Bioconductor パッケージ, TDbasedUFEとTDbasedUFEadvの紹介／TDbasedUFE and TDbasedUFEadv: bioconductor packages to perform tensor decomposition based unsupervised feature extraction

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Abstract

We have proposed tensor decomposition (TD) based unsupervised feature extraction (FE) six years ago and applied it to wide range of bioinformatics problem. Although TD based unsupervised FE was generally applied to bioinformatics, it can have capability to select features under the situation of **large p small n** problem. In spite of successful applications, TD based unsupervised FE cannot be popular in the field of bioinfotmatics. In order to let the reserachers who are not familiar with TD to perform TD based unsupervised FE, we developed R packages, TDbasedUFE and TDbasedUFEadv and submit it to Bioconductor, which is a long running R package repository for bioinformatics. In this poster, we introduce **mathematical background** behind TD based unsupervised FE.

Introduction

In bioinformatics, **large p small n** problem is very usual, since the number of genes (features) is as many as 10^4 whereas the number of subjects (conditions) is as small as 10 to 10^2. Thus, it is required to have some method to deal with **large p small n** problem effectively. We have proposed a method, TD based unsupervised FE six years ago and applied it to various problems in bioinformatics. In spite of successful applications to various problems, its popularity is not enough. Then we have released two bioconductor packages by which one can make use of TD based unsupervised FE.

Feature selection procedure

Feature selection

❶Suppose that we have a tensor $x_{ijk} \in \mathbb{R}^{N \times M \times K}$ that represents the amount of the value of the ith feature of the jth and kth conditions (although we assume here three mode tensor, extension to tensors with higher modes is straightforward).

❷Apply higher order singular value decomposition (HOSVD) to x_{ijk} and get Tucker decomposition as

$$x_{ijk} = \sum_{\ell_1=1}^{N} \sum_{\ell_2=1}^{M} \sum_{\ell_3=1}^{K} G(\ell_1 \ell_2 \ell_3) u_{\ell_1 i} u_{\ell_2 j} u_{\ell_3 k} \qquad (1)$$

where $G(\ell_1 \ell_2 \ell_3) \in \mathbb{R}^{N \times M \times K}$ is a core tensor that represents the weight of product, $u_{\ell_1 i} u_{\ell_2 j} u_{\ell_3 k}$ to x_{ijk}, $u_{\ell_1 i} \in \mathbb{R}^{N \times N}$, $u_{\ell_2 j} \in \mathbb{R}^{M \times M}$, $u_{\ell_3 k} \in \mathbb{R}^{K \times K}$ are singular value matrices and orthogonal matrices.

❸Identify singular value vectors of interest, $u_{\ell_2 j}$ and $u_{\ell_3 k}$, among those attributed to conditions, j and k (e.g., distinction between class labels, etc).

❹Select a $u_{\ell_1 i}$ associated with the largest absolute value of $G(\ell_1 \ell_2 \ell_3)$ with fixed ℓ_2 and ℓ_3 selected in the previous step among those attributed to features.

❺Optimize the standard deviation, σ_{ℓ_1}, (see below) of the Gaussian distribution that the selected $u_{\ell_1 i}$ is supposed to obey (the null hypothesis).

❻Attribute P-values to ith feature as

$$P_i = P_{\chi^2}\left[> \left(\frac{u_{\ell_1 i}}{\sigma_{\ell_1}} \right) \right] \qquad (2)$$

where $P_{\chi^2}[> x]$ is the cumulative χ^2 distribution where the argument is larger than x.

❼P_is are corrected by Benjamini-Hochberg (BH) criterion (multiple comparison correction) and is associated with the threshold value (typically, 0.01 or 0.05) are selected.

Optimization of standard deviation

The standard deviation is overestimated if we include outliers that are supposed to be deviated from the null distribution. To exclude outliers from the estimation of the standard deviation, we perform as follows.

Optimization of SD

❶Set threshold adjusted P-value, P_0, and the initial value of standard deviation, σ_{ℓ_1}.

❷Compute P_i and correct P_i with BH criterion.

❸Exclude is with adjusted P-values less than P_0 as outliers.

❹Compute histogram, h_n, of P_i (with arbitrary bins).

❺Compute the standard deviation, σ_{h_n}, of h_n.

❻Update σ_{ℓ_1} such that σ_{h_n} decreases (with arbitrary minimization algorithm).

❼Go back to the step 2 and repeat until we can find σ_{ℓ_1} that enables σ_{h_n} to have mimnimum values.

The purpose of the above procedure is to find a set of is whose associated P_is filly obey Gaussian, since h_n should be constant, i.e., $\sigma_{h_n} = 0$, if a set of is is that associated P_is fully obey Gaussian.

Integration of multiple profiles

Shared conditions

Suppose that we have K multiple profiles $x_{i_k jk} \in \mathbb{R}^{N_k \times M \times K}$ that represents the amount of value of i_kth feature of jth condition of kth profile. We compute matrices as $x_{jj'k} = \sum_{i_k=1}^{N_k} x_{i_k jk} x_{i_k j' k} \in \mathbb{R}^{M \times M \times K}$ to which HOSVD is applied and we get

$$x_{jj'k} = \sum_{\ell_1=1}^{M} \sum_{\ell_2=1}^{M} \sum_{\ell_3=1}^{K} G(\ell_1 \ell_2 \ell_3) u_{\ell_1 j} u_{\ell_2 j'} u_{\ell_3 k} \qquad (3)$$

After identifying $u_{\ell_1 j}$ of interest, $u_{\ell_2 i_K}$ is recovered as $u_{\ell_1 i_k} = \sum_{j=1}^{M} x_{i_k jk} u_{\ell_1 j}$. The remaining procedure till feature selection is similar to the above.

Shared features

Suppose that we have K multiple profiles $x_{ij_k k} \in \mathbb{R}^{N \times M_k \times K}$ that represents the amount of value of ith feature of j_kth condition of kth profile. We compute matrices as $x_{ii'k} = \sum_{j_k=1}^{M_k} x_{ij_k k} x_{i' j_k k} \in \mathbb{R}^{N \times N \times K}$ to which HOSVD is applied and we get

$$x_{ii'k} = \sum_{\ell_1=1}^{N} \sum_{\ell_2=1}^{N} \sum_{\ell_3=1}^{K} G(\ell_1 \ell_2 \ell_3) u_{\ell_1 i} u_{\ell_2 i'} u_{\ell_3 k} \qquad (4)$$

Missing singular value vectors attributed to conditions, $u_{\ell_1 j_k}$, can be recovered as $u_{\ell_1 j_k} = \sum_{i=1}^{N} x_{ij_k k} u_{\ell_1 i}$. The remaining procedure till feature selection is similar to the above.

Integration of two profiles

Shared conditions

Suppose that we have two profiles $x_{ij} \in \mathbb{R}^{N \times M}$ and $x_{kj} \in \mathbb{R}^{K \times M}$ that represents the values of ith and kth feature of jth condition, respectively. Generate tensor $x_{ijk} \in \mathbb{R}^{N \times M \times K}$ as $x_{ijk} = x_{ij} x_{kj}$ and apply the feature selection procedure as described above. Only modification is that we need to identify only one signgular value vector, $u_{\ell_2 j}$, of interest whereas we need to identify two singular value vectors, $u_{\ell_1 i}$ and $u_{\ell_3 k}$ that have the largest absolute value of $G(\ell_1 \ell_2 \ell_3)$ with fixed ℓ_2.

Since $N \times M \times K$ can be very large, we often ought to reduce the size of matrices. For this we take partial summation of x_{ijk} as $x_{ik} = \sum_{j=1}^{M} x_{ijk}$ and singular value decomposition (SVD) was applyed to $x_{ik} \in \mathbb{R}^{N \times K}$ as

$$x_{ik} = \sum_{\ell=1}^{L} \lambda_\ell u_{\ell i} u_{\ell k} \qquad (5)$$

and missing singular value vectors attributed to conditions, js, can be recovered as $u_{\ell j}^{(i)} = \sum_{i=1}^{N} x_{ij} u_{\ell i}, u_{\ell j}^{(k)} = \sum_{k=1}^{K} x_{kj} u_{\ell k}$.

After identifying the singular value vector, $u_{\ell j}^{(i)}$ or $u_{\ell j}^{(k)}$, of interest, the corresponding $u_{\ell i}$ or $u_{\ell k}$ is used to attribute P-values to ith or kth feature with eq. (2) (For k, i must be replaced with k). Features is and ks with adjusted P-values less than threshold value are selected.

Shared features

Suppose that we have two profiles $x_{ij} \in \mathbb{R}^{N \times M}$ and $x_{ik} \in \mathbb{R}^{N \times K}$ that represents the values of ith feature of jth and kth conditions, respectively. Generate tensor $x_{ijk} \in \mathbb{R}^{N \times M \times K}$ as $x_{ijk} = x_{ij} x_{ik}$ and apply the feature selection procedure as described above. Since $N \times M \times K$ can be very large, we often ought to reduce the size of matrices. For this we take partial summation of x_{ijk} as $x_{jk} = \sum_{i=1}^{N} x_{ijk}$ and singular value decomposition (SVD) was applied to $x_{jk} \in \mathbb{R}^{M \times K}$ as

$$x_{jk} = \sum_{\ell=1}^{L} \lambda_\ell u_{\ell j} u_{\ell k} \qquad (6)$$

and missing singular value vectors attributed to features, is, can be recovered as $u_{\ell i}^{(j)} = \sum_{j=1}^{M} x_{ij} u_{\ell j}, u_{\ell i}^{(k)} = \sum_{k=1}^{K} x_{ik} u_{\ell k}$. After identifying the singular value vector, $u_{\ell j}$ or $u_{\ell k}$, of interest, the corresponding $u_{\ell i}^{(j)}$ or $u_{\ell i}^{(k)}$ is used to attribute P-values to ith feature with eq. (2). Features is with adjusted P-values less than threshold value are selected, although there are two distinct sets of is selected dependent upon whether j or k is considered.

Integration of multiple profiles II

Shared conditions

Suppose that we have K multiple profiles $x_{i_k jk} \in \mathbb{R}^{N_k \times M \times K}$ that represents the amount of value of $i_k$the feature of jth condition of kth profile. We applied SVD to them as $x_{i_k jk} = \sum_{\ell=1}^{L} \lambda_\ell u_{\ell i_k} u_{\ell jk}$. HOSVD was applied to $u_{\ell jk} \in \mathbb{R}^{L \times M \times K}$ as

$$u_{\ell jk} = \sum_{\ell=1}^{L} \sum_{j=1}^{M} \sum_{k=1}^{K} G(\ell_1 \ell_2 \ell_3) u_{\ell_1 \ell} u_{\ell_2 j} u_{\ell_3 k}. \qquad (7)$$

Missing singular value vectors attributed to features can be recovered as $u_{\ell_2 i_k} = \sum_{j=1}^{M} x_{i_k jk} u_{\ell_2 j}$ after identifying the $u_{\ell_2 j}$ of interest. The remaining procedure till feature selection is similar to the above.

Shared features

Suppose that we have K multiple profiles $x_{ij_k k} \in \mathbb{R}^{N \times M_k \times K}$ that represents the amount of value of $i$the feature of j_kth condition of kth profile. We applied SVD to them as $x_{ij_k k} = \sum_{\ell=1}^{L} \lambda_\ell u_{\ell ik} u_{\ell j_k}$. HOSVD was applied to $u_{\ell ik} \in \mathbb{R}^{N \times L \times K}$ as

$$u_{\ell ik} = \sum_{\ell=1}^{L} \sum_{i=1}^{N} \sum_{k=1}^{K} G(\ell_1 \ell_2 \ell_3) u_{\ell_1 \ell} u_{\ell_2 i} u_{\ell_3 k}. \qquad (8)$$

Missing singular value vectors attributed to conditions can be recovered as $u_{\ell_2 j_k} = \sum_{i=1}^{N} x_{ij_k k} u_{\ell_2 i}$ then $u_{\ell_2 j}$ of interest is selected. The remaining procedure till feature selection is similar to the above.

TDbasedUFE and TDbasedUFEadv

TDbasedUFE

TDbasedUFEadv

We released two bioconductor packages to perform the above analyses easily.

TDbasedUFE implemented "2. Feature selection procedure" and "4. Integration of multiple profiles" whereas TDbasedUFEadv implemented "5. Integration of two profiles" and "6. Integration of multiple profiles II", respectively. Both implemented "3. Optimization of standard deviation" as well.

TDbasedUFE and TDbasedUFEadv

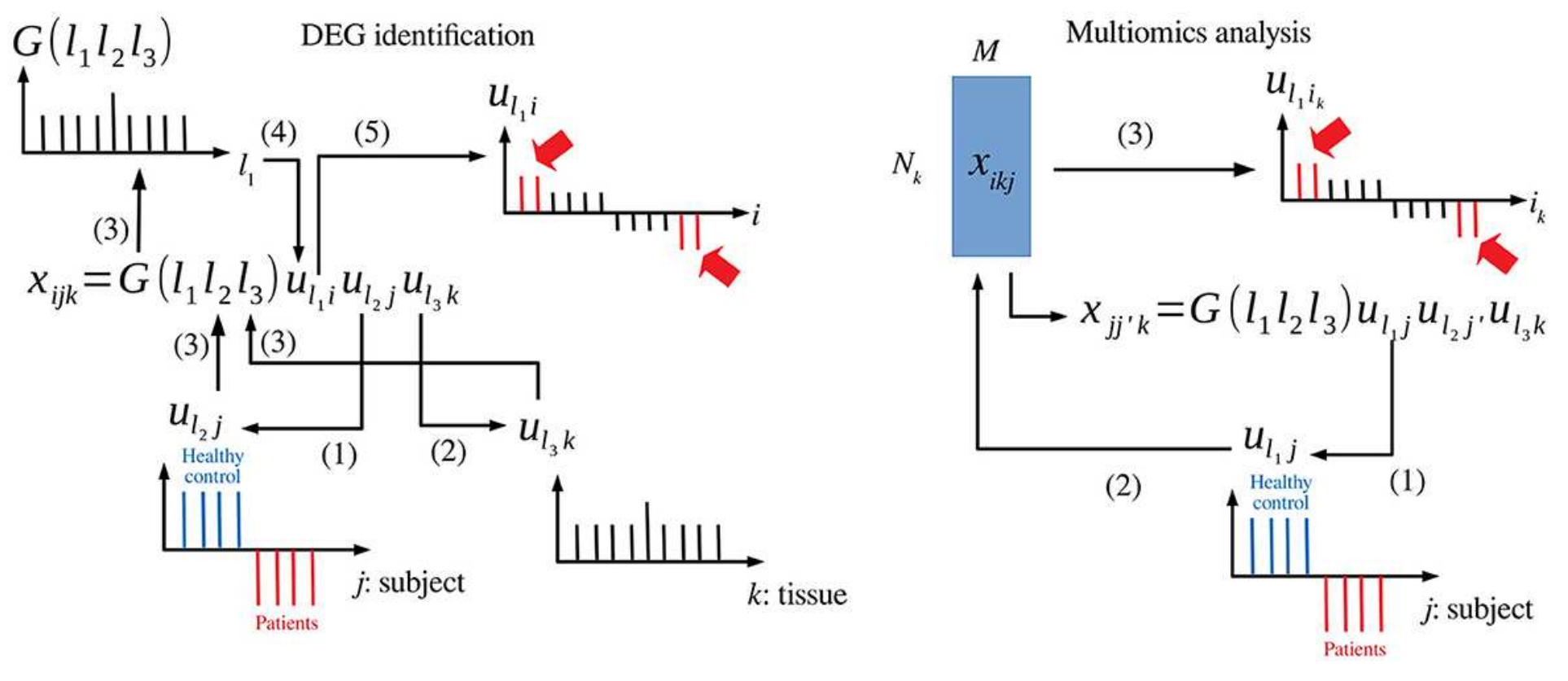
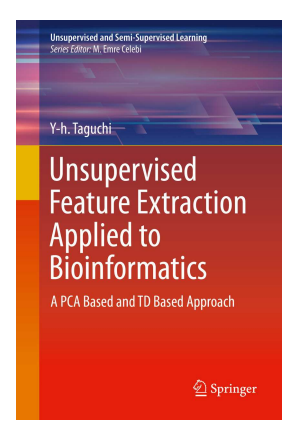


Figure 1:Schematic diagram that explains TD-based unsupervised FE. Left: DEG identification, (1) $u_{\ell_2 j}$ associated with the distinction between patients and healthy controls is selected. (2) $u_{\ell_3 4}$ associated with tissue specificity is selected. (3) $G(\ell_1 \ell_2 \ell_3)$ is investigated with fixed ℓ_2 and ℓ_3. (4) $u_{\ell_1 i}$ with G of the largest absolute value is selected. (5) is (indicated in red) whose absolute values are significantly larger than expected are selected. Right: Multiomics analysis, (1) $u_{\ell_1 j}$ associated with the distinction between patients and healthy controls is selected. (2) $u_{\ell_1 i}$ is computed from $u_{\ell_1 j}$. (3) is (indicated in red) whose absolute values are significantly larger than expected are selected.

Here, we present a few examples to demonstrate the usefulness of TDbasedUFE based on the ACC.rnaseq data from RTCGA.rneseq package in Bioconductor. The labels used to select singular value vectors attributed to samples and coincident with labels were patient.stage_event.pathologic_stage composed of four classes ("stage i" to "stage iv"). A tensor $x_{ijk} \in \mathbb{R}^{N \times 9 \times 4}$ represents the expression of ith gene of jth replicates of kth stage. HOSVD was applied to x_{ijk}, and we obtained TD as in eq. (1). Since $u_{\ell_2 j}$ is attributed to replicates, $u_{\ell_2 j}$ is expected to have constant value regardless of how j and $\ell_2 = 1$ turned out to satisfy this requirement. On the other hand, $u_{\ell_3 k}$ is expected to have monotonic dependence on k; and we found that $\ell_3 = 3$ was most coincident with monotonic dependence on k. Once ℓ_2 and ℓ_3 are selected by the user with the interactive interface, TDbasedUFE automatically selects $u_{\ell_1 i}$ with which is are selected. As a result, 1,692 genes were selected with the threshold adjusted P-value of 0.01.

To demonstrate the capabilities of TDbasedUFE on a multiomics dataset, we used the curatedTCGA package to retrieve profiles other than the gene expression of the ACC dataset in TCGA. We have collected miRNA ($x_{i_1 j} \in \mathbb{R}^{1046 \times 79}$), gene expression ($x_{i_2 j} \in \mathbb{R}^{120501 \times 79}$), and methylation data($x_{i_3 j} \in \mathbb{R}^{48577 \times 79}$) from curatedTCGA, and applied TDbasedUFE on these data. After applying HOSVD to the generated tensor $x_{jj'k} \in \mathbb{R}^{79 \times 79 \times 3}$, we found that u_{7j} is associated with the distinction between four stages and u_{1k} is constant regardless of k (i.e., omics). P_{i_k} is attributed to i_k by eq. (2) using $u_{7 i_k}$ generated from u_{7j}. After correcting P_{i_k}, we found that 23 out of 1,046 miRNAs, 1,016 out of 20,501 mRNAs, and 7,295 out of 485,577 methylation probes are associated with adjusted P_{i_k} less than 0.01 (these features are expected to be distinct between the four stages as well).

References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A PCA Based and TD Based Approach
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