

Running title: Patient stratification of cancer via integrated genomic and transcriptomic profiles coupling with network-aware biclustering

1. Background and Significance:

Significance: As a realization of Precise Medicine (PM), Stratified Medicine (SM) has been recently pointed out by Willis and Lord¹ in a recent review in 2015. Cancer, as a complex (in mechanism) and heterogeneous (among patients) disease, can be better understood and cured by gaining insights of the hidden samples structures driven by shared underlying mechanisms. Patient stratification can be considered and solved as an unsupervised clustering problem.

Existing works: Many efforts have been made on patient stratification in cancer studies based on individual mutations², combination of mutated genes³, expression profiles⁴, or the combination of several data types^{5,6}. In terms of clustering approach, hierarchical clustering (HC) is commonly seen in many cancer studies⁷ like TCGA, it is simple to perform but fails to capture local structures as it based on global similarities. Other advanced unsupervised methods including probabilities models^{5,8}, factor analysis⁹, SVD¹⁰ and self-organizing map (SOM)¹¹ are also employed to this problem, however they suffer various limitations like instable result, single data source and so on. After reviewing those methods, the consensus is that a desirable stratification should be comprised of 1) an efficient clustering method, 2) a comprehensive integration of different level of molecular data and 3) a proper use of biological networks for interactions among molecular features. Following this line, a recent deep learning-based work developed a deep belief network (DBN)¹² to stack multiple data types, however it ignores biological networks when constructing abstract features. Another popular method, called iCluster⁹, also provides good data integration but ignores the feature correlations like gene-gene network. A successful work based on non-negative matrix factorization (NMF) named NBS provides a network-aware clustering. However, it only uses mutation data which limits the comprehensiveness of stratifying patients, and the nature of NMF tends to assign patients to many groups requiring subsampling to correct. In another study using network-based NMF, only expression level datasets are integrated¹³.

Novelty: To our best knowledge, there is no existing model that provides both integration of mutation and expression data and leveraging network of molecular feature interaction for patient stratification problem. Here we present a NMF-based model, performing patient stratification based on patterns from combination of mutation and gene expression coupling with known gene-gene or protein-protein network. On the top of that, technically we optimized the standard NMF allowing a compact and simultaneous clustering between molecular signatures with patients. This could help us reduce subsampling and may also increase accuracy.

2. Proposed Method:

Outline: Performing NMF with a patient-group matrix V simultaneously with both mutation-group W_1 and expression-group matrix W_2 . Integrating network knowledge as a quadratic form penalty term for each input data type. K_1 can be adjacency matrix of network derived from Hotnet2, K_2 can be a gene-gene network. Additional regularization (smooth term S) is added to enhance compact patient and molecular feature as biclusters to enhance the result reproducibility, which reduces the time spent on subsampling and enhances clustering efficiency.

Objective function: First we need to format a matrix V , where values in it are mutation and expression measurements. Based on this given matrix $V \in \mathbb{R}^{n \times p}$, we proposed the network-regularized non-smooth NMF model to perform clustering. This is achieved by minimizing the following objective function:

$$\min_{W, H} \|V - W_1 S H\|^2 + \|V - W_2 S H\|^2 - \text{trace}(W_1^T K_1 W_1) - \text{trace}(W_2^T K_2 W_2)$$

where basis vectors $W \in \mathbb{R}^{n \times q}$ (W_1, W_2 are mutation-cluster and expression-cluster matrix respectively) and encoding vectors $H \in \mathbb{R}^{q \times p}$ is patient-cluster matrix which is just defined as standard NMF. Besides network constraints elaborated above, another layer of constrain is S as a smoothing matrix is defined as $S \in \mathbb{R}^{q \times q}$, $S = (1 - \theta)I + \frac{\theta}{q} \mathbf{1}\mathbf{1}^T$. θ is used to control the sparseness of the model, ranging between 0 to 1¹⁴. This allows the sparseness generated on both W and H as demonstrated by Pascual-Montano et al.. Note that the parameter θ cannot be learned from the data and need to be experimented. And the rank q is also needed to be estimated via a consensus clustering method that commonly used for selection of the rank¹⁶.

For optimizing the objective function, we will just follow the standard NMF updating rule¹⁶ with the modification corresponding to added constrains to iterate until convergence. Since the randomized initiation is commonly adopted by variations of NMF, it is always preferred to repeat NMF multiple times for robustness¹⁷ and we will use subsampling to enhance the clustering reproducibility.

3. Proposed Data Analysis:

First, we construct simulation dataset based on a given network and then analyzing the performance on it. This is to benchmark the proposed method against existing methods including standard NMF, NBS and iCluster.

Second, we perform the analysis on real cancer mutation data from TCGA (for comparison, use the same dataset used by Hofree et al.¹⁸). This analysis should be done in comparison with standard NMF, NBS and iCluster. We will use survival time as a benchmark to evaluate performance. We will explore mutation-expression signatures for stratified patients, with the hope of being confirmed with known mechanism and discover new ones.

4. Expected Timeline:

The proposed work should be finished following timeline below:

Use 5 days to prepare data and implement the proposed method in python or R.

Use 5 days to perform analysis and debug.

Use 5 days to finish the comparison and evaluation.

Use 10 days to draft manuscript and address any remaining problems in the project.

Reference

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