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Topology-based Clinical Data Mining for Discovery of Hidden Patterns in Multidimensional Data

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ABSTRACT

Clinical trial data is notoriously heterogeneous, incomplete, noisy, and multidimensional. These data may contain valuable information, and novel insights may be encapsulated in various patterns hidden deep within it. While the majority of approaches to mining clinical trial data focus on univariate relationships between a handful of variables, there is a lack of data integration and visualization tools that can improve our understanding of the entire data set.

The aim of this paper is to describe the application of a holistic, topology-based clinical data mining (TCDM) methodology to discover multivariate patterns in clinical trial outcomes. This geometric, data-driven approach allows researchers to identify meaningful relationships in data that would otherwise be left unidentified by traditional biostatistical approaches.

The TCDM methodology was adopted to develop a prototype of software platform, which facilitates the extraction and analysis of low-dimensional representations (data maps) of the full set of interdependent clinical outcomes. The prototype was developed using Python®, R, and SAS®, and combines state-of-the-art machine learning algorithms, statistical tools, and data visualization libraries. Computational experiments were performed on sample studies and included the analyses of both publicly available and proprietary data sets.

We discuss the key steps involved in the TCDM workflow: data integration, generation of topological data maps, visual inspection of interesting data maps, statistical analysis, and interpretation of discovered relationships. The paper concludes that TCDM can be used in all phases of clinical trials for the integrated assessment of drug safety and efficacy as well as for exploratory research.

INTRODUCTION

Clinical trials are designed and conducted with the primary goal of answering pre-specified questions about the safety and efficacy of biomedical or behavioral interventions. A relatively small fraction of the data collected in the course of a clinical trial is typically used by the investigators to demonstrate the efficacy and safety of an intervention. However, clinical trials generate significant amounts of data that can subsequently be explored using data mining techniques to identify unexpected factors that influence the outcomes of interest and lead to new hypotheses.

Performing comprehensive analysis of a clinical trial dataset to improve our understanding of the entire dataset can be challenging. While the majority of approaches to mining clinical data focus on univariate relationships between a specific outcome and a few predictive variables, there is a lack of data integration and visualization tools available that can improve our understanding of the entire dataset. Examining clinical data with a focus on a specific single outcome in isolation from other factors may lead to an incomplete, or even misleading, view of complex settings. Standard biostatistical methods are used as technical tools to confirm (or refute) the hypotheses generated by an investigator and, hence, rely on the researcher's ability to develop solid hypotheses. However, in the case of clinical trial datasets, the number of possible hypotheses to explore is very large, and it can be very difficult to select the most valuable.

In this paper, we describe the application of a novel holistic approach – topology-based clinical data mining (TCDM) – to discover multivariate patterns in clinical trial outcomes. TCDM allows an investigator to extract comprehensive topological maps of the data without first having to develop a model or hypothesis. A topological map provides a compressed, graphical representation of a multidimensional set of interrelated clinical outcomes. It zooms in on robust, geometric properties of the data that do not change under "small" perturbations or deformations. The robust data patterns and relationships, which remain invariant under (properly defined) small perturbations of the data, are referred to as topological properties. This focus on topological properties is what makes TCDM less sensitive to noise and, thus, helps to identify and visualize the key features of a clinical trial dataset despite the risk of errors, irregularities or missing values occurring in the data.

A group of related mathematical methods that are collectively known as topological data analysis (TDA) has recently been applied in different branches of bioinformatics, epidemiology, neuroscience, and oncology with promising results. TDA is a rapidly expanding field that is being actively developed by research teams in leading academic centers both in the US and Europe, including renowned establishments such as Stanford, Duke, UPenn, Princeton Neuroscience Institute, INRIA (France), among many others. TDA methods are based on the underlying idea of using topology – the mathematical study of qualitative properties of space and spatial relations – to detect and display hidden robust relationships in complex datasets. Thus far, this idea has been successfully applied to discover a coherent subgroup of breast cancer patients with 100% survival, which is characterized by a unique molecular signature [1]; to reveal unexpected statistically significant patterns in traumatic brain injury and spinal cord injuries [2]; to distinguish resilience to malaria in human populations [3]; and to identify in silico drug leads from a diverse library of compounds [4].

The paper is organized as follows. In Section 2, the mathematical foundations of the topological approach are briefly introduced. First, we explain what information can be encoded in a topological data map and how to construct the latter. We then discuss methods of pre-processing an original clinical trial dataset obtained in CDISC SDTM or ADaM format as a means of preparing a table of outcomes – a synthetic dataset used as an input to the TCDM workflow. Next, the general TCDM workflow is outlined. The section concludes with a short description of a software prototype that provides a computational environment in which researchers can perform data mining experiments on clinical datasets. Section 3 describes a case study in which TCDM was applied to a sample clinical study. We examine the implementation of the full cycle of TCDM methodology in practice, from raw data preprocessing to the interpretation of the findings. We conclude by describing some of the potential areas in which TCDM can be applied in clinical research.

2. METHODS

2.1. TOPOLOGY AND DATA MINING

Topology is a field of mathematics that deals with the properties of objects that remain invariant under continuous deformation. Imagine a surface that is made of very thin and elastic material. You can bend, stretch or crumple the surface any way you like; however, you can not tear it or glue any parts of it together. As you deform the surface, it will change in many ways, but some properties will remain the same. The idea that underpins topology is that some geometric properties depend not on the exact shape of an object, but rather on how its parts are combined.

As a simple example, consider geometric figures on the plane representing the numerical digits: 0, 1, 2, …9. For a topologist, various representations of zero are equivalent since they can all be transformed into each other in a continuous way without cutting or gluing (Figure 1 a-d). It is possible to change the size, thickness, or slope of the digit 0 by a continuous deformation; however, one property remains invariant: The object separates the plane into two regions, interior, and exterior. At the same time, 0 is not topologically equivalent to 1 or 8: 1 does not encircle a region, and 8 contains two holes (Figure 1e). The topological classification of the digits results in the following six classes:

{0}, {1}, {2, 3, 5, 7}, {4}, {6, 9}, {8}.

The digits in any of the classes are topologically identical, but no two digits that are taken from distinct classes are the same.

The number of holes in a geometric object is a basic topological property. Another significant property is connectedness. Intuitively, an object is connected if it consists of single piece. For example, the curve representing 0 is connected; if one removes any two points from it, it will become disconnected. Pieces of a disconnected object that are, themselves, connected, are referred to as connected components. In the mathematical study of topology, all of these intuitive concepts are examined on a rigorous basis and generalized to higher dimensions.

a) b) c) d) e)

Figure 1. Different representations of the digit 0 (a-d) are topologically equivalent. All of them share a common topological property: They divide the plane into an interior region and an exterior region. The digit 8 (e) is not equivalent to 0 since it encloses two internal regions.

2.1.1. HOW CAN TOPOLOGY FACILITATE THE UNDERSTANDING OF COMPLEX DATA?

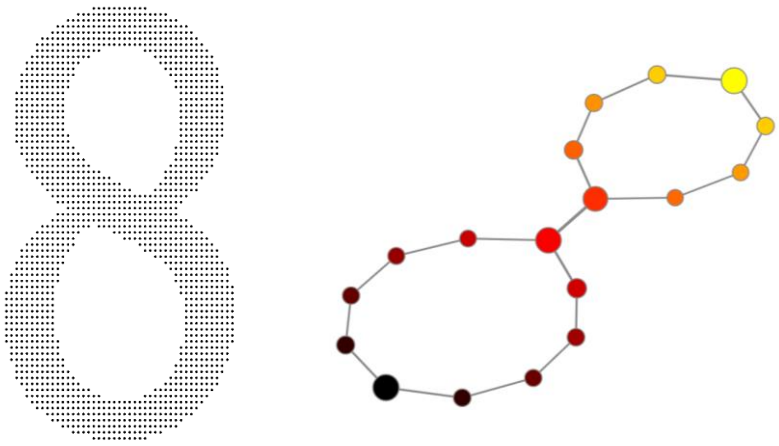
Topology deals with abstract mathematical entities, such as curves and surfaces, that consist of an infinite number of points. In practice, however, all datasets are necessarily finite. Recently, a new field has emerged at the crossroad of topology and data science. Topological data analysis (TDA) aims to extract topological data, i.e., qualitative information, from finite sets of data points. It involves exploring datasets (viewed as finite clouds of points in a multidimensional space) at multiple scales or resolutions, from fine- to coarse-grained. Given a complex dataset, TDA is used to extrapolate the underlying topology and build a compressed, yet comprehensive, topological summary of the dataset. TDA exploits a variety of methods and algorithms stemming from computational topology and geometry, cluster analysis, statistics, and data mining. For detailed expositions of the mathematical theories that underpin TDA together with some applications in biology see [5-7] and the references therein.

Topology was originally developed to distinguish between the qualitative properties of geometric objects. It can be used in conjunction with the usual data-analytic tools for the following tasks:

1. **Characterization and classification.** Topological features succinctly express qualitative characteristics. In particular, the number of connected components of an object is of importance for classification.
2. **Integration and simplification.** Topology is focused on global properties. From the topological perspective, a straight line and a circle are indistinguishable locally; however, they are not equivalent if they are considered as a whole. Topology offers a toolbox by which local information about an object can be integrated into a global summary. Thus, topology can provide a researcher with a natural “big-picture” view of complex, multidimensional data.
3. **Features extraction.** Topological properties are stable. The number of components or holes is likely to persist under small perturbations or measurement errors. This is essential in data mining applications because real data is always noisy.

2.1.2. WHAT IS A TOPOLOGICAL DATA MAP?

In Figure 2a, the digit 8 is represented as a granular cloud, consisting of hundreds of dots. Every dot corresponds to a pixel and can be uniquely determined by its coordinates (x_1, x_2)on a two-dimensional grid. Suppose we are only interested in the fundamental qualitative properties of this geometric dataset and do not care about finer details, such as its exact shape or the variation in the intensity of the pixels. Using topological methods, we can build a compressed representation of the dataset in the form of a topological data map (Figure 2b). It contains only 18 nodes and 19 edges and captures the essential feature of the original figure; namely, that the latter consists of two loops.



a) b)

Figure 2. The digit 8 as a "granular dataset" (a) and its topological map (b)

A topological data map is a graphical representation of a dataset in which each node denotes a specific subgroup of data points. There is an edge between two nodes if, and only if, the respective subgroups of data points share common elements. A topological data map retains the relevant information about the dataset in a compact and efficient manner. One well-known class of topological maps is that of subway maps, which preserve the order of subway stops on each line and the interconnections between different lines.

In the context of clinical research, the dataset under study is typically a table of outcomes in a particular clinical trial. The table rows correspond to the individual participants in the clinical trial, and columns contain information on specific outcome measures of interest such as lab tests, vitals, questionnaires, etc. Given a table of clinical outcomes, two types of parameters are required to generate its topological data map. The first of these is a dimension reduction projection, a function that is used to stratify patients into subpopulations. The second is a distance function that measures the proximity between patients. The distance function makes it possible to split each subpopulation into clusters of related patients with similar outcomes.

To be considered for further analysis, a topological data map should meet certain requirements. Namely, it should:

- accurately represent the original dataset;
- eliminate the features of the dataset that are not relevant to the purpose of the study;
- reduce the complexity of the features that are represented on the data map;
- be insensitive to small noise such as errors of measurement.

When the suitable projection, distance, and scale of a topological data map are selected, some information will be eventually lost from the table of outcomes. For example, individual patients will be

combined into clusters. The goal of TCDM is to create a data map that highlights the most significant and meaningful features of the original dataset while secondary unimportant features are eliminated from the constructed visualization.

2.2. PREDICTORS AND OUTCOMES IN TCDM

A very common situation in statistics occurs when the distribution of an outcome (or response variable) is related to one or several predictors (or explanatory variables). A standard approach through which researchers study the relationship between the predictor and the outcome is the application of a suitable statistical model. The model selection is determined by the type of the predictor and outcome (quantitative, binary, categorical, etc.) and often depends on additional assumptions concerning the distribution of the outcome. For example, linear regression is often used when both the predictor and the outcome are quantitative (e.g., BMI and blood pressure); Fisher's exact test or χ^2 test can be applied when both variables are binary or categorical (e.g., gender and ECOG score); and logistic regression can be a suitable model for evaluating the relationship between a quantitative predictor and a binary outcome. The application of such approaches can be problematic in the context of complex settings that have multivariate outcomes; i.e., when many related outcomes are recorded for the same individuals.

TCDM is naturally designed to assist researchers to deal with multivariate heterogeneous outcomes in such a manner that it is possible to study several related outcomes of different types (quantitative, ordinal, categorical) together. An incomplete list of multivariate outcomes includes a series of repeated evaluations of some response variable over time; simultaneous evaluations of different, but potentially correlated biomarkers (e.g., levels of serum creatinine, blood urea nitrogen, and neutrophil gelatinase-associated lipocalin as a means of evaluating kidney function); and questionnaire data to assess patient's general health or quality of life, etc.

TCDM takes a panel of personalized outcomes of a clinical trial as its input. More specifically, the outcomes panel is a synthetic dataset that consists of row vectors $\boldsymbol{x} = (x_1, x_2, \dots, x_n)$, with each vector corresponding to a single participant. Here, x_i denotes the i-th outcome reading for the participant labeled $\boldsymbol{x}$. Outcomes are either calculated or directly extracted from original "raw" datasets that were collected during the course of the clinical trial and are presented in the CDISC SDTM or ADaM format.

From the clinical research perspective, an outcome is an evaluation of some aspect of a participant's health that results in a recorded datum. There is more than one way of classifying clinical trial outcomes (see Table 1). Depending on the research goal, it is useful to differentiate between outcomes linked to biomarkers and clinical outcome assessments (COA) (see [8]). A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [9]. A COA is any assessment that may be influenced by human choices, judgment, or motivation, and it may provide either direct or indirect evidence of the benefits associated with a given treatment. In contrast to biomarkers, which are determined using automated processes or algorithms, COAs depend on a participant's or clinician's implementation, interpretation, and reporting of the data.

Table 1. Classifications of clinical trial outcomes.

Clinical Trial Goal	Specialty	CDISC Domain	Data Type	Variable Type
Safety Efficacy Effectiveness Quality of life	Allergy/Immunology Cardiology Endocrinology Gastroenterology Hematology/Oncology …	AE EG LB QS VS …	Cross-sectional Longitudinal Aggregate	Quantitative Categorical Ordinal Interval

It is important to note that specific research objectives require customized configurations of outcomes panels. In this paper, we consider several different outcomes panels derived from the same clinical trial dataset to study various aspects of the disease.

2.3. DISTANCES

Distance functions (or simply, distances) is a tool that is used in TCDM to measure the similarity between the data points that belong to a given outcomes dataset. A dataset endowed with a distance becomes a metric space that can be studied using geometric and topological methods. In mathematics, a distance on a set $\boldsymbol{X}$ is a function $d(\boldsymbol{x}, \boldsymbol{y})$ that quantifies proximity between each pair $(\boldsymbol{x}, \boldsymbol{y})$ of elements of $\boldsymbol{X}$. The most popular and intuitive example is, of course, the Euclidean distance:

$$d(\boldsymbol{x}, \boldsymbol{y}) = \sqrt{(x_1 - y_1)^2 + (x_2 - y_2)^2 + \ldots + (x_n - y_n)^2}$$

This measures the length of the straight-line segment between points $\boldsymbol{x} = (x_1, x_2, \ldots, x_n)$ and $\boldsymbol{y} = (y_1, y_2, \ldots, y_n)$ in an n-dimensional Euclidean space. In many applications, the underlying set, $\boldsymbol{X}$, does not have an Euclidean structure or, even it if does, the Euclidean distance is not the most suitable for the problem at hand. Below, we give several examples of distances that can be applicable for the configurations of outcomes tables that typically arise in TCDM.

Normalized Euclidean Distance

The normalized Euclidean distance is represented by:

$$d(\boldsymbol{x}, \boldsymbol{y}) = \sqrt{\left(\frac{x_1 - y_1}{s_1}\right)^2 + \left(\frac{x_2 - y_2}{s_2}\right)^2 + \ldots + \left(\frac{x_n - y_n}{s_n}\right)^2}$$

where s_i is a scaling parameter, which is usually the standard deviation of x_i and y_i over the sample set.

The normalized distance helps to avoid the effect of units in which different outcomes are measured. Normalization should not be applied when all outcomes are expressed in the same units, since doing so may dramatically reduce large effects (when an outcome with a large contribution is divided by a large s_i).

Manhattan Distance

The Manhattan distance is represented by:

$$d(\boldsymbol{x}, \boldsymbol{y}) = |x_1 - y_1| + |x_2 - y_2| + \ldots + |x_n - y_n|$$

It is more robust than the Euclidean distance because it attributes less weight to an outlying value of any particular outcome. It is also better suited to high-dimensional vectors.

Hamming Distance

Hamming distance is one of many proposed distances for purely categorical data. It is defined as follows:

$$d(\boldsymbol{x}, \boldsymbol{y}) = \frac{n - m}{n}$$

Here, m is the number of matches between vectors $\boldsymbol{x}$ and $\boldsymbol{y}$; i.e., the number of outcomes, i, such that $x_i = y_i$, and n is the total number of outcomes in the table.

The situation becomes more complex when several outcomes of different types (quantitative, binary, categorical) are combined in a single outcomes table. In the case of mixed data, none of the distances described above are directly applicable, and one needs to use a more general measure of distance, such as the Gower distance [10]. We will not employ the more complex constructs of distances in this paper.

2.4. PROJECTIONS

A projection function (or simply, a projection) is a numerical function defined on data points. In the TCDM framework, projections are used to extract relevant information from a table of outcomes and to summarize this information in the form of a topological data map. In some regards, TCDM projections are very similar to geographic map projections. Their general characteristics are as follows:

- All projections represent the original data in a compressed form and, therefore, distort the data;
- different projections highlight different features of the data (at the expense of other features);
- there is no limit to the number of projections that can be applied to a given dataset.

TCDM projections can be roughly divided into two classes: domain-dependent and universal projections. Domain-dependent projections are defined in terms of the dataset under study. For example, in the table of outcomes that represents complete blood count readings at the end of a given study, the contents of a specific column (e.g., hemoglobin or white blood cells) can be used as a projection. In contrast, universal projections do not depend on the structure or composition of a dataset and can be derived from statistics, computational geometry, pattern recognition, signal analysis, etc.

While, in principle, an arbitrary mathematical function can be used in TCDM as a projection, in practice, some functions lead to representative and easily interpretable data maps more often than others. We present below a few basic examples of universal, geometric projections that have proven to be helpful in various settings. In what follows, $\boldsymbol{x_1}, \boldsymbol{x_2}, \ldots, \boldsymbol{x_N}$ denote the n-dimensional vector rows corresponding to data points, $\boldsymbol{X}$ is the $N \times n$ matrix (table of outcomes) composed of these rows, $\boldsymbol{x}$ is an arbitrary data point, and $d(\boldsymbol{x}, \boldsymbol{y})$ is a distance function on the dataset.

$\boldsymbol{L_p}$-centrality estimator projection

$\boldsymbol{L_p}$-centrality estimator is defined by the following expression:

$$M_p(\boldsymbol{x}) = \left(\frac{1}{N} \sum_{i=1}^{N} d(\boldsymbol{x}, \boldsymbol{x_i})^p \right)^{1/p}$$

The parameter $p \geq 1$ controls the relative contributions of large terms in the sum. In the case $p = 2$, the estimator assumes the minimal value on the spatial average of vectors $\boldsymbol{x_1}, \boldsymbol{x_2}, \ldots, \boldsymbol{x_N}$:

$$\arg\min_{\boldsymbol{x}} M_2(\boldsymbol{x}) = \frac{1}{N}\sum_{i=1}^{N} \boldsymbol{x_i}$$

Hence, $M_2(\boldsymbol{x})$ measures the proximity of a data point to the spatial average or 'spatial center' of the dataset. In the case $p = 1$, $M_1(\boldsymbol{x})$ is simply an averaged sum of the distances from $\boldsymbol{x}$ to the data points. It is minimized by the so-called spatial median, which is also an important statistical estimator of location. The $\boldsymbol{L_p}$-centrality estimator coincides with the usual median in the one-dimensional setting (i.e., when data points are scalars), but, in the general case, its analytic solution is not known in closed form. However, the explicit central point is not needed to compute $M_p(\boldsymbol{x})$. This estimator provides an intuitive, intrinsic measure of centrality (higher values of $M_p(\boldsymbol{x})$ imply that $\boldsymbol{x}$ is located further away from the 'dataset center'). It can also be used for categorical and mixed data.

PC scores projections

Principal component analysis (PCA) is a statistical procedure that provides a series of best linear approximations for a dataset in which there are many correlated variables. PCA aims to reduce the dimensionality of the dataset while retaining as much of the variation that is present in the data as possible. For a thorough outline of the PCA theory and its various applications see [11].

Let's assume that the data matrix $\boldsymbol{X}$ is filled with purely quantitative values and the columns of $\boldsymbol{X}$ are centered (i.e., the sample mean of each column has been shifted to zero). We also assume that the data set is endowed with the usual Euclidean distance. By definition, the first PC score vector is the N-dimensional vector $\boldsymbol{Xw_1}$, where $\boldsymbol{w_1}$ is the n-dimensional unit vector, which maximizes the sample variance of $\boldsymbol{Xw}$ in comparison to all other unit vectors:

$$\boldsymbol{w_1} = \arg\max_{d(\boldsymbol{w},\boldsymbol{w})=1} (\boldsymbol{Xw})^T \cdot (\boldsymbol{Xw})$$

$\boldsymbol{w_1}$ is referred to as the first loading vector. The coordinates of the vector, $\boldsymbol{Xw_1}$, are the first PC scores and they correspond to the respective data points. We define the first PC score projection on a data point $\boldsymbol{x}$ as the scalar product of $\boldsymbol{x}$ and $\boldsymbol{w_1}$:

$$t_1(\boldsymbol{x}) = \boldsymbol{x} \cdot \boldsymbol{w_1}^T$$

It can be shown that the first PC score vector inherits the maximum possible variance from $\boldsymbol{X}$. One can then progress to successively define the second, third, … n-th PC score vectors. In combination, PC score vectors provide best linear approximations to $\boldsymbol{X}$ of any rank. Figure 3 (a-b) shows the PC scores property to compress data and capture the maximum amount of variance on for a dataset representing a digital image of Baltimore City Hall.

a) The original image contains 877 x 585 pixels.

b) Projection on the first PC

Figure 3. Data compression by PCA. Baltimore City Hall.

The kernel density estimator projection

The kernel density estimator (KDE) is defined as follows:

$$\widehat{f_h}(\boldsymbol{x}) = \frac{1}{Nh^n} \sum_{i=1}^{N} K\left(\frac{d(\boldsymbol{x}, \boldsymbol{x_i})}{h}\right)$$

where h>0 is the bandwidth, and the kernel function, K, is a symmetric density. Usually K is the standard normal density function:

$$K(t) = (2\pi)^{-n/2} \exp\left(-\frac{t^2}{2}\right)$$

KDE is a generalization of the well-known histogram density estimator, where n-dimensional bins are replaced with smoothed 'bumps' centered at data points. The bandwidth, h, is a free smoothing parameter that determines the width of the 'bumps.' KDE is a statistical tool that can provide valuable information on the data distribution properties, such as skewness and multimodality (see [12]). Note that the multivariate KDE is not advised for small datasets in which the number of outcomes is greater than 5 (the required dataset size to ensure that the relative mean squared error is less that 0.1 is 768 for $n = 5$ and 2790 for $n = 6$). For further details, see Chapter 4 in [12].

2.5. TCDM FRAMEWORK

This section outlines the general TCDM workflow; i.e., how topological data maps of clinical trial datasets are generated and studied. The diagram presented in Figure 4 depicts the main stages of the TCDM. The process by which data maps are constructed consists of outcomes table preparation, selection of suitable distance and projection functions to reduce the outcomes table dimension, stratification of clinical trial participants into subgroups, partial clustering of participants within each subgroup, and topological features extraction based on the clustering results.

2.5.1. DRAWING A TOPOLOGICAL DATA MAP

To initiate the TCDM process, two synthetic datasets need to be determined: Outcomes and Predictors (see Section 2.2). In each dataset, a row represents a unique participant within the clinical trial, while the columns represent either observational variables (outcomes), such as safety and efficacy biomarkers, or predictors, such as demographic attributes, medical history, interventions, etc. Extracting the outcomes and predictors from the clinical trial data is a key part of the data pre-processing task. Depending on the objective of the TCDM research and the structure of the data, this task may also involve data cleaning and editing, transformation (e.g., conversion of categorical values into numerical data), normalization, and integration.

As described in Section 2.4, a projection function transforms data points (high-dimensional vector rows of outcomes table) to scalar numeric values. It is used to stratify participants into subgroups. The range of projection values is divided into several overlapping intervals. All individuals that are mapped by the projection to a specific interval define a subgroup of the total population of the clinical trial. The collection of subgroups constitutes a stratification grid of the dataset.

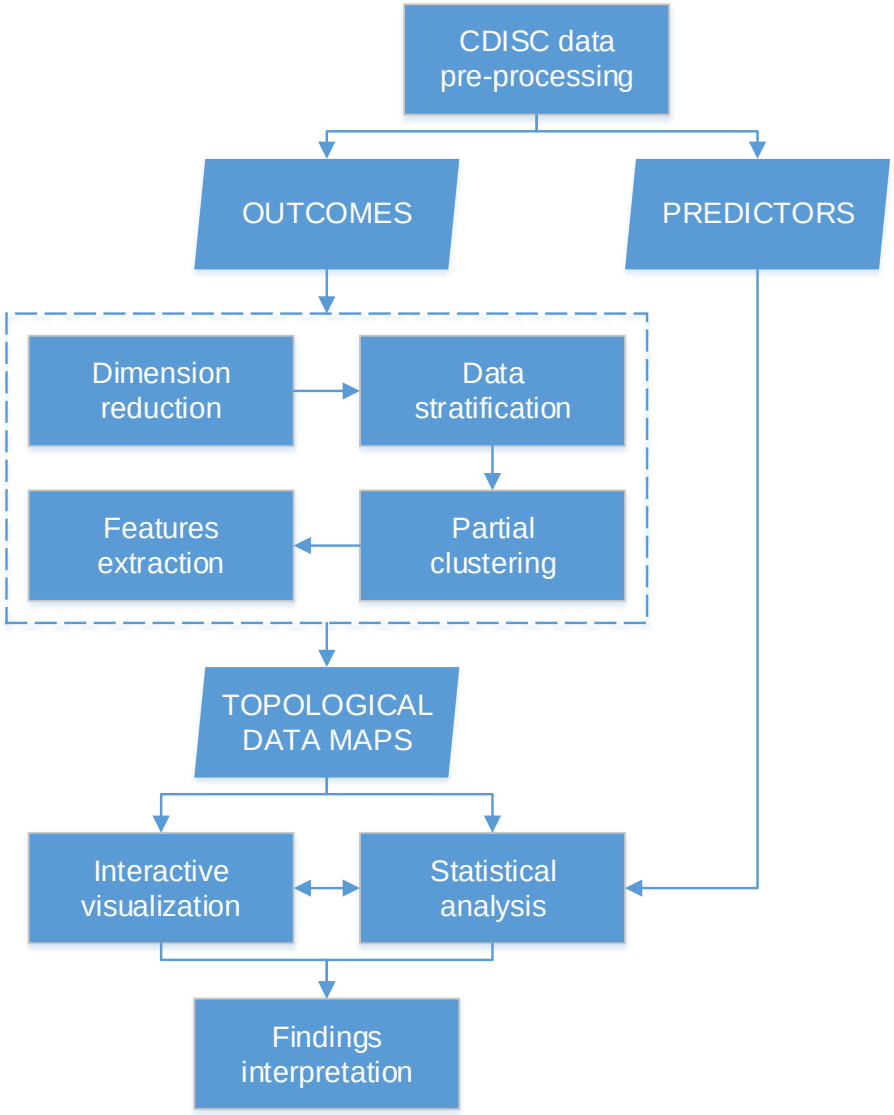


Figure 4. TCDM methodology workflow

The data stratification is controlled by several parameters, including the number of intervals, overlap of two adjacent intervals, balance (to quantify the degree of uniformity of the distribution of the data points across the stratification grid), etc. When one selects a relatively small number of intervals, one gets a coarse view of the data in which many individuals will be placed into a single subgroup within the stratification grid. A relatively large number of intervals lead to a fine-grained stratification, with just a few individuals in each subgroup. The number of intervals is determined according to the level of detail the researcher requires to be reflected in the topological representation of the dataset. Intuitively, the number of intervals controls the scale of a data map. A direct analogy between a data map and standard geographic maps can be drawn in that small-scale maps, such as those of the entire world or continents within it, show large areas of the Earth within a small space, while large-scale maps, such as city plans, show small areas in more detail.

After the data stratification is completed, each subgroup is clustered. Clustering is achieved by grouping individuals into even smaller subgroups (or clusters) such that the individuals in the same cluster have more features in common than those in other clusters. The similarity of individuals is determined by

a distance function (see Section 2.3). The clustering task is solved by one of a whole family of algorithms that differ in terms of how the distances are computed. Apart from the choice of the distance function, one needs to specify the notion of what constitutes a cluster and how to identify such a cluster. The most appropriate clustering algorithm for a given dataset depends on the type of data (continuous, discrete, categorical, mixed, etc.) and often needs to be chosen experimentally.

During the final stage of data map construction, information about the clustering structure of all the subgroups that constitute the stratification grid is assembled and presented in the form of a graph. Since the dataset is stratified into overlapping subgroups, each data point can appear within several clusters. In the final graph, nodes correspond to clusters, and edges connect the nodes for which the respective clusters share common data points. Figure 5 illustrates how a data map is constructed for a simple two-dimensional geometric dataset.

2.5.2. THE USE OF SOFTWARE FOR DATA MAP EXTRACTION AND ANALYSIS

The TCDM methodology was adopted to develop a prototype of a software platform that provides a computational environment in which researchers can perform data mining experiments on clinical datasets. The prototype implements the logic of the TCDM workflow (see Figure 4) and consists of a variety of scripts developed using Python, R, and SAS. It relies on state-of-the-art machine learning algorithms, statistical tools, and data visualization libraries.

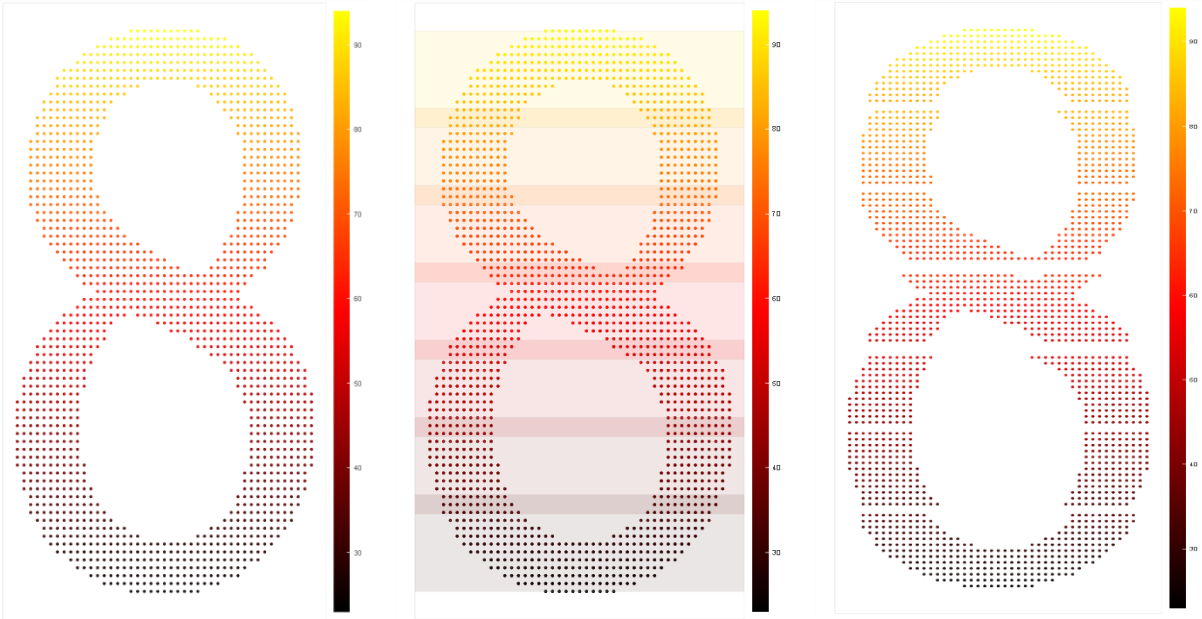
The transformation of 'raw' clinical trial data into predictors and outcomes datasets is performed by a dedicated SAS script. To launch the analysis, the researcher sets up the ranges of parameters required to construct the topological data maps that represent the outcomes table. The parameters include projection, distance, stratification grid, and others. Each combination of parameters produces a different data map. The resulting collection of data maps provides researchers with an opportunity to look at the dataset from different perspectives.

In the next step, the computing platform generates a large number of topological data maps (from a few thousands to several million) that correspond to the various combinations of parameters within the originally defined ranges. The ‘features extraction’ proprietary algorithm was developed to reduce the massive volume of topological data maps generated for a pre-defined set of parameters into a more narrow set of data maps that present meaningful insights. In other words, the features extraction module filters the most representative and stable data maps and reduces the collection size of the data maps from thousands, or even millions, to just a few dozen.

After a topological data map is extracted, the researcher visually explores the data map with the purpose of discovering interesting subgroups within the data. These subgroups can be further studied by utilizing standard statistical methods to determine the predictors that may be responsible for the similarity of responses observed within the identified subgroup of clinical trial participants.

Each node on a topological data map corresponds to a subgroup of clinical trial participants while, at the same time, nodes that share the same participants are connected. The size of the node illustrates the number of participants, and the width of the line connecting two adjacent nodes indicates the number of individuals in common. A node color depicts the median value of the projection for the group of individuals constituting the node.

The interactive visualization module provides researchers with an opportunity to manually perform a visual inspection of a topological data map that they can analyze to identify regions of interest. For example, the nodes that form Y-shapes or loops might be of interest for further research. In addition, isolated components or highly concentrated groups of nodes that form communities may indicate meaningful relationships in the outcomes dataset. While performing a visual inspection, the researcher can also re-color the data map in accordance with the median value of an outcome or predictor selected from the corresponding datasets generated at the beginning of the TCDM workflow. The use of color codes may highlight how a subgroup of individuals represented by a given region of the data map might be different from the rest of the clinical trial participants.



a)

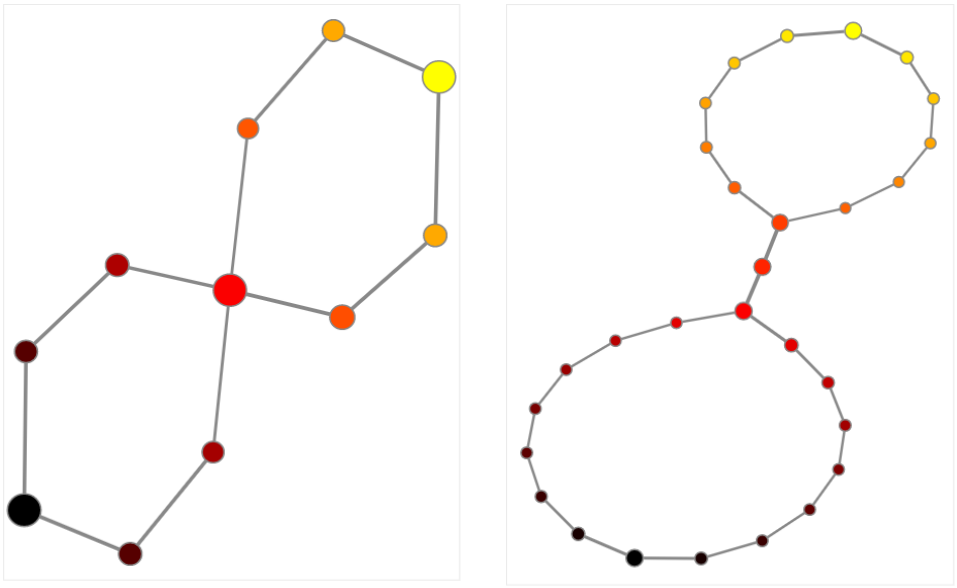
The original two-dimensional dataset on the plane. The projection maps a data point to its y-coordinate

b)

The stratification grid contains seven overlapping subgroups. The narrow pink horizontal bands contain points that are shared by two subgroups

c)

Clusters within subgroups



d)

A data map corresponding to the dataset stratification into 7 subgroups (a coarse-grained view of the dataset).

e)

A data map corresponding to the dataset stratification into 20 subgroups (a detailed view of the dataset).

Figure 5. Drawing a topological data map of a simple dataset

The researcher can select any region of the data map that exhibits interesting geometric properties to perform a further statistical analysis. After running statistical tests, a table of predictors with the corresponding p-values can be calculated to determine if the distribution of the predictors for the selected subgroup of participants is different to that of the rest of the study population. If the desired significance level of any predictor is found to be significant, the researcher can construct a histogram that represents normalized frequency distributions of the predictor for both the individuals in the selected region of the map and the rest of the population. At any time, interesting findings can be bookmarked and documented for further in-depth analysis by a clinical study group.

3. RESULTS

In this section, we demonstrate how TCDM can be applied to sample clinical study that was designed to test two treatment arms over two treatment periods. The total study population included 89 patients. We concentrated mainly on the efficacy findings of the sample study, which were represented by a composite efficacy score and the panel data from the Patient Health Questionnaire (PHQ-4). The observational data was collected at baseline and at weeks 8, 16, 24, 48, 72, and 96 during the course of the study.

3.1. PREDICTORS AND STATISTICAL TESTS

We selected 10 univariate characteristics of the study patients as primary predictors for the quantitative evaluation of any association between these characteristics and the study outcomes (Table 2). 4 predictors corresponded to basic demographic data (age, sex, race, and study arm), 4 variables summarized exposure attributes for each treatment period, and the remaining 2 predictors captured the aggregated characteristics of medical history records.

Table 2. Predictors

Variable Name	Interpretation
SDMAGE	Age
SDMSEXN	Sex
SDMRACEN	Race
SDMARMN	Study arm
SEXDUR1	Duration of the first treatment period in days
SEXDOSNT1	Total number of doses taken in the first treatment period
SEXDUR2	Duration of the second treatment period in days
SEXDOSNT2	Total number of doses taken in the second treatment period
SMHONUM	Number of reported ongoing medical conditions
SMHBNUM	Number of reported past medical conditions

For the purpose of the statistical analyses, we distinguished between continuous, mixed, binary and categorical (non-binary) univariate predictors according to the variable type. Continuous predictors were examined using the traditional two-sample Kolmogorov-Smirnov test. This method verifies whether two data samples were obtained from the same distribution. The test assumes that the underlying distributions are continuous (no ties in the variable's values are allowed). In the case the distributions were not entirely continuous, we used a bootstrap version of the Kolmogorov-Smirnov test that has previously been found to yield accurate results in the more general setting (see [13]). To examine the statistical association between two samples the categorical data, we used Fisher's exact test and χ^2 test for the binary and non-binary categorical variables respectively.

3.2. ANALYSIS OF TOPOLOGICAL DATA MAPS

We analyzed the two data maps obtained for various subsets of efficacy outcomes. In each case, the L_p-centrality estimator was used as a projection (see Section 2.4). This projection allowed us to evaluate and visualize the stratification of patients according to their proximity to the 'spatial center' of the population. The 'spatial center' can be viewed as a generalized multivariate version of the population average or median.

3.2.1. A COMPOSITE EFFICACY SCORE

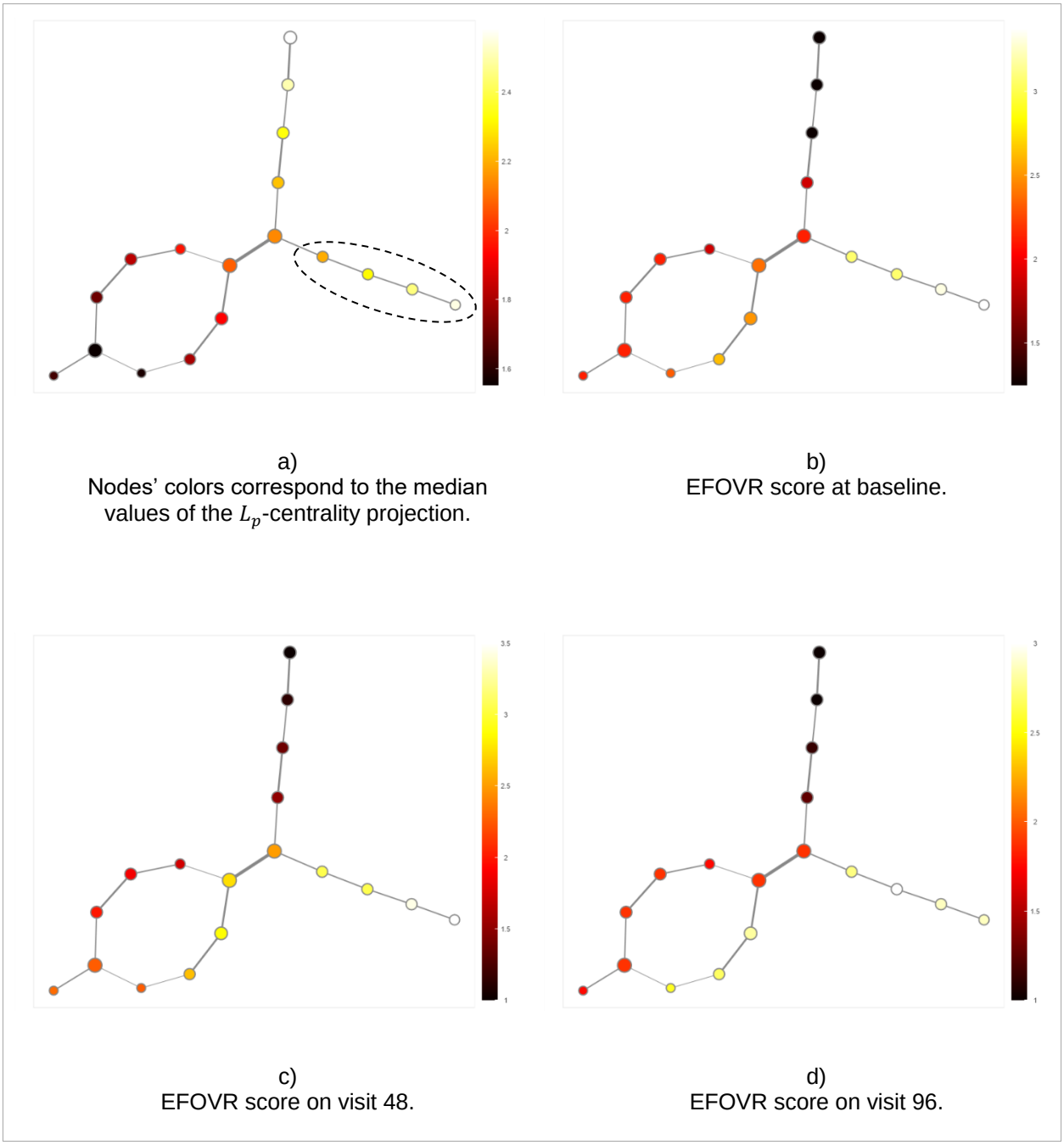
We first considered a table of outcomes that contained measurements of the overall efficacy score (EFOVR). The EFOVR is a continuous variable that can assume values that range from 1.0 to 4.0. In the current sample study, each outcome corresponded to a single measurement of the score at baseline and 6 subsequent visits. This resulted in the development of a 7-dimensional dataset that was composed of vector rows of EFOVR readings at various times.

Figure 6a represents a topological data map of the table of outcomes containing 49 patients whose score records were available for all visits (at this stage of the experiment we included data from only 49 of the 89 patients because we discovered missing values in the remaining 40 patients' data). Note that the 'tines' of the fork-like part of the graph corresponded to patients that exhibited higher projection values than those observed in the rest of the population. This implied that the patients in the tines were located further away from the population spatial center (in terms of the distance between the vectors of the EFOVR readings). We recolored the data map according to the value of the score at baseline and observed that one of the tines was predominantly populated by patients with high scores (median EFOVR ≥ 3.0) while patients in the other tine had consistently lower scores (median EFOVR ≤ 2.0), see Figure 6b. This pattern persisted for EFOVR records at other visits. Moreover, as the time progressed, the median scores of patients with relatively high scores at baseline continued to increase, and the median scores of patients with relatively low scores at baseline decreased; so the discrepancy in outcome values between patients occupying different tines became even more pronounced (Figure 6 c-d). Finally, we recolored the data map according to the frequency of adverse events and found that the patients located in the tine with high EFOVR readings also had substantially higher AE frequency than the patients in the other tine.

We grouped together all patients from the 'higher EFOVR' and 'higher AE frequency' tine (9 patients) and compared them with the rest of the population using non-parametric statistical tests on the set of predictors defined in Section 3.1. The analysis revealed a statistically significant predictor ($P < 0.05$) that could account for the observed discrepancy in efficacy outcomes: SMHBNUM (see Figure 7).

3.2.2. PHQ-4

PHQ-4 is a combined ultra-brief screener for depression and anxiety developed by Drs. *K. Kroenke, RL. Spitzer, JB Williams and colleagues* [14]. It is a multiple choice 4-item questionnaire with each item measured on a discrete scale from 0 to 3. The corresponding table of outcomes in our analysis contained 62 patients for whom all data was recorded at baseline and weeks 8, 16, 24, 48. The outcomes are defined by the day when the record was made and the item number within PHQ-4. Hence, each row is represented by a 20-dimensional vector with integer-valued coordinates. Figure 8a shows the data map of the table of outcomes. We again observe the fork-like feature with the tines occupied by the data points lying at the periphery of the dataset (i.e. the points with relatively high values of the L_p-centrality projection). Recoloring of the data map by the total PHQ-4 score at baseline revealed that the patients in one of the tines as a group had higher median scores than the rest of the population (see Figure 8b). This group (10 patients) also had higher median scores on the subsequent visits. Statistical analysis identified a significant predictor SDMARMN distinguishing the group (P = 0.012). Specifically, 9 out of 10 patients in the group constituting the tine with higher PHQ-4 score at baseline belonged to the same arm of the study (Figure 8c).



a)
Nodes' colors correspond to the median values of the L_p-centrality projection.

b)
EFOVR score at baseline.

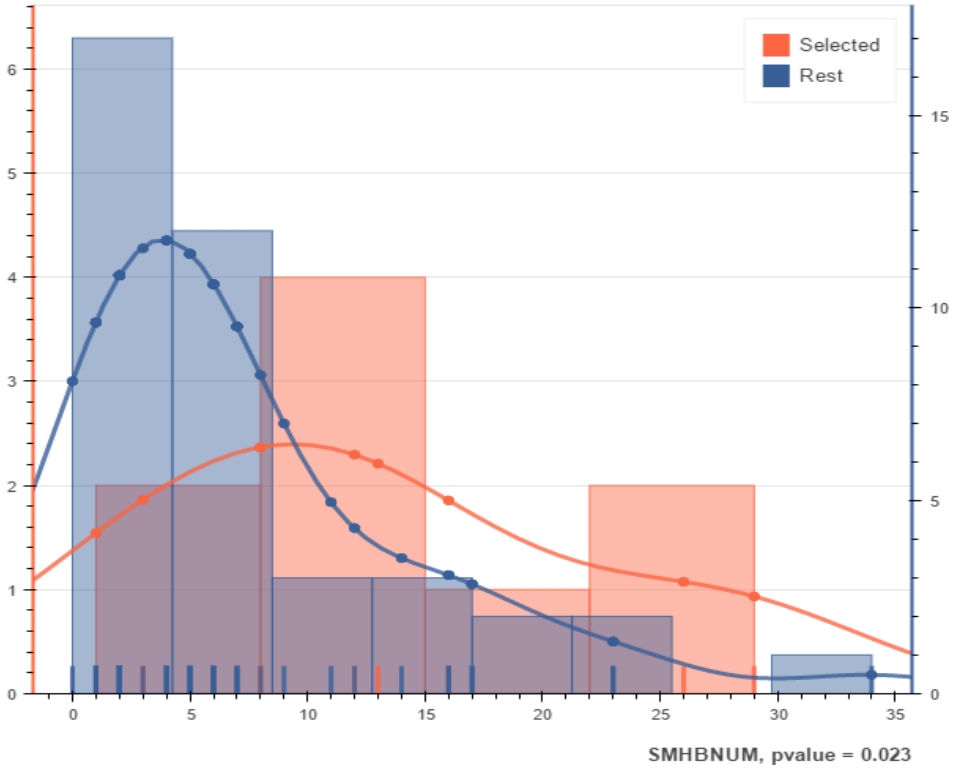
c)
EFOVR score on visit 48.

d)
EFOVR score on visit 96.

Figure 6. Topological data map of the composite efficacy score table

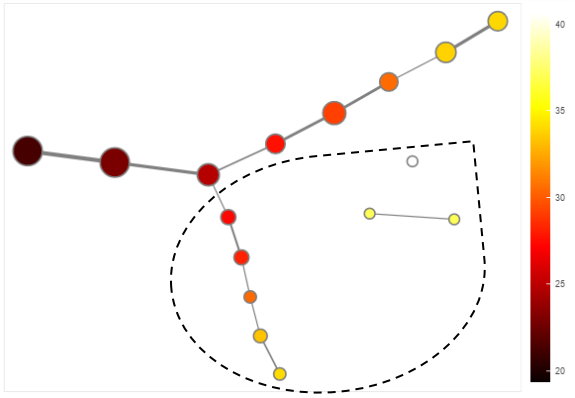
#	Predictor	Type	Pvalue
7	SMHBNUM	mixed	0.027
1	SDMAGE	mixed	0.125
3	SEXDUR2	mixed	0.149
5	SEXDOSNT2	mixed	0.265
8	SDMSEXN	binary	0.322
10	SDMRACEN	discrete	0.454
9	SDMARMN	binary	0.463
2	SEXDUR1	mixed	0.665
6	SMHONUM	mixed	0.7
4	SEXDOSNT1	mixed	0.935

a)
Table of predictors and their p-values calculated to assess discrepancy between the group of patients constituting the 'high EFOVR score tine' (9 patients) and the rest of the population (40 patients).

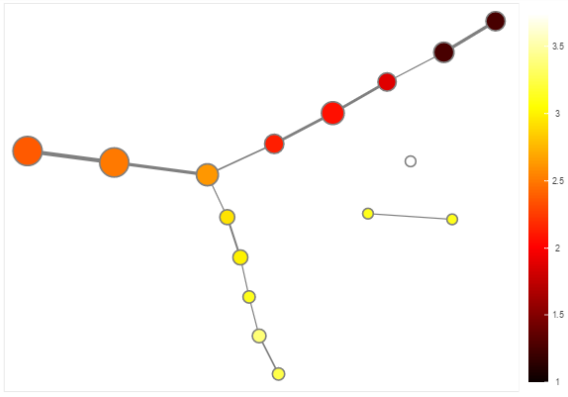


b)
Frequency histograms and KDE plots of the SMHBNUM variable for the selected group and the remaining subjects.

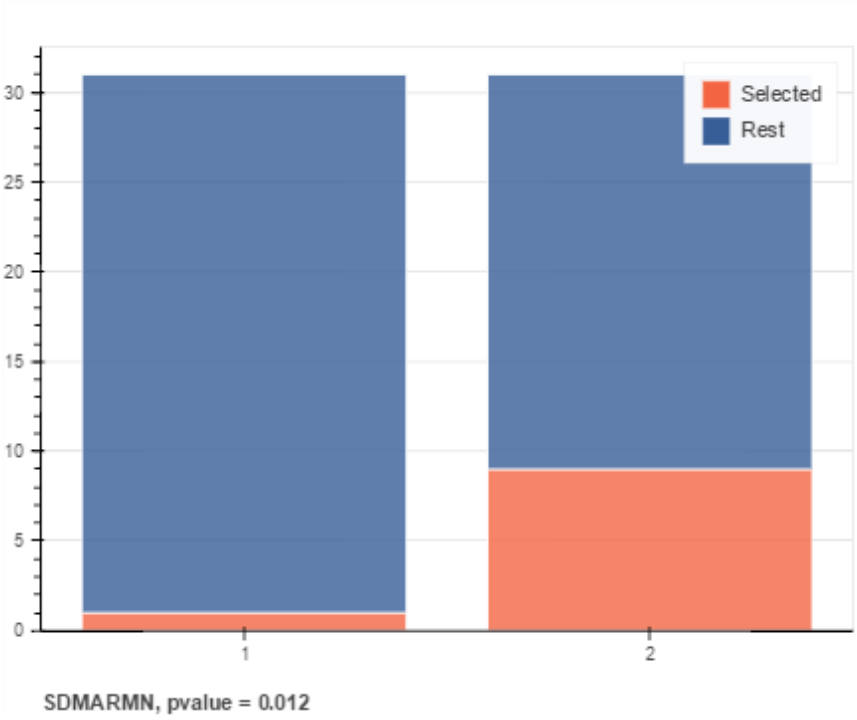
Figure 7. Statistical analysis of predictors to account for discrepancies in the outcomes



a)
Nodes' colors of the data map correspond to the median values of the L_p-centrality projection



b)
The data map is recolored by the PHQ-4 total score at baseline.



c)
Distributions of the patients from the selected group of nodes constituting the 'higher PHQ-4 score tine' (10 patients) and the rest of the population (52 patients) among two study arms.

Figure 8. TCDM of the table of outcomes based on PCQ-4 panel data

3.2.3. ADDITIONAL EXPERIMENTS

Due to the limited format of this paper and the format of the conference, results from only one clinical study were discussed in this paper. A number of additional computational experiments were performed on sample studies that included the analyses of both publicly available and proprietary clinical datasets. If you are interested in more details about additional experiments that were conducted, please contact the authors directly using the contact information that is presented at the end of this paper.

CONCLUSION

In this paper, we presented a novel, topology-based methodology (TCDM) and a prototype of a software platform that allowed researchers to gain visual insights into clinical trial data and to generate new exploratory hypotheses using these insights. The approach was illustrated on a sample clinical study, and the application of TCDM generated several interesting findings in multivariate outcomes that would otherwise have been difficult to identify through the use of standard statistical methods alone.

TCDM provides a flexible framework of data-driven, model-independent methods that can be readily adapted to various clinical research goals. The main application areas for TCDM include, but are not limited to, the following:

- Identification of subpopulations based on similarity of responses.
- New indication discovery for an existing molecule.
- Composite analysis and pattern recognition of multiple outcomes:
  - evaluation of safety data;
  - efficacy evaluation;
  - hidden adverse event signaling.

TCDM should not be considered to represent a competitor of, or substitute for, traditional model-based biostatistical approaches; however, it is a complementary approach that can be used at all stages of planning and conducting clinical trials as well as for exploratory and confirmatory analyses of clinical data.

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