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An interactive tool for identifying patient subgroups based on arbitrary characteristics for medical research

Abstract: We present an analysis tool for subgroup identification in medical research based on feature analysis. Our use case is intracranial aneurysms. In the tool, an aneurysm-of-interest's most similar aneurysms within a database are found. Similarity is defined via user-selected parameters, which can be entirely arbitrary. Different interactive outputs and visualizations include a heatmap view and a graph, which give an intuitive feedback to support researchers in the consideration of research questions, which in the present use case often relate to rupture risk analysis. The tool was evaluated with a pilot study and phantom database and received favorable results for its requirements of reliability and appropriate and clear outputs.

Keywords: subgroup selection, feature analysis, intracranial aneurysms.

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1 Introduction

When researching pathologies and their causalities, finding cases with similar features, i.e. identifying certain patient subgroups, is an important step in determining possible risk factors. This is not only relevant for research, but also for clinical practice, as finding similar features of incoming patients to those of already treated ones can support physicians in diagnosis and treatment decisions.

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In this paper, we focus on the application area of intracranial aneurysms (IAs). IAs are pathological deformations of the intracranial blood vessel walls that bear the risk of rupture with the consequence of subarachnoid hemorrhages, which have a high mortality rate [1, 2]. The morphological parameters of such aneurysms can be used as preliminary rupture risk assessment by comparing an aneurysm-of-interest's morphology to that of already treated ones and their outcomes [3, 4]. Metadata and hemodynamics can also be crucial to analyze and possibly give an idea of which patients are at a higher risk [5].

Careful consideration of treatment is particularly important for IAs, as both endovascular treatment and microsurgical clipping may entail unnecessary complications for the patients, especially for aneurysms with a low rupture risk [1]. Rupture risk assessment and subgroup selection therefore are of high value in this area [1, 3, 4, 5].

The identification of such subgroups is not trivial. The complexity of the task rises with the number of both patients and features based on which similarity shall be determined, and as well as with the different kinds of features that shall be considered. With manual selection of similar cases, it is often only possible to select few features that shall match, and these matches often have to be exact or are based on a threshold, making no use of the distances of continuous variables [6, 7, 8].

To make this clinical research task automatic, reliable and capable of answering complex research questions, we present a tool that identifies subgroups of user-defined sizes among a database of patients based on arbitrary, user-selected features, including an additional feature classification.

2 Method

Using Matlab R2020a (MathWorks, Natick, U.S.), we extended a previously developed tool for case-based

reasoning and rupture risk assessment support for IAs based on their morphological parameters [9].

The base tool loads a database of aneurysms and their morphological parameters, normalizes them, and then calculates distances between them, with special consideration given to one aneurysm-of-interest (AOI). The distances represent how similar two aneurysms are based on the input features, here morphological parameters, and thus the most similar aneurysms to the AOI have the smallest distances.

All distances d calculated make use of the Euclidean distance measure:

$$d(p, q) = \sqrt{\sum_{i=1}^n (q_i - p_i)^2} \quad (1)$$

where p and q are features of two aneurysms, i is the current feature and n is the total number of features

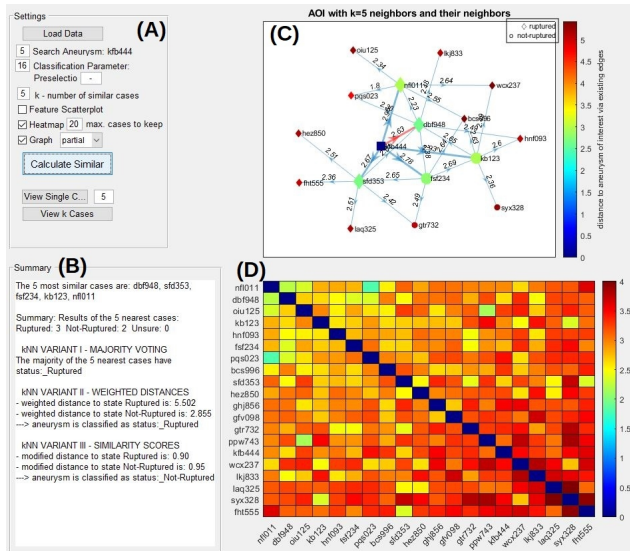


Figure 1: The Graphical User Interface, showing the settings (A) and result (B) panels as well as the graph (C) and heatmap (D) visualization.

Another functionality is classification of rupture status: using the most similar aneurysms, three different k-nearest-neighbor classifiers predict if the AOI's morphology is more similar to that of ruptured or unruptured aneurysms. Since the aneurysms in the database have already been treated, the classification result can support the rupture risk assessment and treatment decision for the AOI.

In this study, we extend the described tool to patient subgroup identification. This includes enabling the use of arbitrary features in the database and no longer limiting similarity calculation to morphological parameters and classification of rupture status. Instead, nominal and numerical features with categorical and continuous values can be part of the database, and classification can be done for

an arbitrary parameter. To further make the tool more suitable and robust for use in clinical practice, it also accounts for missing data values by treating them as non-equal categorical values.

Another new functionality is preselection. Here, the user can select any feature that is part of the database and select a value. Similarity calculation and subgroup identification will then only be executed within the preselected subgroup that has the value in the selected feature.

Other additions include direct feedback to user-defined variables and a more user-friendly and intuitive input via a csv table (e.g. Figure 2) rather than having to manually load multiple individual files.

	A	B	C	D	E	F	G	H	I	J
1	Sex	Age	Date	Diabetes	pAVK	Stroke	Birth control	AspectRatio	CHSurface	EI
2	1: male 2: female			1: Type 1 2: Type 2 3: none	1: yes 2: no	1: yes 2: no	1: yes 2: no			
3	2	76	30.11.2010	3	2	1	2	1,12885909	85,370461	0,2685
4	2	51	16.06.2007	2	1	2	2	0,68864899	111,15713	0,3261
5	2	76	09.12.2009	3	1	2	1	0,922457	116,7903	0,2728
6	1	42	03.01.2013	1	1	2	2	1,32605265	280,4328	0,2489
7	1	46	31.12.2014	3	2	2	2	2,12632752	256,48678	0,2365
8	1	81	28.04.2009	1	2	1	2	0,72081902	74,011244	0,2697

Figure 2: An example database with categorical and numerical metadata and continuous morphological parameters.

All data and features used are anonymized patient data of verified IA diagnoses, acquired during clinical routine at the neurosurgery department at the university hospital in Magdeburg, Germany. Thus we gain image data, manual annotations, and derived data, including metadata and anatomy and pathology and treatment developments as categorical data, as well as hemodynamic and morphological values as continuous data.

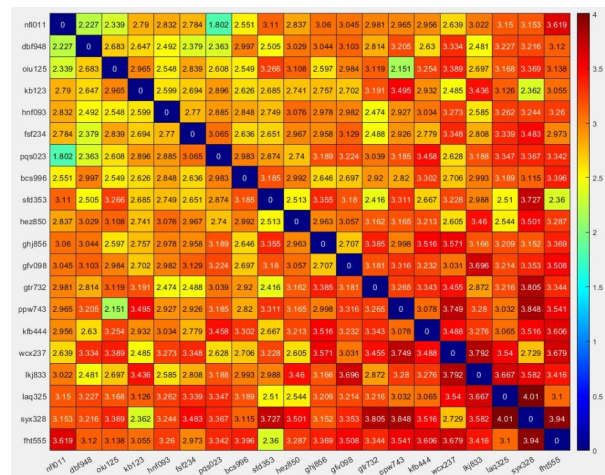


Figure 3: Heatmap visualization. Each entry encodes the distance between the row and column aneurysm.

The Graphical User Interface (GUI), visible in Figure 1, of the tool includes a Settings panel (A) that handles all user input, and three output panels. One output panel is a text field that returns the defined subgroup and patient names, as well

as the results of the classification (B). The two other output panels (C and D) are visualizations that illustrate the similarity relationships of the patients based on their calculated distances across the defined features. The user furthermore has the option to view segmented 3D models of the AOI and its most similar aneurysms, as well as view a scatterplot matrix visualization that gives information about the correlations and information gain of the individual features used for similarity calculation.

The first visualization in the GUI is a heatmap (see Figure 3). Here, each row and each column represents one aneurysm in the database, and each corresponding entry of the heatmap represents the distance between them. The distances are color-coded based on similarity according to a rainbow color map selected by the end users.

The second visualization is a graph (see Figure 4) that illustrates information about distances within the defined subgroup and the aneurysms immediately outside of it as partial graph. Each node is an aneurysm, and the edges between nodes represent their distance. The AOI and its most similar aneurysms are highlighted, and the classification feature is encoded in node shape. Node colors again encode distance to the AOI, using the same color scheme as in the heatmap. The graph can be shown as partial graph (as in Figure 1), or a full graph with all aneurysms in the database and their distance to the AOI being visible (as in Figure 4).

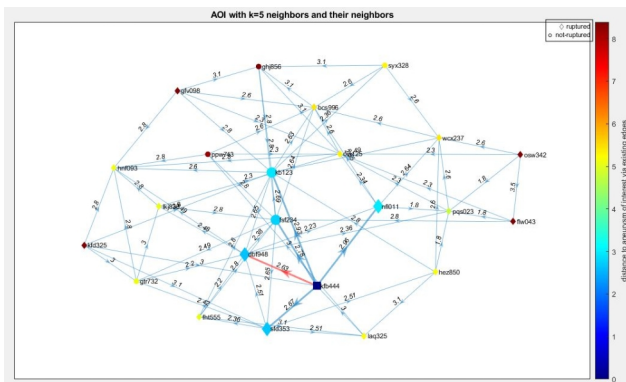


Figure 4: Graph visualization. Each node represents an aneurysm and their connecting edges the distances between them. Only distances between most similar aneurysms are depicted by edges.

3 Evaluation

In dialogue with the end users of the application, three criteria were determined to be crucial for the tool to fulfill:

- *Reliability*: It shall reliably return the most similar cases to the AOI. Similarity shall be defined by the closest possible match within the user-selected features.
- *Appropriate feedback*: The output of the tool shall correspond to the selected features.
- *Clear visualization*: the visualizations shall put the numerical results into context, and it shall be immediately clear which cases are most similar.

To assess reliability, a phantom database of IAs based on true patient data was created by a medical engineer familiar with the field. In this phantom database, the resulting subgroups were known, providing a ground truth to compare the tool's results to.

For feedback and visualization evaluation, a survey was presented to clinicians where they could rate the different components of the tool and its output.

Within the phantom database, several clusters around example AOIs were created to check if the tool identified them as subgroups, and if the order of most to least similar cases would be recognized. There were five AOI with corresponding subgroups. The most similar aneurysm was found reliably for all AOIs. In two cases, one of the aneurysms that belonged to the subgroup was not identified, however, in both of those cases the aneurysm that wasn't assigned to the subgroup was the one that was the least similar to the AOI. The order from most to least similar aneurysm within the identified subgroup was not always correct, but errors within the order were only found towards the least similar ones, never within the most similar aneurysm. Out of the five subgroups, two had perfect orders. In many of the research questions posed during discussion with clinicians, finding the most similar case or a subgroup as a whole was sufficient, rather than finding the specific order of similarity within a subgroup. The tool can therefore reliably identify the most similar aneurysm to an AOI.

The survey was sent to eight medical researchers within the fields of neurosurgery and medical engineering who had experience ranging from one to ten years. This included two practicing doctors, and all participants were familiar with IA research. The participants were asked to rate the different outputs and visualizations on a five-point Likert scale.

Overall, the tool's output was rated as appropriate, with an average of 4.6 out of 5. The heatmap received the best ratings, it was deemed the most helpful and appropriate. The result panel was rated as the least

intuitive, but more participants said they would use it when considering a research question than the graph, though the classifier results need elaboration to be understood. It is important to note that preferences varied significantly between users. This was illustrated when the participants were asked for their favorite of the outputs, where answers were non-conclusive. Overall, the graph was mentioned the most when asked for the most helpful, intuitive and appropriate output, despite the heatmap receiving the most favorable rating.

The tool's evaluation in regards to reliability, appropriate and clear feedback was therefore positive. However, there were limitations.

Especially the graph visualization, while receiving good ratings, was mentioned to be confusing. This is because only the distances between nodes connected by edges have meaning, and even these distances are not always true to scale due to Matlab's internal handling. Additionally, the graph isn't always readable. Completely re-working the graph to make all distances meaningful would be desired, especially in combination with a state-of-the-art dimension reduction that could reduce the distances to a 2D problem.

Another valuable addition could be an overview of the similar and non-similar features of the identified subgroup. Such additions could be made in the results panel.

4 Conclusion

We presented an interactive tool for patient subgroup identification based on arbitrary characteristics. The tool supports a mix of categorical and continuous features and includes a classification feature as well as visualizations of the most similar cases to the case of interest. It can account for missing values and automatically identifies subgroups of patients according to their similarities in user-defined features. It can thus not only find an arbitrary number of cases for a subgroup, but also find the most similar case to the one of interest. It was tested in context of intracranial aneurysms and grants sufficient results to support clinicians in research questions. As features and cases are arbitrary, the tool can be used for any pathology or even outside of the medical research field.

Future work will include a suitable, state-of-the-art dimension reduction to address curse of dimensionality. In this context, a weighting of different parameters shall additionally be enabled as different parameters have different

impacts on research questions [8], which shall also be visualized. This will also lead to an overworking of the graph visualization to give all distances within it a meaning, rather than just the ones encoded via an edge.

Author Statement

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