Subgraph Augmented Non-Negative Tensor Factorization (SANTF) for Modeling Clinical Narrative Text

Yuan Luo1,*, Yu Xin1, Ephraim Hochberg2, Rohit Joshi1, Ozlem Uzuner3, Peter Szolovits1

ABSTRACT

Objective Extracting medical knowledge from electronic medical records requires automated approaches to combat scalability limitations and selection biases. However, existing machine learning approaches are often regarded by clinicians as black boxes. Moreover, training data for these automated approaches are often sparsely annotated at best. The authors target unsupervised learning for modeling clinical narrative text, aiming at improving both accuracy and interpretability.

Methods The authors introduce a novel framework named subgraph augmented non-negative tensor factorization (SANTF). In addition to relying on atomic features (e.g., words in clinical narrative text), SANTF automatically mines higher-order features (e.g., relations of lymphoid cells expressing antigens) from clinical narrative text by converting sentences into a graph representation and identifying important subgraphs. The authors compose a tensor using patients, higher-order features, and atomic features as its respective modes. We then apply non-negative tensor factorization to cluster patients, and simultaneously identify latent groups of higher-order features that link to patient clusters, as in clinical guidelines where a panel of immunophenotypic features and laboratory results are used to specify diagnostic criteria.

Results and Conclusion SANTF demonstrated over 10% improvement in averaged F-measure on patient clustering compared to widely used non-negative matrix factorization (NMF) and k-means clustering methods. Multiple baselines were established by modeling patient data using patient-by-features matrices with different feature configurations and then performing NMF or k-means to cluster patients. Feature analysis identified latent groups of higher-order features that lead to medical insights. We also found that the latent groups of atomic features help to better correlate the latent groups of higher-order features.

Key words: non-negative tensor factorization; unsupervised learning; subgraph mining; natural language processing

INTRODUCTION AND RELATED WORK

One primary source of medical knowledge lies in clinical patient cases that are documented in electronic medical records (EMRs) with increasing detail. The transformation from clinical cases and experiences to knowledge is largely an expert task and faces an ongoing need for periodic labor-intensive revision. Within oncology, for example, the most recent revision of the lymphoma classification guideline by the World Health Organization (WHO) lasted >1 year, involving an eight-member steering committee and over 130 pathologists and hematologists worldwide. Moreover, only around 1400 cases from Europe and North America were reviewed in the context of this revision, subjecting this process to substantial selection bias. To assist with expert review, an automated approach that can cover a much broader and larger patient population and minimize selection bias is clearly needed.

Advances in machine learning have opened avenues toward more effective mining and modeling of EMRs to facilitate translational research. However, clinicians often regard existing machine learning models as hard-to-interpret black boxes. In lymphoma pathology reports, immunophenotypic features may be expressed in the form of relations among medical concepts such as lymphoid cells and antigens (e.g., “[large atypical cells] express [CD30]”). We refer to the above relations as higher-order features, and the words (e.g., “large,” “cells”) as atomic features. When interpreting pathology reports and evaluating lymphoma subtypes, clinicians usually reason at the level of higher-order features (e.g., cell-antigen relations) besides atomic features (e.g., individual words). Moreover, multiple higher-order features (such as “[large atypical cells] express [CD30],” “[large atypical cells] express [CD15],” and “[large atypical cells] have [Reed-Sternberg appearance]”) can...
strengthen the confidence of suspected lymphoma (Hodgkin lymphoma here). Such a group of higher-order features naturally encodes medical knowledge as in the WHO lymphoma classification guideline1 (referred to as WHO guideline later), where a panel of morphologic and immunophenotypic features are used to specify diagnostic criteria. For computational modeling, atomic features can help correlate higher-order features in order to discover medically meaningful groupings. For example, the above relations all share the words “large,” “atypical,” and “cells,” which indicates that they all describe the characteristics of tumor cells. However, extracting higher-order features is itself a difficult task and often involves manually constructed rules and domain knowledge.4–7 In addition, modeling interactions between higher-order features and atomic features are usually ignored by machine learning algorithms that mostly adopt a flat patient-by-feature matrix view (patients as rows and features as columns). Although theoretically one can add interactions as additional features or embed graphical models to account for feature interactions, the problem quickly becomes intractable for large feature dimensionality.

On the other hand, limited availability of expert annotation leads to the fact that most clinical data are still either unannotated or sparsely annotated. Thus unsupervised machine learning approaches have often been used to analyze biomedical data.8,9 Moreover, the expense of expert engineered features also argues for unsupervised feature learning instead of manual feature engineering.10–12 In particular, non-negative matrix factorization (NMF) has been a highly effective unsupervised method13 to cluster similar patients14 and sample cell lines,15 to identify subtypes of diseases16 and to learn groups of atomic features or expert engineered features such as temporal patterns from predefined events17 and genetic expression patterns.18–22 As the multi-dimension extension of NMF, non-negative tensor factorization (NTF)23–25 has recently been studied to model the genetic associations with phenotypes26–28 and interaction between cellular activities.29 However, none of these approaches model the correlations among higher-order features, and some even do not consider higher-order features. Our work is more closely related to previous works on applying NMF and NTF in text mining in the general domains such as email and security surveillance.30–33 In particular, our approach differs from the NTF based text document analysis30,33 in that we augment the NTF with subgraphs to capture relation oriented higher-order features instead of standalone entities. In addition, we adopted the Tucker tensor factorization model instead of the PARAFAC model,34 where the support for factor matrices with different group numbers better serves our application purpose.

In this paper, we develop an unsupervised framework that can generate machine learning models naturally interpretable to clinicians. The framework adopts NTF to discover groupings of subgraph encoded higher-order features, hence the name subgraph augmented non-negative tensor factorization (SANTF).

METHODS

Workflow of SANTF

We first outline SANTF workflow in Figure 1. Narrative text sentences are first converted to graph representations. The graph representation is derived from natural language processing (NLP) steps for pathology reports as shown in Figure 2. We use frequent subgraph mining (FSM)35 tools to collect important subgraphs, which are relations among medical concepts mentioned in the sentences. Examples of higher-order features for clinical narrative text are shown in Figure 2. With such representations, subgraphs naturally encode higher-order features, and we use “subgraphs” and “higher-order features” interchangeably throughout the paper. We jointly model the higher-order features and atomic features, and apply NTF to discover groups of features and patients, and then perform unsupervised learning to identify the association between feature groups and patient groups. We next explain the tensor modeling and factorization in more detail.

Representing text as graphs

Figure 2 shows the steps to convert text to graphs for clinical narrative text, with an example sentence. We apply several NLP steps, including sentence breaking, tokenization, part-of-speech tagging, and a two-phase sentence parsing step that utilizes UMLS Metathesaurus,10 to convert narrative sentences into graph representation (also described in the Supplementary data).
Our subgraph mining approach differs from previous works (e.g., 36–39) in that we extract subgraphs whose nodes usually correspond to UMLS (Unified Medical Language System) concepts instead of individual tokens in the sentence. The highly variable ways of expressing concepts in clinical narrative text favors this method. In order to generate similar representation for semantically similar but grammatically different language constructs (e.g., active voice vs. passive voice), we do not distinguish edge labels and we use the root form of verbs in the actual graph/subgraph representation. We then collect frequent subgraphs from the resultant graph corpus.

**Frequent subgraph mining**

We perform FSM, which is defined on the notion of graph subisomorphism. We say one graph is subisomorphic to another if all its nodes and edges coincide with part of the other one. A subgraph occurs once in a corpus whenever it is subisomorphic to a graph in that corpus. FSM identifies those subgraphs that occur in a corpus above a given threshold number of times. In this work, we use the frequent subgraph miner GASTON with the frequency threshold set to 5. Example frequent subgraphs from pathology report narrative text are shown in Figure 2.

**Joint modeling of higher-order features and atomic features using a tensor**

In clinical narrative text, higher-order features are often correlated with each other in medically meaningful ways. For example, the two subgraphs in Figure 2 both describe the surface markers expressed by the “large atypical cells” that are often tumor cells. However, as pointed out in the introduction, with a flat matrix view and binary feature representation, such correlations are difficult to account for. Motivated by the need to explicitly model correlations among the higher-order features, we compose a three-mode tensor, in which one mode represents the patients, a second the higher-order features (subgraphs), and a third the atomic features. Note that in tensor terminology, we speak of mode in place of dimension. Figure 3 shows the schematic view of tensor modeling. We select as atomic features the words that are covered by or next to a subgraph node (neighborhood window size was set to two for this work). The intuition is that subgraphs that share affiliated (covered and contextual) words are likely to be conceptually related. By taking the union over all words that are affiliated with the nodes of a sentence subgraph, we obtain the distributional representations of that sentence subgraph. Each entry of the tensor is the count of a certain combination of patient, subgraph, and word, and is non-negative (see Figure 3 for an example). We then used a generalized tf-idf weighting of co-occurrence counts of subgraph-word pairs (i.e., counting and weighting subgraph-word pairs instead of counting and weighting words), which leads to better empirical performance.

**Patient and feature group discovery using SANTF**

The non-negative tensor is then factorized to reduce dimensionality and obtain groups for each mode. We follow the Tucker factorization scheme, where the data tensor is factorized into a core tensor multiplied by factor matrices (one factor matrix for each mode, and is orthogonal in our setting). The core tensor specifies the level of interaction between groups from different modes. The column vectors in a factor matrix specify the grouping in the corresponding mode. Such groupings can capture similar patients, similar sentence subgraphs and similar words; meanwhile they allow sharing of an element among different groups as specified by its fractional weights across groups. In Figure 3, two example subgraph groups are shown. The top subgraphs in the subgraph group 1 correlate with Hodgkin lymphoma. The top subgraphs in the subgraph

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**Figure 2:** Graph generation and subgraph collection in SANTF. The graph representation for the example sentence: “Immunostains show the large atypical cells are positive for OCT2 and BOB1, and negative for CD10, CD15 and CD30.” Example frequent subgraphs are shown after the frequent subgraph mining (FSM) steps.
group 2 correlate with diffuse large B-cell lymphoma (DLBCL). Meaningful groupings will not only improve the performance of multiple machine learning tasks but also identify panels of characteristic features of patient subcategories, in the same form as specified by the diagnostic guidelines.

SANTF differs from previous NTF related works 26–28 by introducing a mode that captures higher-order features. SANTF performs group discovery over sentence subgraphs based on the intuition that these higher-order features encode more aggregated information. In addition, SANTF simultaneously identifies the groups of the atomic features, which indirectly helps the group discovery for higher-order features through the core tensor. This is possible as the core tensor encodes the interactions among the groups of patients, higher-order features, and atomic feature groups. We refer the reader to the supplement for detailed SANTF algorithm.

**EXPERIMENTS AND RESULTS**

We experimented with SANTF on clustering lymphoma subtypes based on pathology report narrative text. SANTF itself identifies the groups of the atomic features, which indirectly helps the group discovery for higher-order features through the core tensor. This is possible as the core tensor encodes the interactions among the groups of patients, higher-order features, and atomic feature groups. We refer the reader to the supplement for detailed SANTF algorithm.
To study the impact of being able to model the interactions among multiple types of features, we establish three types of baselines for non-NMF and two configurations of k-means, a frequently used clustering method. The two configurations of k-means differ in their distance metrics used: Euclidean distance and cosine distance. The first type of baseline applies NMF or k-means on the (patient, atomic feature) matrices. The second baseline applies NMF or k-means on the (patient, higher-order feature) matrices. The third baseline applies NMF or k-means on the (patient, combined feature) matrices, where the combined features are generated by adjoining the atomic features and the higher-order features, because we want to exclude the possibility that the improvements of SANTF only come from simply adding features. Under orthogonality constraints, NMF is equivalent to simultaneous clustering of rows and columns of a matrix, and similar arguments can be made for NTF. Thus for each factorization scheme, we obtain the factor matrix of (patient, patient group), and translate this matrix into a clustering interpretation in that for each patient case, we pick the maximum column as its cluster label. For the pathology reports, recorded texts reflect results from tests and labs that are performed in order to make differential diagnoses among possible subtypes of lymphoma. Thus it is reasonable to expect that clustering based on these data will lead to patient groupings that reflect the lymphoma subtypes.

The tensor has 3773 higher-order features and 2841 atomic features. The patient group number is set to three, the same as the number of lymphoma subtypes. Because our method is unsupervised, there is no a priori mapping from patient groups to lymphoma subtypes. We therefore consider the label permutation that yields the best evaluation metrics as a parameter. For SANTF, the ideal group numbers for the higher-order features and for the atomic features are also parameters. All parameters are selected using 5-fold cross-validation on the training data and then applied to the held-out testing data.

For the evaluation of clustering performance, we use the commonly adopted metrics of averaged precision, recall, $f$-measure, and accuracy that all apply to multi-class clustering. Let $TP$ denote the number of true positives in the contingency table, $FP$ denote the number of false positives, and $FN$ denote the number of false negatives, the definition of precision is $P = TP/(TP + FP)$, recall is $R = TP/(TP + FN)$, $F$-measure is $F = 2 \times P \times R / (P + R)$. Averaging computes a direct arithmetic average over classes. The accuracy computes the proportions of the sum of diagonal entries out of all entries from the multi-class contingency table. Because neither the NMF nor the NTF has a global convergence guarantee, we use random initialization for all factorization schemes and average the clustering evaluation metrics from 100 runs. We show the results in Table 2 for the lymphoma subtype clustering. We also perform significance testing based on the student $t$-test with $\alpha = 0.05$. We see that SANTF significantly outperforms all nine baselines, and in particular, by over 10% margins in average $F$-measure to all baselines. Given that the classes are highly imbalanced, the results seem to suggest that improvements by SANTF come not only from the fact that more patient cases are correctly grouped (better accuracy), but also from more balanced clustering among multiple classes (better averaged precision, recall and $F$-measure). We refer the reader to the supplement Table 2 for detailed per-class evaluations.

### FEATURE ANALYSIS

We performed feature analysis to identify groups of higher-order feature contributing to lymphoma subtype clustering. The analyzed subgraph groups correspond to the core tensor size of $3 \times 180 \times 60$ selected by cross-validation. We follow the standard approach of analyzing groups in factorization models and make necessary adaptation to SANTF output. Based on the core tensor after factorization, we associate subgraph groups with patient clusters using the following calculation. Adopting the standard notation, for each slice $G_i$, $(i = 1, 2, 3)$ corresponding to a particular patient cluster, we sum over its word mode (mode 3) to get a vector whose elements correspond to the subgraph groups. We then sort the vector and retain the top 10 subgraph groups for each patient cluster. For each subgraph group, we sort the subgraphs according to their weights in the subgraph factor matrix and display the top subgraphs, where the weight is the entry value

<table>
<thead>
<tr>
<th>Clinical Narrative Text</th>
<th>Lymphoma</th>
<th>All</th>
<th>Train</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>589</td>
<td>305</td>
<td>284</td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>184</td>
<td>101</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Hodgkin</td>
<td>124</td>
<td>65</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Statistics of the lymphoma subtype corpus

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Clinical Narrative Text</th>
<th>Lymphoma</th>
<th>All</th>
<th>Train</th>
<th>Test</th>
</tr>
</thead>
<tbody>
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<td>DLBCL</td>
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<td></td>
<td>124</td>
<td>65</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>
WHO guideline, which reflects the current consensus on the identification of DLBCL (see Chapter 10 of the WHO guideline). Thus these features all together offer insights into the differential diagnosis of DLBCL.

For the DLBCL cluster as shown in Table 3, the first associated subgraph group recognizes the following histologic (light microscope-visible) facts: the cells are atypical in appearance and are large lymphoid cells with vesicular nuclei (the critical visual hallmarks of DLBCL). Immunohistochemically the group appropriately identifies staining for the B cell markers CD79a and CD20. Although the staining for CD79a, CD20 can also be seen in the scattered large lymphocyte-predominant (LP) cells in nodular LP Hodgkin lymphoma (NLPHL) (see p. 324 of the WHO guideline), these LP cells generally lack CD30 staining. Also, the predominance of large cells helps to rule out NLPHL. Thus these features all together offer insights into the differential diagnosis of DLBCL (see Chapter 10 of the WHO guideline). The second DLBCL associated subgraph group is again highly consistent with the current pathologic definition of DLBCL and in this group the additional feature of monotypic light chain expression is identified. This group appears to be directed toward the identification of the activated B cell-like subtype of DLBCL. Immunohistochemically the group states the following interesting facts: Ki67 proliferation index point out that the index is moderately high in the second follicular lymphoma associated subgraph group is consistent with frequent BCL2 overexpression, accompanied sclerosis, and enlargement and effacement in the architecture of lymph nodes in the setting of follicular lymphoma. The third follicular lymphoma associated subgraph group summarizes typical immunophenotypic features such as lack of expression for the cell surface marker CD5, and mixed expression levels of CD10 (together with the first and second follicular lymphoma associated subgraph groups) and CD23, all of which are consistent with Table 8.01 in the WHO guideline. The fourth follicular lymphoma associated subgraph group reveals characteristic morphological features including dense infiltration of small lymphoid cells, the presence of cleaved centrocytes, and the staining of cells in follicular dendritic pattern (see p. 220 of the WHO guideline).
For the Hodgkin lymphoma cluster as shown in Table 5, the first associated subgraph group correctly identifies the morphological feature of the large neoplastic Reed-Sternberg cells that are usually multilobated and stain positively for CD15 (see p. 327 of the WHO guideline). The second Hodgkin lymphoma associated subgraph group extracts additional essential hematopathologic features for the malignant cells of Hodgkin lymphoma: CD30 positivity, CD15 positivity, CD20 negativity, and the appearance suggestive of Reed-Sternberg cells, which often express PAX5 and occur with histiocytes (see p. 328 of the WHO guideline).

### Table 3: Top higher-order feature groups associated with diffuse large B-cell lymphoma

<table>
<thead>
<tr>
<th>DLBCL First Subgraph Group</th>
<th>DLBCL Second Subgraph Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6640 atypical cells</td>
<td>0.0530 atypical cells</td>
</tr>
<tr>
<td>0.0929 large lymphoid cells</td>
<td>0.0293 large lymphoid cells</td>
</tr>
<tr>
<td>0.0057 show ... positive cells</td>
<td>0.0240 large cells</td>
</tr>
<tr>
<td>0.0040 large lymphoid cell with vesicular nuclei</td>
<td>0.0070 monotypic staining of immunoglobulin light chains</td>
</tr>
<tr>
<td>0.0025 show the cells are ... B-cells co-expressing</td>
<td>0.0059 show large atypical cells with ... vesicular nuclei</td>
</tr>
<tr>
<td>0.0019 large cells predominate</td>
<td>0.0051 B-lineage antibody PAX5 ... stain ... large cells</td>
</tr>
<tr>
<td>0.0010 cells are CD30+, MUM1+</td>
<td>0.0049 associated cells</td>
</tr>
<tr>
<td>0.0005 large cells stain for CD79a</td>
<td>0.0047 a few large cells</td>
</tr>
<tr>
<td>0.0005 admixed small lymphocytes</td>
<td>0.0037 atypical cells are CD10–, BCL2– ...</td>
</tr>
<tr>
<td>0.0004 large cells stain positively for CD20</td>
<td>0.0034 infiltrate of large ... cells with ... scant cytoplasm</td>
</tr>
<tr>
<td>0.0002 large atypical cell with vesicular nuclei</td>
<td>0.0034 sheet of ... cells</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DLBCL Third Subgraph Group</th>
<th>DLBCL Fourth Subgraph Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0385 diffuse infiltrate of large ... cells</td>
<td>0.0144 negative for cytokeratin</td>
</tr>
<tr>
<td>0.0329 large lymphoid cells</td>
<td>0.0111 stain positively for CD20</td>
</tr>
<tr>
<td>0.0312 large atypical cells</td>
<td>0.0104 in-situ hybridization show</td>
</tr>
<tr>
<td>0.0137 diffuse infiltrate of large ... cells with ... vesicular nuclei</td>
<td>0.0103 positive for immunoglobulin kappa chains</td>
</tr>
<tr>
<td>0.0082 B-lineage antibody PAX5 ... stain ... large cells</td>
<td>0.0101 cells show ... stain</td>
</tr>
<tr>
<td>0.0077 infiltrate of large ... cells with ... scant cytoplasm</td>
<td>0.0094 Ki67 proliferation index is greater than 70%</td>
</tr>
<tr>
<td>0.0051 sections show ... tissue with ... infiltrate of ... cells</td>
<td>0.0086 Ki67 proliferation index is &gt;60%</td>
</tr>
<tr>
<td>0.0041 positive for CD20, BCL2</td>
<td>0.0075 positive for CD79a</td>
</tr>
<tr>
<td>0.0028 cells ... form</td>
<td>0.0060 stain for Ki67</td>
</tr>
<tr>
<td>0.0014 atypical large cells ... positive for CD20</td>
<td>0.0053 large cells stain positively for CD20</td>
</tr>
<tr>
<td>0.0009 monotypic staining with immunoglobulin lambda chains</td>
<td>0.0044 positive for cytokeratin</td>
</tr>
</tbody>
</table>

Subgraphs are translated to partial sentences. In each list item, e.g., “0.0010, ... cells are CD30+, MUM1+ ...”, 0.0010 indicates its weight in the group. The “... cells are CD30+, MUM1+ ...” is the partial sentence translated from the corresponding subgraph. Partial sentences that are not mentioned in feature analysis are grayed out. For brevity, we omit the leading and trailing “...” for partial sentences in the table.
WHO guideline\(^1\)). The third Hodgkin lymphoma associated subgraph group is mostly consistent with the nodular sclerosis subtype of classical Hodgkin lymphoma, where the lymphoma contains Reed-Sternberg cells as well as a microenvironment of non-neoplastic inflammatory cells, the lymph nodes show a nodular growth pattern, collagen bands often surround nodules, and necrosis may occur (see p. 330 of the WHO guideline\(^1\)). The fourth Hodgkin lymphoma associated subgraph group is mostly consistent with the subtype of NLPHL, in that large neoplastic cells (LP cells) are positive for CD45, OCT2, PAX5, and immunoglobulin light (kappa and/or lambda) chains. The subgraph group is also consistent with the co-occurrence of LP cells and CD3 positive T-cells (see p. 324 of the WHO guideline\(^1\)).

We note the advantage of using subgraph groups as features compared to using individual subgraphs as features. For example, in the third follicular lymphoma associated subgraph group, standalone positivity or negativity on CD5, CD10, and CD23 may not be discriminative enough, but collectively they offer medically important information favoring follicular lymphoma.

We next look into why the atomic feature groups as jointly discovered by SANTF help to better group individual subgraphs, in order to validate our intuition that exploiting interactions between both feature types is beneficial. Continuing from the analysis of important higher-order feature groups, we give an analysis on word group distributions associated with individual subgraphs. In the first DLBCL associated subgraph group in Table 3, the following subgraphs (partial sentences) are together ranked among the top subgraphs: “... large cells predominate...”, “... large cells stain for CD79a...”, “... large cells stain positively for CD20...”, “... large lymphoid cells...”, “... cells are CD30”, “MUM1”...”.

| Table 4: Top higher-order feature groups associated with follicular lymphoma |
|------------------------------------------|------------------------------------------|
| **Follicular First Subgraph Group**      | **Follicular Second Subgraph Group**     |
| 0.0308 interstitial lymphoid aggregates  | 0.0583 nodal architecture effaced         |
| 0.0196 predominantly small ... cell      | 0.0213 B-cells co-expressing BCL2, CD10 |
| 0.0171 paratrabecular lymphoid aggregates| 0.0201 biopsy of lymph node              |
| 0.0149 focal                             | 0.0091 sclerotic tissue                  |
| 0.0127 cells in the follicles            | 0.0063 lymph node architecture effaced by ... follicular proliferation |
| 0.0117 large paratrabecular lymphoid aggregates | 0.0061 sections show enlarged lymph nodes |
| 0.0107 diffuse infiltrate of small lymphoid cells | 0.0059 cell with reduced size |
| 0.0093 infiltrate consisting of ... lymphoid cells | 0.0055 sections show ... lymph nodes |
| 0.0080 CD10+/− B-cell population        | 0.0045 residual ... follicle center cells |
| 0.0062 core needle biopsy                | 0.0043 cells stain positively for ... BCL2 |
| 0.0050 follicles contain ... centroblasts| 0.0021 flow cytometry demonstrate ... population |
| **Follicular Third Subgraph Group**      | **Follicular Fourth Subgraph Group**     |
| 0.0829 B-cells are negative for CD5     | 0.0642 lymphoid infiltration             |
| 0.0466 B-cells express                  | 0.0269 atypical infiltration             |
| 0.0405 CD5−, ... , CD23−                | 0.0267 dense lymphoid infiltration       |
| 0.0315 negative for CD10                | 0.0133 mucosa infiltration               |
| 0.0271 positive for CD23                | 0.0102 small lymphoid cells              |
| 0.0251 positive for CD10                | 0.0095 small lymphocytes                 |
| 0.0148 positive for CD19, CD20, CD23    | 0.0084 cleaved centrocytes               |
| 0.0060 containing ... large atypical cells ... | 0.0082 diffuse infiltrate of small lymphoid cells |
| 0.0041 positive for CD3                 | 0.0060 cells ... in follicular dendritic pattern |
| 0.0024 show B-cells are positive for CD3, CD20 | 0.0059 fibroadipose tissue               |
| 0.0018 CD5−, CD10− ... B-cells         | 0.0044 dense infiltrate containing lymphoid cells |

Subgraphs are translated to partial sentences. Partial sentences that are not mentioned in feature analysis are grayed out.
“... atypical cells ...” By contrast, we did not find a similar grouping in patterns generated by those baselines that have subgraphs as features (baselines 2 and 3 in Table 2, k-means clustering does not produce subgraph groups). The positivity for the antigens CD79a and CD20 may associate with the scattered large LP cells in NLPHL, but the group includes additional positive staining for MUM1 and CD30, which favors the differential diagnosis of DLBCL.

We look into the above six subgraphs and identify word groups associated with each subgraph. Intuitively, such associations are expressed in the core tensor and one can sum out the patient mode to explicitly associate a subgraph with the word groups (see SANTF algorithm section in the supplement on how to identify word groups associated with a specific subgraph from the tensor factorization results). The associated word group distribution for each subgraph is shown in Figure 4, and their correlation coefficients are shown in Figure 5. It becomes evident from Figure 5 that each of the subgraphs is correlated with at least one other subgraph with a correlation coefficient above 0.5, indicating relatively strong correlation. Figure 4 gives details on which word groups help to correlate subgraphs. For example, the word groups 10, 13, 16, 17, 26, 28, 33, and 52 help correlate subgraphs “... large cells stain positively for CD20 ...” and “... large cells stain for CD79a ...”. This illustrates the benefits of using word group distribution to correlate subgraphs. In summary, analysis of word groups suggests that adding the word mode (including covered and contextual words) to the tensor and jointly learning the subgraph groups and the word groups help to better capture the correlations between subgraph features.

### Table 5: Top higher-order feature groups associated with Hodgkin lymphoma

<table>
<thead>
<tr>
<th>Hodgkin First Subgraph Group</th>
<th>Hodgkin Second Subgraph Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0362</td>
<td>large cells</td>
</tr>
<tr>
<td>0.0312</td>
<td>atypical cells</td>
</tr>
<tr>
<td>0.0303</td>
<td>large cells stain</td>
</tr>
<tr>
<td>0.0263</td>
<td>positive for CD15</td>
</tr>
<tr>
<td>0.0196</td>
<td>scattered large ... cells</td>
</tr>
<tr>
<td>0.0117</td>
<td>infiltrate of large ... cells with lobated nuclei</td>
</tr>
<tr>
<td>0.0103</td>
<td>many large cells</td>
</tr>
<tr>
<td>0.0064</td>
<td>large neoplastic cells</td>
</tr>
<tr>
<td>0.0046</td>
<td>stain positively for CD15</td>
</tr>
<tr>
<td>0.0042</td>
<td>multilobated ... cells</td>
</tr>
<tr>
<td>0.0027</td>
<td>background contain ... lymphocytes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hodgkin Third Subgraph Group</th>
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</tr>
</thead>
<tbody>
<tr>
<td>0.0233</td>
<td>necrosis</td>
</tr>
<tr>
<td>0.0142</td>
<td>dense sclerosis</td>
</tr>
<tr>
<td>0.0106</td>
<td>vaguely nodular pattern</td>
</tr>
<tr>
<td>0.0099</td>
<td>collagen fibrosis</td>
</tr>
<tr>
<td>0.0098</td>
<td>mixed inflammatory cells</td>
</tr>
<tr>
<td>0.0073</td>
<td>nodular pattern</td>
</tr>
<tr>
<td>0.0053</td>
<td>atypical infiltration</td>
</tr>
<tr>
<td>0.0043</td>
<td>collagen bands</td>
</tr>
<tr>
<td>0.0042</td>
<td>nodular lymphoid proliferation</td>
</tr>
<tr>
<td>0.0018</td>
<td>areas of vague nodularity</td>
</tr>
<tr>
<td>0.0017</td>
<td>cells ... with Reed-Sternberg forms</td>
</tr>
</tbody>
</table>

Subgraphs are translated to partial sentences. Partial sentences that are not mentioned in feature analysis are grayed out.
DISCUSSION AND FUTURE WORK

Currently the selection of SANTF parameters such as core tensor size relies on cross validation. We recognize the potential of using a nonparametric Bayesian approach to discover such parameters directly from data. For example, in the nonparametric Bayesian setting, each patient in a dataset can be associated with hidden variables describing groups (causes) that are responsible for generating the patient’s data. Although there can be an infinite number of possible groups to choose from, under proper prior distributions (e.g., specified using the Indian buffet process), only a finite number of groups would be selected. Care needs to be taken when defining generative processes for multiple types of features to account for the fact that atomic features aggregate into higher-order features and to allow for an efficient inference algorithm. Clearly, the performance of SANTF depends on the nature of the relationships among the various modes of the tensor. We suspect that there is an information-theoretic analysis that can shed light on quantifying these relationships, where the suggested generative model could provide a basis for such an analysis.

SANTF applies to any medical subdomain where information can be represented as higher-order features and atomic features. For example, we recognize the potential benefits of applying SANTF to physiologic time series. Recent studies called for learning risk stratification models automatically from patient physiologic times series, for example, laboratory test values and vital measurements of patients monitored in the intensive care units. Progression of multiple physiologic variables can be summarized into temporal patterns (higher-order features) using graph representation and mining. Intuitively, similar numerical values (atomic features) of various physiologic measurements are helpful in identifying groupings of physiologic temporal trends by indicating similar states through which the patients have passed. Thus it is reasonable to expect that SANTF is also likely to improve modeling of physiologic time series in predictive tasks such as mortality risk stratification.

SANTF is currently computationally intensive. The tensor factorization on average takes 22 min on a computer with Intel Core 2 Duo P8600 and 8 GB RAM. The steps of document preprocessing including parsing, UMLS concept identification and graph/subgraph construction also take considerable amount of time. We parallel the computations into batches of 50 patients and run them on the pHPC clusters at Partners...
Health Care which has 600 processing cores in total and a maximum 100 core concurrency per user. The paralleled pre-processing time is within 30 min, which could be improved by parallelization into smaller batches on a larger cluster. We also plan to explore parallelization and approximation techniques such as stochastic gradient descent to speed up tensor factorization in future work.

Parsing challenges may arise with less formal clinical notes such as discharge summaries. For example, many connecting parts of speech (conjunctions, articles, prepositions) may be elided, which makes parsing dependency difficult for even statistical parsers. For less formal clinical notes, we expect a hybrid form of NLP may work better. Namely, for longer sentences, graph construction can be based on dependency parsing, while for shorter sentences, graph construction can be based on co-occurrence of concepts. Choosing the threshold of longer versus shorter sentences is non-trivial and may depend on the characteristics of clinical notes, we intend to explore such trade-offs in future work. On the other hand, different institutions may have different clinical documentation systems and styles. Such generalizability challenges are partly addressed by our clinical text subgraph mining approaches such as using UMLS concepts as subgraph nodes and ignoring dependency types, which can mitigate the impact of the terminology and style differences between institutions. Using atomic features to correlate higher-order features as done by SANTF also helps connect higher-order features whose differences are mainly in writing style. We are expanding the lymphoma classification project across institutions and across nations, and systematic generalizability analysis is part of our future work.

CONCLUSIONS
We proposed a novel unsupervised framework of subgraph augmented non-negative tensor factorization (SANTF), which can automatically generate machine learning models that are naturally interpretable to clinicians. SANTF can jointly model the interactions among different types of features by integrating them into the learning objective. We applied SANTF to unsupervised learning tasks on clustering lymphoma subtypes based on narrative text from pathology reports. We established nine baselines with widely used non-negative matrix factorization (NMF) and $k$-means clustering methods. For each of NMF or $k$-means configuration, the first baseline explores the atomic features. The second baseline explores the higher-order subgraph features. The third baseline explores both types of features but not their correlations. Experimental evaluation demonstrated that SANTF significantly outperforms all nine baselines, in particular, by over 10% margins in average $F$-measure to all baselines. A closer look at the subgraph groups that are generated by SANTF offers more clinical insights about lymphoma subtypes than atomic features or even standalone subgraphs. We also found that the atomic feature groups as jointly discovered by SANTF help to better correlate individual subgraphs, validating our intuition that exploiting interactions between different feature types is beneficial.

COMPETING FINANCIAL INTERESTS
None.

ETHICS APPROVAL
The Institutional Review Boards governing oncology care at the Massachusetts General Hospital approved this study. A waiver
of informed consent was obtained. The intensive care data are from a dataset distributed under a limited data use agreement, which was approved by the Beth Israel Deaconess Hospital's IRB.

**FUNDING**
The work described was supported in part by Grant Number U54LM008748 from the National Library of Medicine and by the Scullen Center for Cancer Data Analysis.

**CONTRIBUTORS**
YL is the primary author and was instrumental in developing the subgraph and tensor modeling, and performed data analysis. YX contributed to tensor modeling and analysis. EH provided expertise on lymphoma pathology. RJ provided input to feature analysis. OU contributed to the subgraph modeling and evaluation. PS provided expertise in machine learning and data analysis. EH and PS are the principal investigator for the grants involving the secondary use of clinical data. All co-authors reviewed and edited the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Library of Medicine or the National Institutes of Health.

**SUPPLEMENTARY MATERIAL**
Supplementary material is available online at http://jamia.oxfordjournals.org/.

**REFERENCES**


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