Unsupervised tensor decomposition-based method to extract candidate transcription factors as histone modification bookmarks in post-mitotic transcriptional reactivation

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ABSTRACT

The histone group added to a gene sequence must be released during mitosis to halt transcription during the DNA replication stage of the cell cycle. However, the detailed mechanism of this transcription regulation remains unclear. In particular, it is not realistic to reconstruct all appropriate histone modifications throughout the genome from scratch after mitosis. Thus, it is reasonable to assume that there might be a type of "bookmark" that retains the positions of histone modifications, which can be readily restored after mitosis. We developed a novel computational approach comprising tensor decomposition (TD)-based unsupervised feature extraction (FE) to identify transcription factors (TFs) that bind to genes associated with reactivated histone modifications as candidate histone bookmarks. To the best of our knowledge, this is the first application of TD-based unsupervised FE to the cell division context and phases pertaining to the cell cycle in general. The candidate TFs identified with this approach were functionally related to cell division, suggesting the suitability of this method and the potential of the identified TFs as bookmarks for histone modification during mitosis.

Keywords: advanced unsupervised learning, tensor decomposition, histone modification, bookmark, mitosis, transcription

1 INTRODUCTION

During the cell division process, gene transcription must be initially terminated and then reactivated once cell division is complete. However, the specific mechanism and factors controlling this process of transcription regulation remain unclear. Since it would be highly time- and energy-consuming to mark all genes that need to be transcribed from scratch after each cycle of cell division, it has been proposed that genes that need to be transcribed are "bookmarked" to easily recover these positions for reactivation (Festuccia et al., 2017; Bellec et al., 2018; Zaidi et al., 2018; Teves et al., 2016). Despite several proposals, the actual mechanism and nature of these "bookmarks" have not yet been identified. John and Workman (1998) suggested that condensed mitotic chromosomes can act as bookmarks, some histone modifications were suggested to serve as these bookmarks (Wang and Higgins, 2013; Kouskouti and Talianidis, 2005; Chow et al., 2005), and some transcription factors (TFs) have also been identified as

potential bookmarks (Dey et al., 2000; Kadauke et al., 2012; Xing et al., 2005; Christova and Oelgeschläger, 2001; Festuccia et al., 2016).

Recently, Kang et al. (2020) suggested that histone 3 methylation or trimethylation at lysine 4 (H3K4me1 and H3K4me3, respectively) can act as a "bookmark" to identify genes to be transcribed, and that a limited number of TFs might act as bookmarks. However, there has been no comprehensive search of candidate "bookmark" TFs based on large-scale datasets.

We here propose a novel computational approach to search for TFs that might act as "bookmarks" during mitosis, which involves tensor decomposition (TD)-based unsupervised feature extraction (FE) (Fig. 1). In brief, after fragmenting the whole genome into DNA regions of 25,000 nucleotides, the histone modifications within each region were summed. In this context, each DNA region is considered a tensor and various singular-value vectors associated with either the DNA region or experimental conditions (e.g., histone modification, cell line, and cell division phase) are derived. After investigating singular-value vectors attributed to various experimental conditions, the DNA regions with significant associations of singular-value vectors attributed to various experimental conditions were selected as potentially biologically relevant regions. The genes included in the selected DNA regions were then identified and uploaded to the enrichment server Enrichr to identify TFs that target the genes. To our knowledge, this is the first method utilizing a TD-based unsupervised FE approach in a fully unsupervised fashion to comprehensively search for possible candidate bookmark TFs.

2 MATERIALS AND METHODS

2.1 Histone modification

The whole-genome histone modification profile was downloaded from the Gene Expression Omnibus (GEO) GSE141081 dataset. Sixty individual files (with extension .bw) were extracted from the raw GEO file. After excluding six CCCTC-binding factor (CTCF) chromatin immunoprecipitation-sequencing files and six 3rd replicates of histone modification files, a total of 48 histone modification profiles were retained for analysis. The DNA sequences of each chromosome were divided into 25,000-bp regions. Note that the last DNA region of each chromosome may be shorter since the total nucleotide length does not always divide into equal regions of 25,000. Histone modifications were then summed in each DNA region, which was used as the input value for the analysis. In total, $N = 123,817$ DNA regions were available for analysis. Thus, with approximately $120,000$ regions of $25,000$ bp each, we covered the approximate human genome length of 3×10^9.

2.2 Tensor Data Representation

Histone modification profiles were formatted as a tensor, $x_{ijkms} \in \mathbb{R}^{N\times 2\times 4\times 3\times 2}$, which corresponds to the kth histone modification ($k = 1$: acetylation, H3K27ac; $k = 2$: H3K4me1; $k = 3$: H3K4me3; and $k = 4$:Input) at the ith DNA region of the jth cell line ($j = 1$: RPE1 and $j = 2$: USO2) at the mth phase of the cell cycle($m = 1$: interphase, $m = 2$: prometaphase, and $m = 3$: anaphase/telophase) of the sth replicate ($s = 1, 2$). x_{ijkms} was normalized as $\sum_i x_{ijkms} = 0$ and $\sum_i x^2_{ijkms} = N$ (Table 1).

2.3 Tensor Decomposition

Higher-order singular value decomposition (HOSVD) (Taguchi, 2020) was applied to x_{ijkms} to obtain the decomposition

$$x_{ijkms} = \sum_{\ell_1=1}^{2}\sum_{\ell_2=1}^{4}\sum_{\ell_3=1}^{3}\sum_{\ell_4=1}^{2}\sum_{\ell_5=1}^{N} G(\ell_1\ell_2\ell_3\ell_4\ell_5)u_{\ell_1 j}u_{\ell_2 k}u_{\ell_3 m}u_{\ell_4 s}u_{\ell_5 i}, \quad (1)$$

where $G \in \mathbb{R}^{2\times4\times3\times2\times N}$ is the core tensor, and $u_{\ell_1 j} \in \mathbb{R}^{2\times2}, u_{\ell_2 k} \in \mathbb{R}^{4\times4}, u_{\ell_3 m} \in \mathbb{R}^{3\times3}, u_{\ell_4 s} \in \mathbb{R}^{2\times2}$, and $u_{\ell_5 i} \in \mathbb{R}^{N\times N}$ are singular-value vector matrices, which are all orthogonal matrices. The reason for using the complete representation instead of the truncated representation of TD is that we employed HODSVD to compute TD. In HOSVD, the truncated representation is equal to that of the complete representation; i.e., $u_{\ell_1 j}, u_{\ell_2 k}, u_{\ell_3 m}$, and $u_{\ell_4 s}$ are not altered between the truncated and the full representation. For more details, see Taguchi (2020).

Here is a summary on how to compute eq. (1) using the HOSVD algorithm, although it has been described in detail previously (Taguchi, 2020). At first, x_{ijkms} is unfolded to a matrix, $x_{i(jkms)} \in \mathbb{R}^{N\times48}$. Then SVD is applied to get

$$x_{i(jkms)} = \sum_{\ell_5=1}^{N} u_{\ell_5 i}\lambda_{\ell_5} v_{\ell_5 jmks} \tag{2}$$

Then, only $u_{\ell_5 i}$ is retained, and $v_{\ell_5,jmks}$ is discarded. Similar procedures are applied to x_{ijkms} by replacing i with one of j, k, m, s in order to get $u_{\ell_1 j}, u_{\ell_2 k}, u_{\ell_3 m}, u_{\ell_4 s}$. Finally, G can be computed as

$$G(\ell_1\ell_2\ell_3\ell_4\ell_5) = \sum_{i=1}^{N}\sum_{j=1}^{2}\sum_{k=1}^{4}\sum_{m=1}^{3}\sum_{s=1}^{2} x_{ijmks}u_{\ell_5 i}u_{\ell_1 j}u_{\ell_2 k}u_{\ell_3 m}u_{\ell_4 s} \tag{3}$$

2.4 TD-based unsupervised FE

Although the method was fully described in a recently published book (Taguchi, 2020), we summarize the process of selecting genes starting from the TD.

- To identify which singular value vectors attributed to samples (e.g., cell lines, type of histone modification, cell cycle phase, and replicates) are associated with the desired properties (e.g., "not dependent upon replicates or cell lines," "represents re-activation," and "distinct between input and histone modifications"), the number of singular value vectors selected are not decided in advance, since there is no way to know how singular value vectors behave in advance, because of the unsupervised nature of TD.
- To identify which singular value vectors attributed to genomic regions are associated with the desired properties described above, core tensor, G, is investigated. We select singular value vectors attributed to genomic regions that share G with larger absolute values with the singular value vectors selected in the process mentioned earlier, because these singular value vectors attributed to genomic regions are likely associated with the desired properties.
- Using the selected singular value vectors attributed to genomic regions, those associated with the components of singular value vectors with larger absolute values are selected, because such genomic regions are likely associated with the desired properties. Usually, singular value vectors attributed to genomic regions are assumed to obey Gaussian distribution (null hypothesis), and P-values are attributed to individual genomic regions. P-values are corrected using multiple comparison correction, and the genomic regions associated with adjusted P-values less than the threshold value are selected.
- There are no definite ways to select singular value vectors. The evaluation can only be done using the selected genes. If the selected genes are not reasonable, alternative selection of singular value vectors should be attempted. When we cannot get any reasonable genes, we abort the procedure.

To select the DNA regions of interest (i.e., those associated with transcription reactivation), we first needed to specify the singular-value vectors that are attributed to the cell line, histone modification, phases of the cell cycle, and replicates with respect to the biological feature of interest, transcription reactivation. Consider selection of a specific index set $\ell_1, \ell_2, \ell_3, \ell_4$ as one that is associated with biological features of interest, we then select ℓ_5 that is associated with G with larger absolute values, since singular-value vectors $u_{\ell_5 i}$ with ℓ_5 represent the degree of association between individual DNA regions and reactivation. Using ℓ_5, we attribute P-values to the ith DNA region assuming that $u_{\ell_5 i}$ obeys a Gaussian distribution (null hypothesis) using the χ^2 distribution

$$P_i = P_{\chi^2}\left[> \left(\frac{u_{\ell_5 i}}{\sigma_{\ell_5}}\right)^2\right], \tag{4}$$

where $P_{\chi^2}[> x]$ is the cumulative χ^2 distribution in which the argument is larger than x, and σ_{ℓ_5} is the standard deviation. P-values are then corrected by the BH criterion (Taguchi, 2020), and the ith DNA region associated with adjusted P-values less than 0.01 were selected as those significantly associated with transcription reactivation.

2.5 Enrichment analysis

Gene symbols included in the selected DNA regions were retrieved using the biomaRt package (Durinck et al., 2009) of R (R Core Team, 2019) based on the hg19 reference genome. The selected gene symbols were then uploaded to Enrichr (Kuleshov et al., 2016) for functional annotation to identify their targeting TFs.

3 RESULTS AND DISCUSSION

We first attempted to identify which singular-value vector is most strongly attributed to transcription reactivation among the vectors for cell line ($u_{\ell_1 j}$), histone modification ($u_{\ell_2 k}$), cell cycle phase ($u_{\ell_3 m}$), and replicate ($u_{\ell_4 s}$) (Fig. 2). First, we considered phase dependency. Fig. 3 shows the singular-value vectors $u_{\ell_3 m}$ attributed to cell cycle phases. Although u_{2m} and u_{3m} were associated with reactivation, we further considered only u_{3m} since it showed a more pronounced reactivation profile. Next, we investigated singular-value vectors $u_{\ell_2 m}$ attributed to histone modification (Fig. 4). There was no clearly interpretable dependence on histone modification other than for u_{1k}, which represents the lack of histone modification, since the values for H3K27ac, H3K4me1, and H3K4me3 were equivalent to the Input value that corresponds to the control condition; thus, u_{2k}, u_{3k}, and u_{4k} were considered to have equal contributions for subsequent analyses. By contrast, since u_{1j} and u_{1s} showed no dependence on cell line and replicates, respectively, we selected these vectors for further downstream analyses (Fig. 5).

Finally, we evaluated which vector $u_{\ell_5 i}$ had a larger $\sum_{\ell_2=2}^{4} G(1, \ell_2, 3, 1, \ell_5)^2$ (Fig. 6); in this case, we calculated the squared sum for $2 \leq \ell_2 \leq 4$ to consider them equally. It is common practice to use squared sum of vectors and matrices; for example, squared sum of PC components is known to exhibit cumulative contribution and is used to evaluate the weight of individual PC components. Based on its largest contribution, $\ell_5 = 4$ was further employed. The P-values attributed to the ith DNA regions were calculated using eq. (4), resulting in selection of 507 DNA regions associated with adjusted P-values less than 0.01.

We next checked whether histone modification in the selected DNA regions was associated with the following transcription reactivation properties:

1. H3K27ac should have larger values in interphase and anaphase/telophase than in prometaphase, as the definition of reactivation.
2. H3K4me1 and H3K4me3 should have constant values during all phases of the cell cycle, as the definition of a "bookmark" histone modification
3. H3K4me1 and H3K4me3 should have larger values than the Input; otherwise, they cannot be regarded to act as "bookmarks" since these histones must be significantly modified throughout these phases.

To check whether the above criteria are fulfilled, we applied six *t* tests to histone modifications in the 507 selected DNA regions (Table 2). The results clearly showed that histone modifications in the 507 selected DNA regions satisfied the requirements for transcription reactivation; thus, our strategy could successfully select DNA regions that demonstrate reactivation/bookmark functions of histone modification.

After confirming that selected DNA regions are associated with targeted reactivation/bookmark features, we queried all gene symbols contained within these 507 regions to the Enrichr server to identify TFs that significantly target these genes. These TFs were considered candidate bookmarks that remain bound to these DNA regions throughout the cell cycle and trigger reactivation in anaphase/telophase (i.e., after cell division is complete). Table 3 lists the TFs associated with the selected regions at adjusted P-values less than 0.05 in each of the seven categories of Enrichr.

Among the many TFs that emerged to be significantly likely to target genes included in the 507 DNA regions selected by TD-based unsupervised FE, we here focus on the biological functions of TFs that were also detected in the original study suggesting that TFs might function as histone modification bookmarks for transcription reactivation (Kang et al., 2020). RUNX was identified as an essential TF for osteogenic cell fate, and has been associated with mitotic chromosomes in multiple cell lines, including Saos-2 osteosarcoma cells and HeLa cells (Young et al. 2007). Table 4 shows the detection of RUNX family TFs in seven TF-related categories of Enrichr; three RUNX TFs were detected in at least one of the seven TF-related categories. In addition, TEADs (Kegelman et al. 2018), JUNs (Wagner, 2002), FOXOs (Rached et al., 2010), and FosLs citepKang01072020 were reported to regulate osteoblast differentiation. Tables 5, 6,7, and 8 show that two TEAD TFs, three JUN TFs, four FOXO TFs, and two FOSL TFs were detected in at least one of the seven TF-related categories in Enrichr, respectively.

Other than these five TF families reported in the original study (Kang et al., 2020), the TFs detected most frequently within seven TF-related categories in Enrichr were as follows (Table 9): GATA2 (Kala et al., 2009), ESR1 (Kato and Ogawa, 1994), TCF21 (Kim et al., 2017), TP53 (Ha et al., 2007), WT1 (Shandilya and Roberts, 2015), NFE2L2 (also known as NRF2 (Martin-Hurtado et al., 2019)), GATA1 (Kadauke et al., 2012), and GATA3 (Shafer et al., 2017). All of these TFs have been reported to be related to mitosis directly or indirectly, in addition to JUN and JUND, which are listed in Table 6. This further suggests the suitability of our search strategy to identify transcription reactivation bookmarks.

One might wonder why we did not compare our methods with the other methods. As can be seen in Table 1, there are only two samples each in as many as 24 categories. Therefore, it is difficult to apply standard statistical tests for pairwise comparisons between two groups including only two samples. In addition, the number of features, N, which is the number of genomic regions in this study, is as many as 1,23,817, which drastically reduces the significance of each test if we consider multiple comparison criteria that increase P-values that reject the null hypothesis. Finally, only a limited number of pairwise comparisons are meaningful; for example, we are not willing to compare the amount of H3K4me1 in the RPE1 cell line at interphase with that of H3K27ac in the U2OS cell line at prometaphase. Therefore, usual procedures that deal with pairwise comparisons comprehensively, such as Tukey's test, cannot be applied to the present

data set as it is. In conclusion, we could not find any suitable method applicable to the present data set that has a small number of samples within each of as many as 24 categories, whereas the number of features is as many as 1,23,817.

4 CONCLUSIONS

We applied a novel TD-based unsupervised FE method to various histone modifications across the whole human genome, and the levels of these modifications were measured during mitotic cell division to identify genes that are significantly associated with histone modifications. Potential bookmark TFs were identified by searching for TFs that target the selected genes. The TFs identified were functionally related to the cell division cycle, suggesting their potential as bookmark TFs that warrant further exploration.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

YT planned and performed the study. YT and TT discussed the results and wrote the paper. All authors contributed to the article and approved the submitted version.

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This manuscript will be released as a pre-print at BioRxiv.

SUPPLEMENTAL DATA

Additional file 1: Genes identified by TD-based unsupervised FE; Additional file 2: Potential TFs that target identified genes (in Additional file 1) identified by Enrichr.

DATA AVAILABILITY STATEMENT

All datasets analyzed in this study were obtained from GEO: GSE141139

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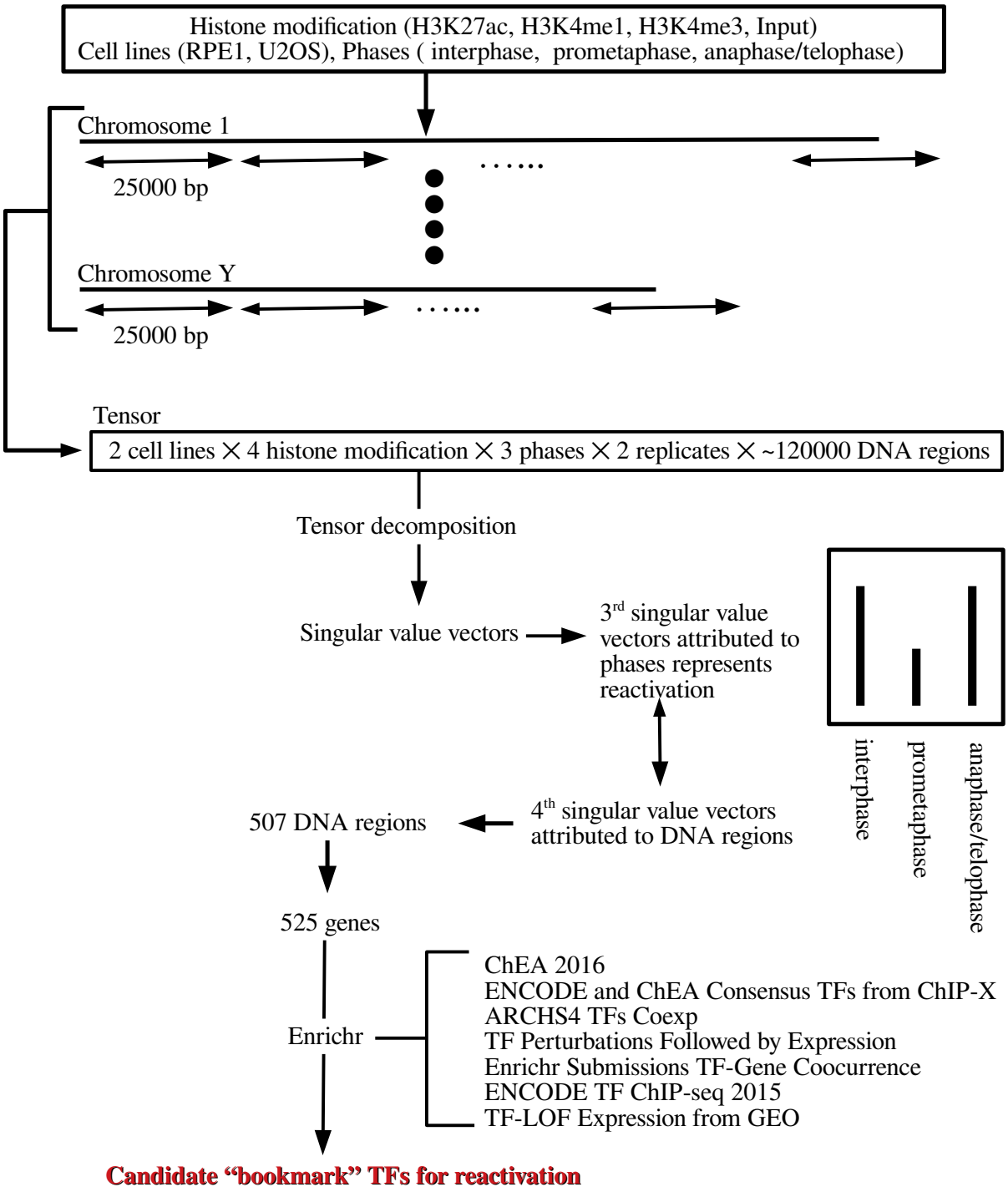

Figure 1. Flow chart of analyses performed in this study

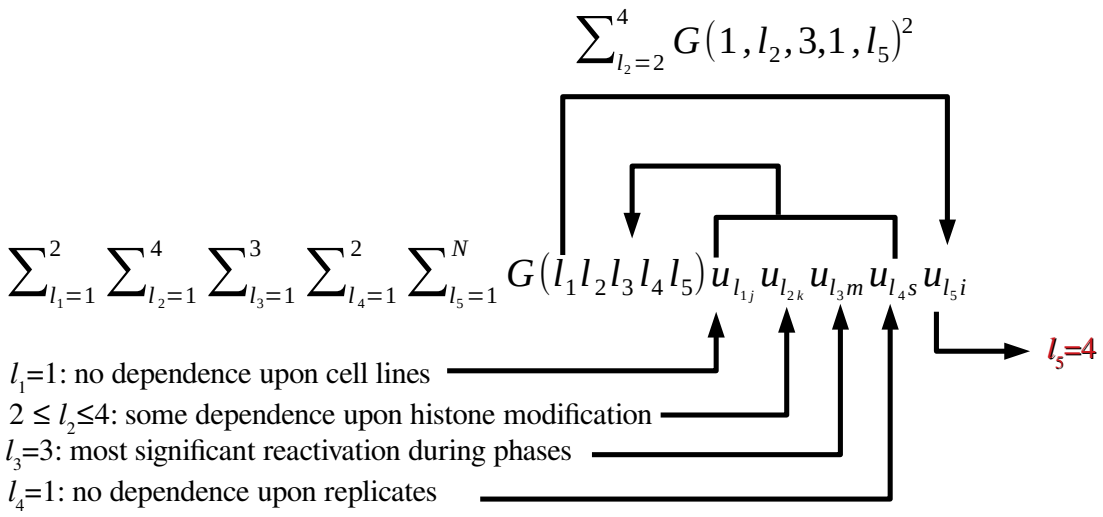

Figure 2. Schematic of the process for selecting u_{4i} to be used for DNA region selection.

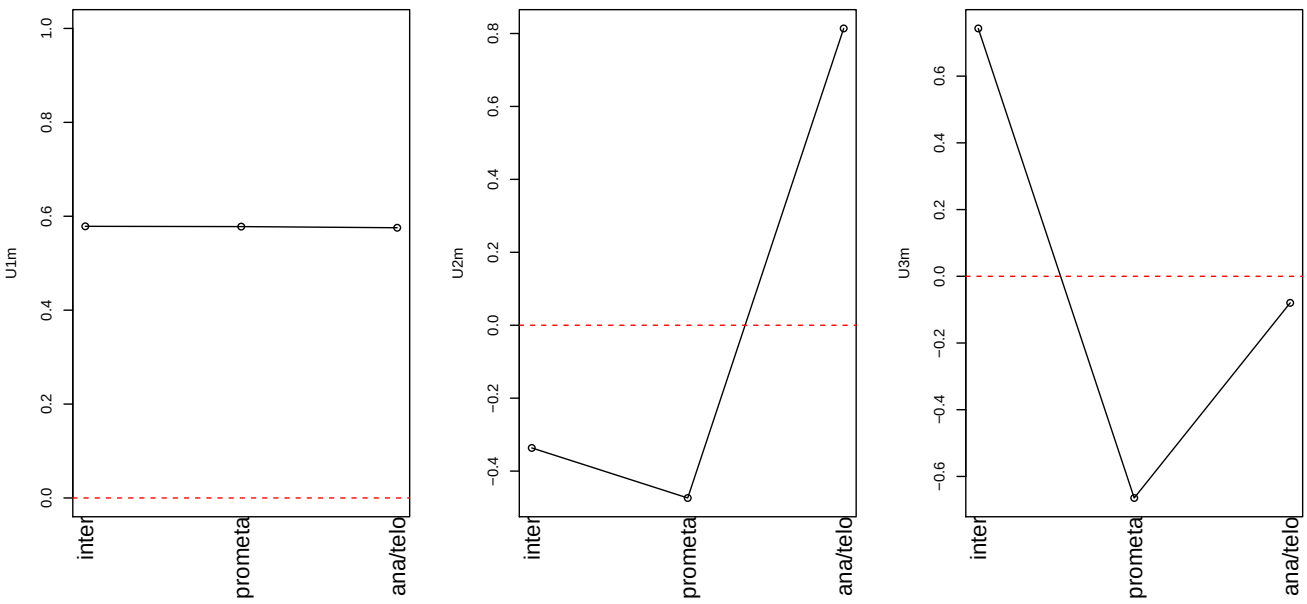

Figure 3. Singular-value vectors associated with cell cycle phase. Left: u_{1m}, middle: u_{2m}, right: u_{3m}

Table 1. Combinations of experimental conditions. Individual conditions are associated with two replicates

Phases	Histone modifications / Cell lines							
	H3K27ac		H3K4me1		H3K4me3		Input	
	RPE1	U2OS	RPE1	U2OS	RPE1	U2OS	RPE1	U2OS
interphase	○	○	○	○	○	○	○	○
prometaphase	○	○	○	○	○	○	○	○
anaphase/telophase	○	○	○	○	○	○	○	○

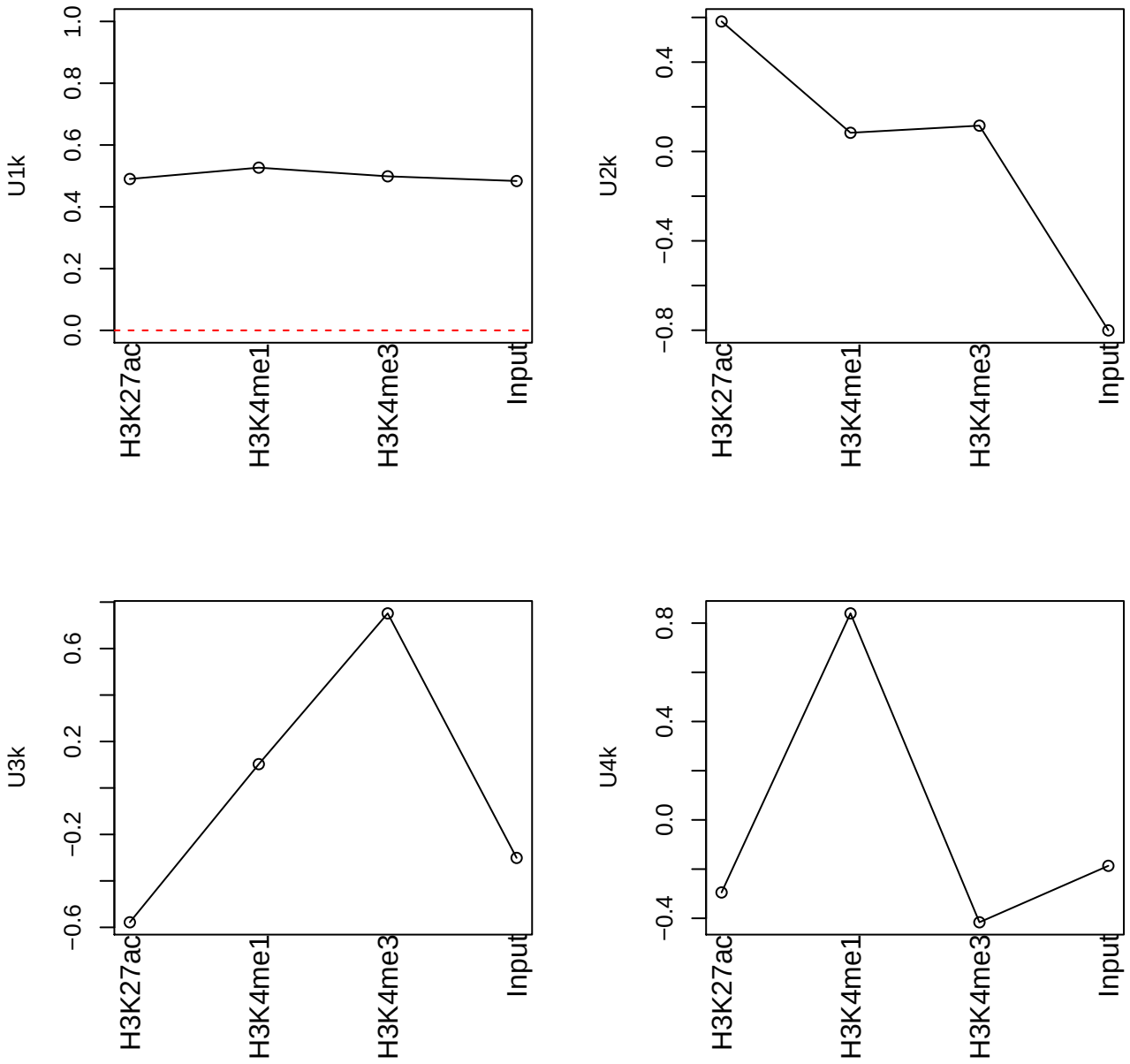

Figure 4. Singular-value vectors associated with histone modification. Upper left: u_{1k}, upper right: u_{2k}, lower left: u_{3k}, lower right: u_{4k}

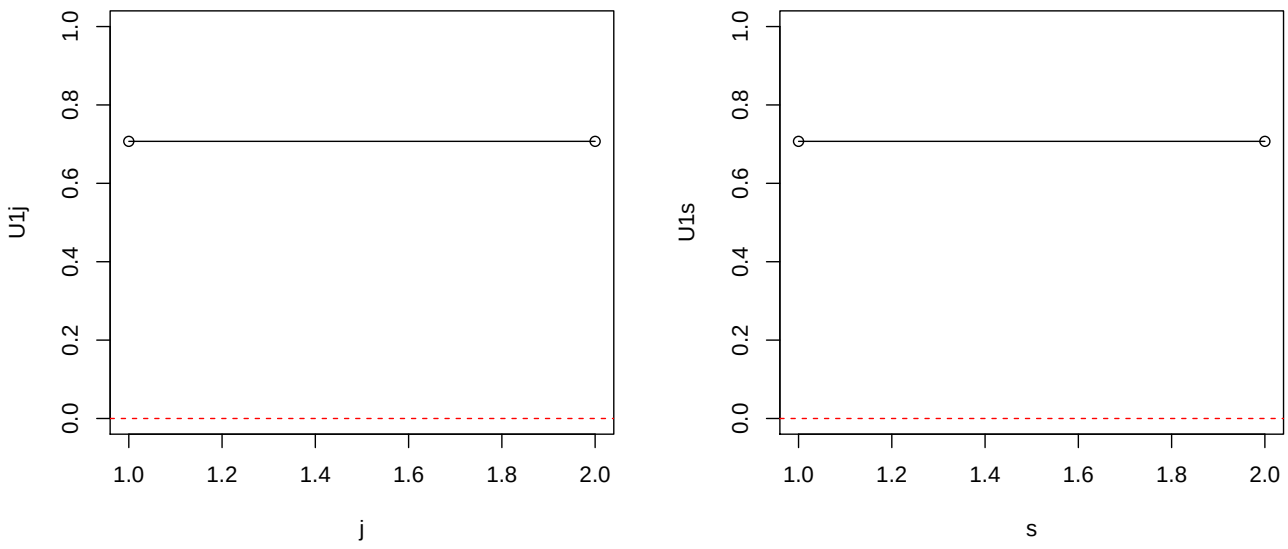

Figure 5. Dependence of vectors on cell line (j) and replicate (s). Left: u_{1j}, right: u_{1s}

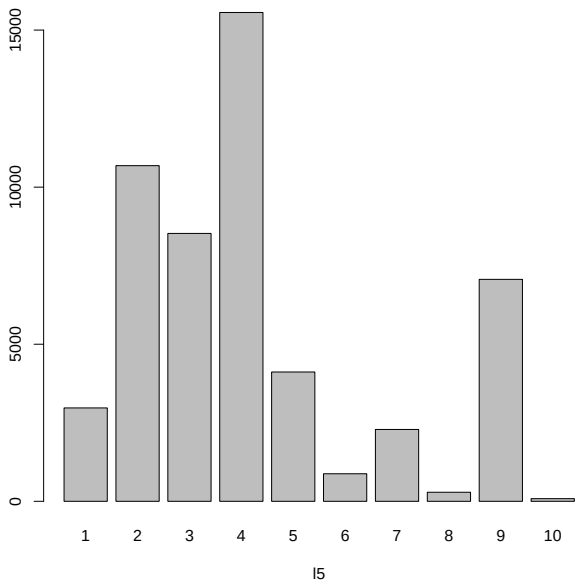

Figure 6. $\sum_{\ell_2=2}^{4} G(1, \ell_2, 3, 1, \ell_5)^2$ Only the top ten were drawn, as smaller ℓs are generally associated with absolutely larger G, because of the HOSVD algorithm.

Table 2. Hypotheses for *t* tests applied to histone modification in the selected 507 DNA regions. The null hypothesis was that the inequality relationship of the alternative hypothesis is replaced with an equality relationship. int: interphase, ana: anaphase, tel: telophase, pro: prometaphase.

Test	Alternative hypothesis	P-value	Description of desired relationships
1	$\{x_{ij1ms} \| m = 1, 3\} > \{x_{ij12s}\}$	3.30×10^{-3}	H3K27ac reactivation (int & ana/tel > pro)
2	$\{x_{ij2ms} \| m = 1, 3\} \neq \{x_{ij22s}\}$	0.60	H3K4me1 bookmark (int & ana/tel = pro)
3	$\{x_{ij3ms} \| m = 1, 3\} \neq \{x_{ij32s}\}$	0.72	H3K4me3 bookmark (int & ana/tel = pro)
4	$\{x_{ij4ms} \| m = 1, 3\} \neq \{x_{ij42s}\}$	0.86	Input as control (int & ana/tel = pro)
5	$\{x_{ij2ms}\} > \{x_{ij4ms}\}$	8.98×10^{-6}	H3K4me1 > Input
6	$\{x_{ij3ms}\} > \{x_{ij4ms}\}$	3.79×10^{-3}	H3K4me3 > Input

Table 3. Number of transcription factors (TFs) associated with adjusted P-values less than 0.05 in various TF-related Enrichr categories

		Adjusted P-values	
	Terms	> 0.05	< 0.05
(I)	ChEA 2016	537	97
(II)	ENCODE and ChEA Consensus TFs from ChIP-X	91	12
(III)	ARCHS4 TFs Coexp	1533	54
(IV)	TF Perturbations Followed by Expression	1577	346
(V)	Enrichr Submissions TF-Gene Coocurrence	587	1135
(VI)	ENCODE TF ChIP-seq 2015	788	28
(VII)	TF-LOF Expression from GEO	239	11

Table 4. Identification of RUNX transcription factor (TF) family members within seven TF-related categories in Enrichr. Roman numerals correspond to the first column in Table 3.

	TF	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
1	RUNX1	○			○			
2	RUNX2	○						
3	RUNX3					○		

Table 5. Identification of TEAD transcription factor (TF) family members within seven TF-related categories in Enrichr. Roman numerals correspond to the first column in Table 3.

	TF	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
1	TEAD4	○					○	
2	TEAD3			○				

Table 6. Identification of JUN transcription factor (TF) family members within seven TF-related categories in Enrichr. Roman numerals correspond to the first column in Table 3.

	TF	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
1	JUN	○			○	○	○	
2	JUND	○			○	○	○	
3	JUNB				○	○		

Table 7. Identification of FOXO transcription factor (TF) family members within seven TF-related categories in Enrichr. Roman numerals correspond to the first column in Table 3.

	TF	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
1	FOXO1				○	○		
2	FOXO3	○						
3	FOXO4					○		
4	FOXO6					○		

Table 8. Identification of FosL transcription factor (TF) family members within seven TF-related categories in Enrichr. Roman numerals correspond to the first column in Table 3.

	TF	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
1	FOSL2		○				○	
2	FOSL1				○		○	

Table 9. Top 10 most frequently listed transcription factor (TF) families (at least four, considered the majority) within seven TF-related categories in Enrichr. Roman numerals correspond to the first column in Table 3.

	TF	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)
1	GATA2	○	○		○	○	○	
2	ESR1	○	○		○	○	○	
3	TCF21	○		○	○	○		
4	TP53	○	○		○	○		
5	JUN	○			○	○	○	
6	JUND	○			○	○	○	
7	WT1	○			○	○		○
8	NFE2L2	○	○		○	○		
9	GATA1	○	○		○	○		
10	GATA3				○	○	○	○