 0.9256 ± 0.13 |

Table 2: Concordance index (C-Index), accuracy, F-1 score, precision, and recall for different combinations of $\varepsilon$ and $K = K$ reported with mean ± standard deviation by four models in the simulation. Highest mean values among an evaluation at certain $K$ were styled in bold text.

To find the survival associated gene clusters, we focused on the smallest $\beta_1$ and largest $\beta_K$ associated with $W$, the estimated labels $\hat{y}_-$ are $\argmin_{L_j} \frac{1}{\sum_j L_j = 1} \sum_j W_{L_j=1} \hat{y}_-$ and $\hat{y}_+$ are $\argmax_{L_j} \frac{1}{\sum_j L_j = 1} \sum_j W_{L_j=1,K} \hat{y}_+$ are determined by the cluster $L_j$ with highest absolute mean value on the $1^{th}$ and $K^{th}$ columns, respectively. The true labels $y_-$ (or $y_+$) for better (or worse) prognosis genes equals to 1 at where the genes reside at $W^{(1)}$ (or at $W^{(K)}$). We concatenated $y_-$ and $y_+$ as $\hat{y}$, and concatenated $\hat{y}_-$ and $\hat{y}_+$ as $\hat{y}$. Then we compared our true labels $y$ and estimated labels $\hat{y}$ via four metrics: accuracy, F-1 score, precision, and recall to quantify the performances of finding survival-associated gene clusters.

From Table 2 we observed that the proposed CoxNMF achieved highest C-Index as well as accuracy, F-1 score, precision, and recall at most cases among all experiments. One of the experimental result with $K = 7$ was presented in Figure 1 where CoxNMF achieved highest concordance index $= 0.9998$ with accuracy $= 0.9671$, F-1 score $= 0.9284$, precision $= 0.9610$, and recall $= 0.9017$.

### 3.2 Human Cancer Gene Expressions

To improve precision health and cancer treatments, we are particularly interested in discovering novel gene clusters behind the gene expression matrix and the corresponding survival information. The goal of discovering latent cancer gene interaction groups can help biologist reveal gene functions, setup biological experiments, or help develop drugs based on targeted genes.
Figure 1: A result with $K = \hat{K} = 7$, $\varepsilon = 0.05$. (A) Ground truth clusters $C_1, C_2, \cdots, C_7$. (B) Ground truth $W$, note that $W^{(1)}$ associated with better prognosis (longer survival time), $W^{(7)}$ associated with worse prognosis. (C) Hierarchical agglomerative clustering results based on $\tilde{W}$ with $\hat{K}$ number of clusters highlighted by most distinct colors. (D) $\tilde{W}$, row orders are permuted according to the hierarchical clustering result. Cluster with highest mean value on the smallest $\beta_1$ and cluster with highest mean value on the largest $\beta_7$ were highlighted with blue rectangle and red rectangle. (E) Ground truth labels in plot A with row permutation according to the hierarchical clustering result. (F) Survival time $t$. (G) $\hat{H}$. Columns of $\tilde{W}$ and rows of $\hat{H}$ were sorted in ascending order of $\beta$.

As an example, breast invasive carcinoma (BRCA), one of the most critical cancer for female patients, was involved in the study. Gene expression data (mRNA-seq) was downloaded from Broad GDAC Firehose (https://gdac.broadinstitute.org/). Since gene expressions remained a considerable amount of noises, 20% of genes with lowest expression mean and 20% of genes with lowest expression variance were excluded according to [32]. All expressions were normalized in log$_2$ scale $X = \log_2(X + 1)$ according to [32]. We ended up with 13,140 genes and 1,079 female patients for BRCA. To save the computational time, we searched $\hat{K}$ from 20 to 200 with step size $= 10$ by using the NMF coordinate descend algorithm. We found $\hat{K} = 20$ for BRCA yield highest silhouette scores. The experiment adopted $\xi = 1 \times 10^3$ for L1 regularization of Cox proportional hazards regression in Equation 5 and $\alpha = 5 \times 10^4$ for CoxNMF in Equation 6. The optimization results $\tilde{W}$ and $\hat{H}$ for BRCA are reported in Figure 2. By performing gene ontology (GO) analysis with ToppGene analysis suite [33], certain GO biological process terms or chromosome location (cytoband) were exploited. The measurement of the enrichment results was based on P-value using the hypergeometric distribution [34]. A smaller P-value indicates a more significant association of gene cluster to the particular GO terms. Top 3 GO terms with smallest P-value were reported for each cluster.

For breast invasive carcinoma (BRCA), a hierarchical clustering was performed (Figure 2AB) according to the derived $\tilde{W}$ (Figure 2C). We also presented the corresponding $\hat{H}$ (Figure 2D) sorted by survival time (Figure 2E) in ascending order. To show the differences between original gene expression matrix $X$ and low-rank reorganized $\tilde{W}$, a t-SNE plot for $X$ with perplexity = 30 was reported in Figure 2F. A cluster spreads over the t-SNE plot in Figure 2F suggests the effectiveness of low-rank reorganization in helping find survival associated clusters rather than in original data $X$. In Table 3 gene cluster $C_{18}$ was identified to be associated with better prognosis, while $C_4$ behaved in contrast. We found the most significant terms are from GO biological process for $C_{18}$ associated with better prognosis, while the most significant terms are from chromosome location
(cytoband) for $C4$ associated with worse prognosis. From the results, we verified that extracellular matrix organization, a descendant of extracellular structure organization, is associated with better prognosis, which is increasingly recognized as an important regulator in breast cancer [35]. We also found that the animal organ morphogenesis is also highly overlapped with gene cluster $C18$. For gene cluster $C4$, we found a strong association with chromosome 1q21.3, which echoes the existed evidence that 1q21.3 amplified breast tumors [36]. These findings demonstrated that CoxNMF can unravel survival associated gene clusters precisely.

| Rank | Term Description | Input genes | Genes in GO term | Genes overlapped | P-value  |
|------|------------------|-------------|-----------------|-----------------|----------|
| 1    | GO:0030198 Extracellular matrix organization | 474 | 399 | 93 | $1.63 \times 10^{-55}$ |
| 2    | GO:0043062 Extracellular structure organization | 474 | 511 | 96 | $5.24 \times 10^{-59}$ |
| 3    | GO:0009887 Animal organ morphogenesis | 474 | 1241 | 113 | $4.88 \times 10^{-37}$ |

Table 3: Gene ontology enrichment analysis results for breast invasive carcinoma (BRCA).

Figure 2: Experimental results on breast invasive carcinoma (BRCA). (A) hierarchical agglomerative clustering with $\hat{K} = 20$ labels (B) according to the derived $\hat{W}$ sorted by $\beta$ in rows (C). (D) The corresponding $\hat{H}$ sorted by survival time (E) in columns and sorted by $\beta$ in rows. Lowest and highest $\beta$ were highlighted on the right side. (E) Survival time, patients who had death events are highlighted with pink vertical lines. (F) t-SNE plot of $X$ with perplexity = 30. Cluster labels are highlighted at the geometrical center in the plot. Points in blue and red colors indicate the true location on $X$ with respect to cluster $C18$ and $C4$, respectively.

4 Conclusion

In this paper, a novel algorithm CoxNMF was proposed by integrating non-negative matrix factorization and Cox proportional hazards regression. We carried out the objective function and update
rules for CoxNMF. To the best of our knowledge, this is the first work that performed non-negative matrix factorization and clustering driven by survival regression, which is accomplished by jointly optimization of the Frobenius norm and partial log likelihood. The proposed algorithm successfully demonstrated its superiority of identifying survival-associated gene clusters among other non-negative matrix factorization algorithms in three different sizes of synthetic data. The experiment conducted on human breast invasive carcinoma cancer helped unravel latent gene clusters which reflect rich biological interpretations, achieved the goal of understanding and interpretation of high-dimensional biological data in precision health.

**Broader Impact**

As a success endeavor towards the central goal of precision health and cancer treatments, this paper proposed the algorithm CoxNMF for understanding and interpretation of high-dimensional biological data. The proposed algorithm can help researchers discover critical genes associated with survival. When the important gene clusters are identified with the association to the survival, it is recommended to conduct further wet-lab experiments such as cancer cell line in order to validate the discovered biomarkers/genes.

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