Kokiri: Random Forest-Based Cohort Comparison and Characterization

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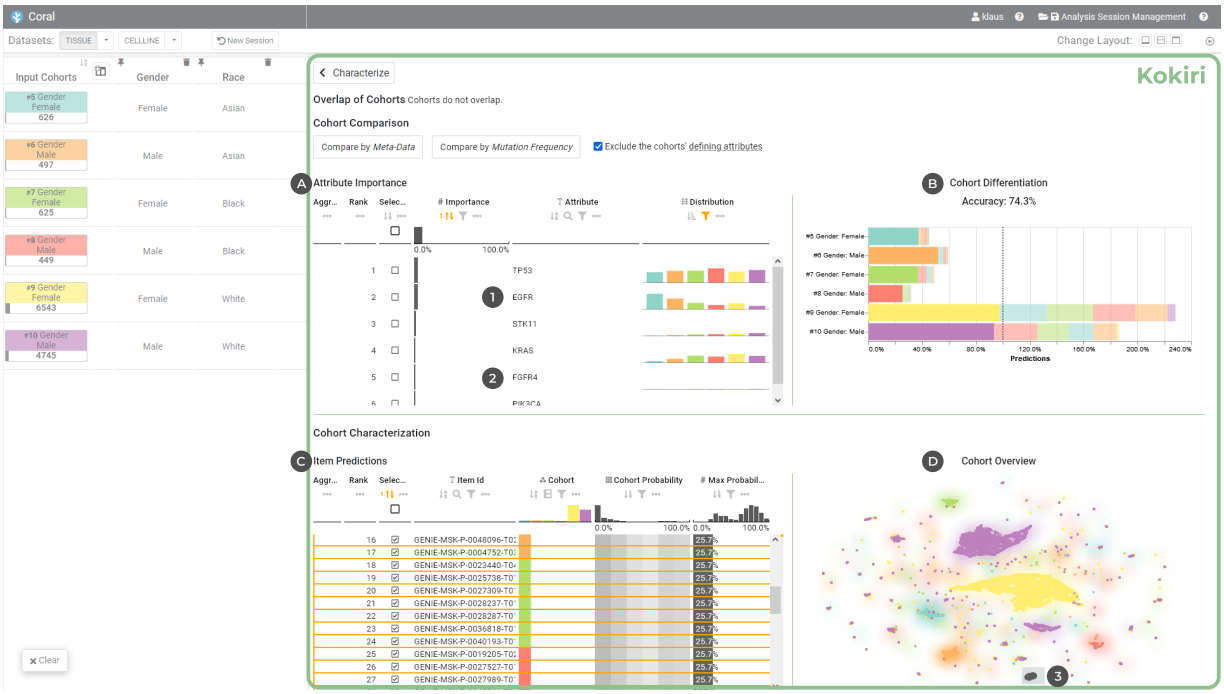

Figure 1: Kokiri integrated in Coral [2] comparing lung cancer patient cohorts of different race and gender. The ranked list A shows the most important attributes to differentiate the cohorts. The overall separability is shown with stacked bar charts B. A scatterplot D gives an overview of the predicted cohort affiliations of the patients, and a second ranked list C displays all items, the cohorts they belong to, and the probabilities to belong to any of the cohorts based on the data.

Abstract

We propose an interactive visual analytics approach for the characterization and comparison of patient subgroups (i.e., cohorts). Despite having the same disease and similar demographic characteristics, patients respond differently to therapy. One reason for this is the vast number of variables in the genome that influence the outcome. Nevertheless, most existing tools do not offer effective means to identify the most differing attributes or look at them in isolation, neglecting combinatorial effects. To fill this gap, we present Kokiri, a visual analytics approach that aims to separate cohorts based on user-selected data, ranks attributes by their importance to distinguish between cohorts, and visualizes the overlap and separability of the cohorts. Using our approach, users can additionally characterize the homogeneity and outliers of the cohort. To demonstrate the applicability of our approach, we integrated Kokiri in the Coral cohort analysis tool for the purpose of comparing and characterizing lung cancer patient cohorts.

Index Terms: Human-centered computing—Visual analytics—;—Applied computing—Genomics—

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1 Introduction

With advances in cancer therapy, it is becoming increasingly important to study information beyond the type and stage of the tumor as well as patient demographics. Newer drugs directly target specific cancer-causing gene mutations, enabling highly targeted treatment for individual patients [19]. However, studies have also shown that gene mutations are not only different across cancer types, but also race and sex [25, 32]. This results in different therapeutic outcomes across patient cohorts. Uncovering the reasons for these differences is a challenge, due to the complexity of the problem but also the amount of data to consider. Thousands of genes, several hundred of which have been identified as tumor-relevant [34], are potential causes. How patient cohorts differ, and what the most important differences are, are key information to further improve therapy.

Large-scale projects, such as the AACR Project GENIE [1], provide clinical and genomic data for thousands of patients from which clinically relevant subtypes can be derived. Reasoning about such large amounts of data is becoming increasingly complex and analysts require powerful tools to gain insights [12]. Visual analytics tools enable domain experts to visually explore and analyze cancer cohorts in such large datasets [2, 8, 13, 35]. Comparison of cohorts, however, is often limited to single attributes, or multiple attributes

that are being considered individually. Combinatorial effects of multiple attributes are thus lost.

To address these challenges, we propose an interactive visual analytics approach, called Kokiri, that allows users to compare cohorts by their high dimensional data with the goal to uncover driving differences between them and to also characterize the homogeneity of individual cohorts. We achieve this by training a random forest model to classify the cohorts based on their high-dimensional data. We report the most important attributes that differentiate between the cohorts and give an overview of the model's classification performance. Users can iteratively refine the classification by limiting the data to a subset of interest, e.g., by excluding genes that are already known to differ, to focus on the remaining data and gain further insights. Additionally, the homogeneity of individual cohorts can be assessed based on the classifier's certainty, and hard-to-classify items can be identified. To demonstrate the utility of our approach, we describe a use case where we compare lung cancer cohorts to verify findings from literature and gain deeper insights into the data by the AACR Project GENIE [1].

2 Related Work

The comparison of cohorts is a fundamental task in cancer research as well as many other domains that can be effectively supported by visual analytics tools. While the comparison of cohorts looks for differences between two or multiple cohorts, the characterization of a cohort looks for potential differences within a cohort.

Coral [2] is a cohort analysis tool specifically designed for creating and characterizing cohorts. However, the visual comparison of cohorts is limited to one or two attributes that need to be manually selected by the user. Additionally, Coral integrates TourDino [10] for pairwise statistical comparisons of cohorts by a user-defined set of attributes. In previous work, we have analyzed cohort differences in low-dimensional embeddings to provide an overview of differences in high-dimensional space [11]. Summary visualizations explain the individual cohorts' data, and difference visualizations highlight differences in attribute distributions between cohorts. Both visualizations are ranked such that the most and least varying attributes can be seen at a glance. Similarly, Duet [21], shows the most similar and different attributes for two selected cohorts and uses textual explanations alongside histograms as summaries of these similarities/differences. Differences in data distributions are also considered by Gotz et al. [14]. Their proposed approach combats the introduction of selection bias when creating cohorts. This bias is determined by calculating the Hellinger distance between pairs of cohorts. Based on this, Borland et al. [4] present a set of visualizations to compare a user-defined focus cohort with a baseline cohort. In contrast to the above works, Somarakis et al. [33] describe a system for the analysis of single-cell omics data where cohorts can be compared based on the abundance of different cell types and combinations thereof. The system ranks attributes by their cohort-differentiating ability and also supports the visual detection of outliers within each cohort. Except for the work of Somarakis et al. [33], all of the above works consider attributes only individually when comparing cohorts. In doing so, they neglect the vast combinatorial space opened up by high-dimensional data, from which further differences can be identified. Moreover, only Coral [2] allows comparison of more than two cohorts.

In machine learning, classification models categorize items into classes based on their data. Classification models take advantage of high-dimensional data to be able to distinguish between classes and provide an alternative to traditional pairwise statistics as used in the works above. Here, the cohorts are the classes that are to be distinguished. Visual analytics tools can support domain experts in the construction and analysis of classification models. Endert et al. [12] reviewed the state-of-the-art in integrating machine learning approaches into visual analytics workflows and also discuss how classification algorithms and people can work together. In BaobabView [38], domain experts can interactively create a decision tree to integrate their domain knowledge into the classification model. The tool provides visualizations for the resulting decision tree to analyze splits of the data made by the decision tree, the predicted classes in comparison to ground truth, and a flow diagram showing how items of different classes are differentiated when flowing through the decision tree. While designed for decision trees, most components of Boababview can also be applied to the random forest model we use in this work. The python package [37] to visualize the flow of items through the decision tree can also visualize individual trees of a random forest. However, our focus is on exploratory analysis of cohorts rather than model building, which is why we do not rely on visualizations for in-depth model analysis. Infuse [20] is a visual analytics system to select attributes for classification models. The large overview visualization ranks attributes by various attribute selection algorithms to keep informative attributes apart from non-informative attributes for the classification process. In Kokiri, we don't use attributes selection algorithms but rank attributes by an importance measure computed from the decisions made by the random forest model. The ranking thus directly reflects the classification model.

Most closely related to our work is the approach by Rauber et al. [30], extending the work by Brandoli et al. [6]: In the first step, low-dimensional representations of the data are shown to visually predict the class separability and presumably classification performance. To improve the separability, attribute subsets can be selected based on their importance in a random forest model. In contrast, we first create the model and then create a low-dimensional representation of its decisions so that the visualization directly reflects the model. A good separation by the model results in good separation of the scatterplot and items where the model's prediction is uncertain are identifiable as outliers. Additionally, we give a preview of the class distribution for each attribute when ranking them.

3 Kokiri

Kokiri compares and characterizes subsets of tabular data, here cohorts. The workflow within Kokiri, as shown in Fig. 2, consists of three steps that correspond to its three views: (i) the *Overlap View* to see which cohorts share items; (ii) the *Comparison View* to compare cohorts and get a ranking of the most important attributes and an overview of the classification performance; and (iii) the *Characterization View* to examine cohort homogeneity and hard-to-classify items. The individual cohorts are consistently colored across all visualizations using a categorical color schema (D3's *Set 3* [5], see Fig. 1).

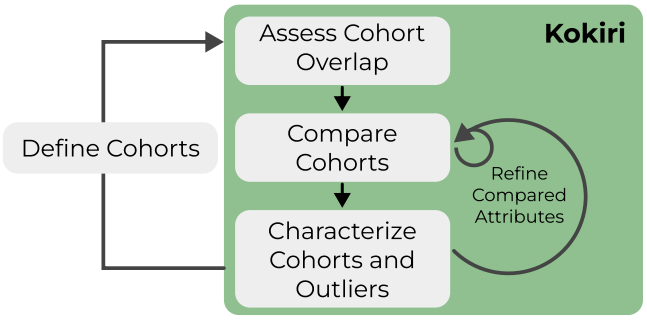

Figure 2: The workflow in Kokiri starts with assessing the overlap between cohorts. Then, the cohorts are compared to find the most important differentiating attributes. In the last step, the cohorts' homogeneity and outliers of the cohorts are characterized. Based on their findings, users can compare cohorts on a different set of attributes or refine cohorts outside of Kokiri.

To compare and characterize the cohorts, we train a random forest classifier [7] that aims to differentiate them based on the data provided. A random forest is an ensemble of decision trees that generalizes better through the introduction of randomness in the training process: (a) each decision tree is trained on a bootstrapped sample of the data, i.e., each tree sees a different subset of the data; and (b) only a random subset of attributes is considered at each split. To which cohort an item belongs is determined by averaging the decisions of the forest's trees. Random forests have the advantages that they are interpretable, have been shown to work well for biomedical data, and can capture complex interactions in the data [9, 16, 27].

Overlap View. The Overlap View shows the pairwise overlap between cohorts that share items. Each cohort is represented by a bar, and bars grow in opposite directions. The length of each bar corresponds to the number of items in the cohort relative to the number of items in both cohorts. For example, the overlap of a cohort with 160 items and a cohort with 320 items that share 80 items (20% of the total items) is visualized as: 

. The visualization thus shows the relative overlap and differences in size, similar to a collapsed representation of an Euler diagram and the visualization proposed by Borland et al. [4]. In the context of Kokiri, we have found this visualization better suited compared to alternatives we've tested—including UpSet [22], Jaccard Similarity [18], and absolute counts of intersecting items.

Comparison View. We iteratively train a random forest classifier by increasing the number of estimators in steps of 25 up to 500 to give early feedback on the performance and most important attributes. This allows users to stop the training early, giving them a chance to incorporate their domain knowledge by excluding already known differences or focusing on a subset of attributes for the next comparison. This way, human and machine pattern recognition capabilities can be combined, users gain a deeper understanding of the resulting classification model, and can also actively improve it [3, 12, 23]. Attributes important to the classification are determined by the Gini importance, which is an attribute importance measure describing the quality of a split on an attribute. The better the split, the higher the Gini importance. The values of all splits from the same attribute are summed per tree and averaged over the whole forest. As the Gini importance is used to select the best attribute for splitting the data, it is already computed while the forest is built [27].

The *Comparison View* gives insights into how well the cohorts are separable by the data and which attributes are most important to differentiate them. It consists of two components that are displayed side-by-side: (i) a ranking of the attributes based on importance; and (ii) an overview of the classifier's performance.

We use a tabular visualization [15] in which the attributes are ranked by their importance for distinguishing the cohorts (see Fig. 1 A). Numerical attributes are represented by a row in the table. Categorical attributes have one row per category, but can be grouped together by the user. By having one row per category, we can show how many items of each cohort fall in this category with a bar chart. This distribution is shown in a separate column so that users can understand why an attribute is important to the classifier. For numerical data, we visualize the distribution of the cohorts using density plots.

The performance overview shows the mean accuracy score and the composition of the cohorts as predicted by the classifier (see Fig. 1 B). We visualize the predicted composition with a stacked bar chart. Each cohort is represented with a bar and colored segments represent the items that were assigned to the cohort by the classifier. The segments are ordered by their size and segments of misclassified items have lower opacity.

Characterization View. To characterize cohorts and outliers we rely on the classification model that was trained in the previous comparison step. To predict the cohort an item belongs to, each tree of the random forest casts a vote and the majority vote decides the class. The more the votes differ, the less certain the classifier is about assigning a cohort to an item and the lower the probability that an item belongs to a cohort. For N items and k cohorts, the probabilities form a vector of size $N \times k$. From this vector, we can characterize items that are (a) clearly assignable to a cohort, (b) assignable to the cohort but with lower probability because the data deviate, (c) assignable to several cohorts, and (d) not assignable to any cohort, which are considered outliers.

We visualize these probabilities following an overview+detail approach with: (i) a ranking of items based on the prediction probability to quickly identify those that the classifier was most uncertain about, and (ii) an embedding scatterplot that gives an overview of the cohort's homogeneity, potential sub-cohorts, and outliers.

Along the lines of the attribute ranking, we use a tabular visualization for presenting the item ranking. Initially, The items are ranked in ascending order according to the maximum in the prediction probability vector. The table shows the individual items, the cohorts they belong to, and to which degree this cohort was predicted (see Fig. 1 C).

For the embedding scatterplot, the prediction probability vector described above is reduced to two dimensions with supervised UMAP [24]. Supervised UMAP preserves the structural properties of the data but reduces the overlap of classes. This allows misclassified items to be identified more easily because overplotting by other classes is reduced. Behind the scatterplot marks, we plot a heatmap that shows the cohort with the highest prediction probability in the respective area with the cohort's color (see Fig. 1 D). The heatmap's opacity decreases with the classifier's confidence, i.e., when the probability of the predicted cohort has little difference from the other cohorts. Users can select items in the table or the scatterplot. The selections are synchronized such that outliers and subgroups can be explored from both visualizations.

4 Implementation

Kokiri uses a client-server architecture. The server-side is written in Python, reads the data from a DuckDB [28], and trains a random forest classifier using scikit-learn [26]. Hyperparameters for our random forest that deviate from the default are (a) *balanced* class weights to account for cohorts of different size; and (b) 80% as the maximum amount of attributes to consider at each split to ensure attributes that differentiate the cohorts well are used more likely by the trees. A two-dimensional embedding of the predicted class probabilities is computed with supervised UMAP [24]. The client-side is a web component written in TypeScript. We use the LineUp technique [15] for the rankings of attributes and items and Vega [31] to visualize the performance overview and the embedding of prediction probabilities in a scatterplot. Kokiri is open-source and available on GitHub: https://github.com/jku-vds-lab/kokiri/.

Integration in Coral We have integrated Kokiri in Coral [2], a web-based visual analysis tool to create, refine, and characterize cohorts. After selecting the cohorts of interest, users can select one of multiple operations to apply. We have integrated Kokiri as *Characterize* operation in Coral. Users can use Kokiri and compare the selected cohorts, either by the metadata of the cohorts, such as age, gender, or tumor type, or the genomics data, including mutation status. Kokiri's attribute ranking gives users an overview of the distribution differences between cohorts. Individual attributes can be explored in more detail using Coral's regular operations.

The prototype integration of Kokiri in Coral is available at https://kokiri.jku-vds-lab.at/.

5 Use Case

In this use case, we use the prototype integration of Kokiri in Coral to analyze lung cancer patient cohorts of different races and gender.

The workflow and interactions are demonstrated in the supplementary video. A recent study [25] has shown differences in *KRAS G12C* mutation frequency between these cohorts. The discovery was based on the AACR Project GENIE [1] data and we were able to reproduce it in Coral [2]. With Kokiri, we want to investigate whether there are any further mutational differences of interest. In contrast to the study, which uses version 8, this use case is based on version 9 of the AACR Project GENIE [1]. The dataset includes 112 935 patients for whom metadata such as age, gender, and tumor type are recorded, as well as information on 3 252 genetic mutations. For the comparison in Kokiri, we consider mutations that result in an amino acid change in any of 719 genes that have been identified as tumor-relevant in the Cancer Gene Census [34]. Our initial analysis of the data has shown that there is little mutation data recorded beyond this set of genes.

We start the analysis from a previous session in Coral[1] in which the respective cohorts have already been created. Coral's cohort evolution view shows that the dataset was filtered to non-small cell lung cancer tumor patients and subsequently split into cohorts of Asian, Black, and White patients and further into female and male patients.

We select female and male cohorts for the three races and open Kokiri in Coral with the Characterize operation. As the cohorts are created by split operations, the *Overlap View* only shows a short note that the cohorts do not overlap. In the *Comparison View*, the cohorts can be compared by their metadata or genetic mutations. Comparison using metadata excludes all attributes used to create the cohorts by default. We compare the cohorts by genetic mutations, which starts the training of the classifier and shows intermediate results after the first 25 decision trees of the random forest are trained.

The initial results show that the genes *TP53, EGFR, STK11, KRAS*, and *FGFR4* are the most different between these cohorts. In the overview of the classifier's performance, we can also see that most items are correctly assigned for the White female and male cohorts—the two largest cohorts. However, also large portions of patients from the other cohorts are assigned to these two cohorts (see Fig. 1 B). In the further progression of the comparison, the order of the best-rated attributes changes only slightly. The distribution column of the attribute ranking shows how many patients have a mutation for the genes. As expected, the mutation frequency of *TP53* is high in all cohorts and it is also the most mutated gene in the whole dataset. We can also see that male cohorts have more *TP53* mutations than the female cohorts of the same race. The opposite is observed in the distribution of EGFR mutations, where the mutation is more prevalent in female patients than in male patients of the same race. A much clearer difference, however, is seen in the distribution of *EGFR* mutations between the two Asian cohorts and the others (see 1 in Fig. 1). A difference in *EGFR* mutation frequency between Asian male and female lung cancer cohorts, as well as Asian and White cohorts, was also described in a study by Shi et al. [32]. The frequency of *KRAS* gene mutations mirrors the distribution of *KRAS G12C* mutations described by Nassar et al. [25]. Noticeable is also the distribution of *FGFR4* mutations, where the bars are hardly visible (see Fig. 1 2). We further investigate the distribution of *FGFR4* mutations and see that there is indeed little difference in the number of mutations (see Fig. 3). However, *FGFR4* is sequenced much less frequently for the two Black cohorts. Presumably, there would be no differences between the cohorts if the same amount of data were available. The difference is nevertheless noteworthy because it points to possible issues in the data. There are huge differences in how comprehensively genomics data is collected at the different sites the patients are treated.

To further analyze the trained classifier and the confusion of Asian and Black cohorts with the two White cohorts, we proceed with the

[1] `http://vistories.org/kokiri-use-case`

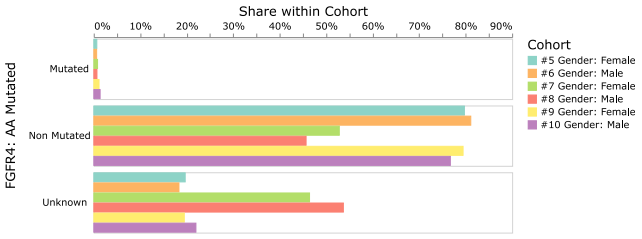

Figure 3: Differences in *FGFR4* mutation in Coral's View operation. Black female and male lung cancer patients have had *FGFR4* sequenced much less frequently than the other cohorts.

Characterization View. The embedding scatterplot shows a distinct cluster for each of the six cohorts, but also many smaller clusters as well as single items. By hovering over one of the smaller clusters (see 3 in Fig. 1) we see that the probability for the assignment to the White female cohort was just 26%. We select the items in this cluster, which also selects them in the item ranking where we can also see probabilities for all other cohorts. Even though the items in the selected cluster originate from different cohorts, the prediction probabilities are very similar, suggesting that their data is similar as well. Ranking the items again by the maximum probability, we see further items that the classifier was uncertain about. This could be a point in the workflow where users leave Kokiri and define new cohorts based on the findings (see Fig. 2).

6 Conclusion

In this paper, we presented Kokiri, a visual analytics approach to compare patient cohorts by their high-dimensional data, explore the driving differences between the cohorts, and characterize the homogeneity and outliers of the cohort. Kokiri can compare multiple cohorts at once and captures combinatorial effects in the data by training a random forest classifier to distinguish between the cohorts.

Kokiri can be applied conceptually and technically to tabular data from other fields, for example, to explain differences between clusters in low-dimensional embeddings. We plan to integrate Kokiri in the Projection Space Explorer [17] for this purpose.

We also plan to enhance the robustness of the classifier and analyze more specific implementations of random forest classifiers. We do think that differences in missing data—as shown in the use case above—can be informative, but want to give users the choice that such differences are not considered. The heterogeneity we saw in the use case, presumably due to different origins of the data, is also a concern when comparing cohorts of multiple datasets. Recent work [29, 39] investigated strategies to enhance random forests to cope with heterogeneous data. Strobl et al. [36] point out a bias in the random forest attribute importances and suggest an implementation that provides unbiased results.

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