

DPVis: Visual Exploration of Disease Progression Pathways

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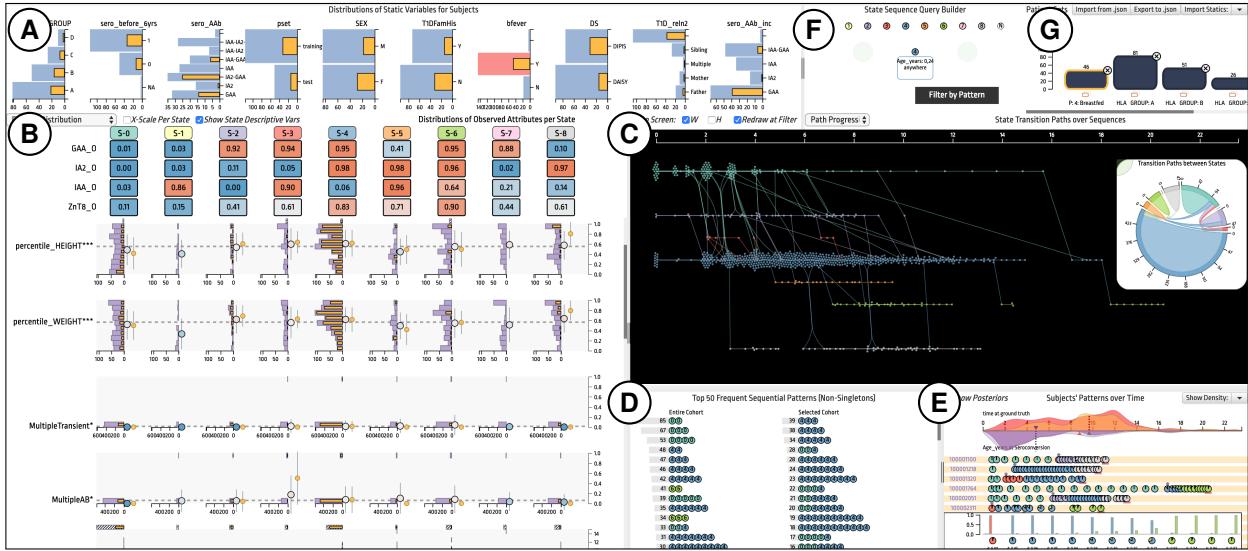


Fig. 1: DPVis consists of seven view areas: (A) Static Variables Distribution View shows distribution over static variables; (B) Panel for Observed Attributes summarizes characteristics of disease states estimated by a hidden Markov model; (C) Panel for State Transitions shows heterogeneous disease progression patterns of multiple subjects; (D) Frequently Occurring State Transition Pattern View summarizes frequently occurring sequential patterns; (E) Subject List View shows subjects' visits over time; (F) State Sequence Query Builder enables users to build and refine cohorts; (G) Cohort View allows users to save and load intermediate results. Users can toggle between multiple views in (B) and (C) depending on their analytic goals.

Abstract— Clinical researchers use disease progression modeling algorithms to predict future patient status and characterize progression patterns. One approach for disease progression modeling is to describe patient status using a small number of states that represent distinctive distributions over a set of observed measures. Hidden Markov models (HMMs) and its variants are a class of models that both discover these states and make predictions concerning future states for new patients. HMMs can be trained using longitudinal observations of subjects from large-scale cohort studies, clinical trials, and electronic health records. Despite the advantages of using the algorithms for discovering interesting patterns, it still remains challenging for medical experts to interpret model outputs, complex modeling parameters, and clinically make sense of the patterns. To tackle this problem, we conducted a design study with physician scientists, statisticians, and visualization experts, with the goal to investigate disease progression pathways of certain chronic diseases, namely type 1 diabetes (T1D), Huntington's disease, Parkinson's disease, and chronic obstructive pulmonary disease (COPD). As a result, we introduce DPVis which seamlessly integrates model parameters and outcomes of HMMs into interpretable, and interactive visualizations. In this study, we demonstrate that DPVis is successful in evaluating disease progression models, visually summarizing disease states, interactively exploring disease progression patterns, and designing and comparing clinically relevant subgroup cohorts by introducing a case study on observation data from clinical studies of T1D.

Index Terms—Disease Progression Model, Hidden Markov Model, Diabetes, Huntington's Disease, Parkinson's Disease, Interpretability

1 INTRODUCTION

Clinical researchers and physician scientists use disease progression models to characterize patterns of disease development and to predict future patient status. Investigators use clinical studies to derive accurate disease prognosis and to understand how each patient's characteristic interplay with the course of disease. This knowledge can ultimately

lead to early detection of diseases and precision care for each patient at appropriate points in time. Large-scale prospective clinical studies make it possible for clinicians to collect serial lab tests, self-reports, and treatments over a long period of time. A major challenge is to find appropriate methods that distill temporal sequences of various measures into clinically useful insights.

One approach for modeling disease progression is to describe a patient's clinical course as a series of transitions between a small number of states, with each state describing a co-occurring pattern of observed measures or symptoms [68]. The states, commonly referred to as latent or hidden variables, are not directly observed but rather must be discovered from the data. Hidden Markov models (HMMs) are a class of unsupervised, statistical models that allow for discovering such latent states, understanding characteristics of progression patterns with the associated observed variables for corresponding states, and predicting a

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patient's future states. Since HMMs can be trained on longitudinal patient data from large-scale clinical studies and electronic health records (EHRs), HMMs have been successfully applied to capture heterogeneous disease progression patterns in various diseases, such as chronic obstructive pulmonary disease [68] and Huntington's disease [63].

Despite the potential usefulness of HMMs for understanding disease progression patterns, it remains challenging for domain experts to make sense of the models and to derive clinically useful insights. Goals of data exploration include discovery of heterogeneous disease progression patterns, observation of interactions between such patterns and patients' characteristics, and testing and refining hypotheses for multiple cohorts in an adhoc manner. HMMs produce relevant outputs that can potentially fulfill these needs, but it is often difficult for domain users to gain useful understanding of clinical observation data by aggregating and connecting various statistical outcomes without the help of interactive visualization systems. Though prior studies introduced inspiring visualization techniques that can partially solve these problems, no system yet integrates such techniques into a visual analytic solution for disease progression modeling using HMMs.

Thus, our goal is to develop a visual analytic system that integrates HMM outcomes on observational data from clinical studies with various visualization techniques. To achieve this goal, we conducted a design study with domain experts, including physicians, statisticians, and visualization experts, to explore the design space of interactive visualization methods. In this process, we summarized tasks and requirements of the users, and extracted outcomes that are relevant to meet the task goals by using HMMs trained on observational data from birth-cohort studies of Type 1 Diabetes (T1D) and EHRs of Parkinson's disease. As a result, we introduce DPVis, which seamlessly integrates outcomes of HMMs into interactive visualizations.

The following three items summarize our main contributions:

1. We developed DPVis that integrates HMMs with interactive visualizations for discovering disease progression patterns from longitudinal observational data collected from clinical studies.
2. Our design study examines tasks of disease progression researchers and provides various ways to visualize the statistical outcomes of HMMs for supporting these tasks.
3. We provide a case study that demonstrates the usefulness of DPVis for domain experts to make sense of HMMs, to detect interesting disease progression patterns, and to derive clinical insights.

In the following sections, we first review prior research on disease progression models, HMMs, and visualization methods that are applied to longitudinal clinical data in Section 2. Next, we introduce our design study methods, where we conceptualize domain experts' goals and characteristics, introduce the datasets and the models used, and summarize the analytic tasks and goals that domain experts seek to perform on the data using HMMs in Section 3. In Section 4, we describe the design of DPVis, and how the views and interactions can help domain experts solve their tasks. In Section 5, we report a case study, where a fictitious investigator named Amy observes 168 subjects diagnosed with T1D and derives clinically useful insights using DPVis. We discuss the implications and lessons learned in Section 6 and provide future work in Section 7.

2 RELATED WORK

In this section, we review disease progression studies in the field of medicine, various modeling techniques in statistics and machine learning, and visual analytic approaches in the visualization domain.

2.1 Disease Progression Research in Clinical Studies

Well-designed longitudinal studies play an important role in clinical research because they provide rich information for tracking the progression of disease by collecting repeated measures from individuals of a target cohort over a long period of time. Such studies are designed and conducted with many present and future goals, such as understanding the etiology or pathogenesis of a disease. One of the most well-known longitudinal studies is the Framingham Heart Study, which has brought great insights into heart disease (e.g., [26, 37]). In particular, many

studies call for research into applying suitable statistical modeling techniques that can explain the mechanism of disease progressions. For example, the Parkinson Progression Marker Initiative (PPMI) [44] is an international observational multi-center study of Parkinson's Disease. PPMI established protocols that were adopted at 21 clinical sites to provide a platform for researchers to gain common access to the data, which includes clinical, socio-demographic, and imaging variables as well as bio-specimens. In case of T1D, researchers seek to understand the diverse pathways from a healthy state to the onset of disease for both individual patients and the overall population [75]. The Type 1 Data Intelligence (T1DI) study group was established to accelerate disease progression research by combining decades of data from birth cohort studies conducted at various institutions around the world: 1) Diabetes Autoimmunity Study in the Young (DAISY) [56]; 2) Diabetes Prediction in Skåne (DiPiS) [28]; 3) Diabetes Prediction and Prevention (DIPP) [48]; and 4) Diabetes Evaluation in Washington State (DEWIT) [70]. We conducted a design study with clinical researchers and statisticians who have been involved in the research groups above.

2.2 Disease Progression Modeling

Disease Progression Models (DPM) [47] include a broad class of models that use mathematical functions to quantitatively predict disease status over time. DPM can be categorized by algorithm into systems biology, data-driven, and semi-mechanistic models [10]. There are many different approaches to model disease progression, including path models [65], tree based models [11], hierarchical latent variable models [57], Gaussian process models [42], and Bayesian networks [3]. In this study, we have chosen to focus on HMMs, a probabilistic, unsupervised class of models. In an HMM, the target disease is represented by a fixed number of typical disease states, its progression is characterized by a Markov process, and the observed measures are the manifestations of the underlying disease states. HMMs were selected for the following reasons: (1) They are probabilistic in nature and represent uncertainties in clinical datasets organically; this uncertainty in state assignment is shown via posterior distributions over states. (2) They work well with missing data, a common issue in observational studies. (3) Users can model various kinds of progressions, such as forward-only progression (e.g., chronic diseases), where the damage caused by the disease is permanent and affected areas gradually lose their functions, and backward-enabled progression, where patients can recover from the diseases. (4) HMMs are unsupervised models that do not require a particular outcome task. (5) They provide interpretability by a small number of 'states' that are associated with multiple observed variables. Examples of HMMs applied to disease progression include [23, 38, 62, 63, 69]. HMMs are described further in Section 3.4.

2.3 Visualizations for Disease Progression Analysis and Various Measures of Patients

In this section, we review previous studies that show inspiring examples to tackle our problem. Prior studies have investigated various visualization methods to represent temporal event sequences. Shneiderman and Plaisant [59] summarize the challenges of analyzing temporal sequence data. Several techniques were proposed to integrate sequence mining algorithms for visualizing the summary of event sequences, including LifeLines [52], LifeLines2 [67], EventFlow [46], and LifeFlow [72], which allow users to visually align and explore various patterns of multiple event sequences. Frequency [50], Care Pathway Explorer [51], and Peekquence [34] visualize frequent event sequences mined from the SPAM algorithm [1]. Outflow [71] and Sequence Synopsis [8] allow users to interactively explore multiple pathways in event sequences. These techniques allow users to steer the algorithm with interaction.

In addition, other techniques integrate automated results with user-defined queries or criteria. TimeStitch [53], Choronodes [54], and Coquito [29] extract frequent mining patterns using algorithms like PrefixSpan [49], and then visualizes the sequences so that users can interactively provide relevant feedback to refine the search. Eventpad [6] and (*s|qu*)eries [73] allow users to build search queries using the progressive visual analytics (PVA) paradigm [61]; the idea was further extended and implemented as the PPMT tool [55]. EventThread [22]

visualizes clusters of event sequences using tensor analysis. Liu et al. [40] and MAQUI [36] allows users to recursively explore hierarchical patterns in event sequences. E² [21], StageMap [7], and Mathisen and Grnbk [45] introduce a composite event sequence to aggregate patterns. CoreFlow [39] and Guo et al. [20] visualize branching alternative paths with uncertainties. IDMVis [74] allows users to fold and align records to derive event sequence patterns.

Previous studies also investigate visual analytic methods to explore and discover patterns from longitudinal data in clinical studies and electronic medical records. DecisionFlow [19] allows users to explore multidimensional event sequences using multiple, coordinated visual analytic systems. PhenoBlocks [17], PhenoStacks [16], and PhenoLines [18] allow users to explore and compare cohorts based on various measures. RetainVis, together with RetainEX, allows users to understand how individual visits and categorical variables contribute to making diagnostic risk predictions [30]. Clustervision [31] help users to find informative cohorts of patients based on their common diseases, treatments, diagnostic measures, and comorbidities. Bernard et al. developed and evaluated static dashboard network that can help users to observe longitudinal changes of multiple patients [4]. Other studies help users make sense of time-series health data, such as Stroscope [9], TimeSpan [41], Marai et al. [43], and RegressionExplorer [12].

Though the previous approaches provide inspiring techniques, there is no unified approach that integrates HMMs for exploring disease progression patterns from longitudinal observational data.

3 DESIGN STUDY METHODS: USER, DATA, MODEL, TASKS

This section describes our design study by introducing characteristics of domain experts, data, HMMs, and tasks and requirements that experts intend to achieve through visualizations.

3.1 Design Study: Partnering with Research Groups

One of the greatest challenges in developing a visualization system for medical application is not only to access appropriate datasets but also to recruit expert groups. Our project started with a goal to create a visual analytics tool that can be applied to various disease progression models. We joined a collaboration project established in 2017 by JDRF and their academic partners for computational modeling of T1D: the T1DI (Type 1 Data Intelligence) study group. Many other research groups with progression modeling studies for Parkinson’s and Huntington’s disease were invited to collaborate and provide feedback.

3.2 User Characteristics: Clinical Researchers

Our primary target users are clinical researchers, such as physician scientists and statisticians, who aim to investigate disease progression patterns in observational data collected from clinical studies. Researchers carefully select patients for long-term prospective clinical research in order to better understand the characteristics that are associated with distinct disease progression patterns. A major goal of these investigators is to formulate and test various known and unknown hypotheses related to patients’ progression patterns, including how various progression patterns relate to patients’ inherent characteristics, such as genetic traits, ethnicity, and family history. In addition, researchers also speculate on the relationship between the onset of diseases and other observed measures, such as lab tests, behavioral patterns (e.g., smoking), and growth measures (e.g., height), collected from clinical studies. Domain experts seek to build and refine multiple cohorts, each of which show common characteristics, that lead to heterogeneous disease progression patterns, and to find biomarkers related to the differences in the progression.

3.3 Data: Observational Data from Clinical Studies

Clinical researchers collect multivariate measures from subjects’ visits through clinical studies. Patients’ visits may occur in equidistant or irregular time intervals, depending on the study. For each visit, subjects undergo lab tests and self-report their life-style patterns and environmental exposures; these measures capture patient status that changes over time (henceforth, ‘observed variables’). Additionally, subjects are also asked to report measures that do not change over time but may be

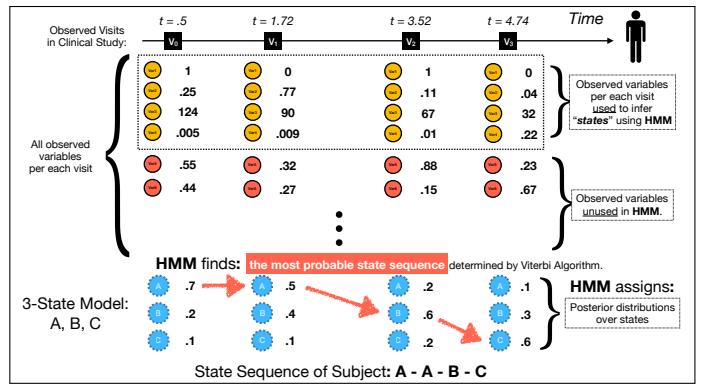


Fig. 2: HMMs estimate a patient’s visit based on observed attribute values chosen by users for training the model. The trained model predicts the most probable state sequences for a patient and assigns posterior probabilities for each visit.

related to the onset and progression of diseases (henceforth, ‘static variables’). The observational data may contain missing and/or erroneous data entries. Each dataset may contain longitudinal health records for multiple subjects. Clinical researchers and statisticians often merge datasets from multiple clinical studies. Therefore, observational data is a form of temporal event sequence data, where each visit is associated with a time stamp and contains a variety of health outcome measures.

3.4 Model: Hidden Markov Models and Variations

For disease progression modeling, we use continuous-time hidden Markov models (CT-HMMs), which suits the longitudinal medical records measured in non-equivalent time intervals between visits. Fig. 2 summarizes a diagram of a subject’s visit and its attribute values as well as states, sequences, and posterior probabilities over states by a pre-trained CT-HMM. In disease progression modeling, CT-HMMs, trained by longitudinal patient records, assign (predict) a latent (hidden) variable, called a “state,” for each visit based on associated observed attribute values at the time. In addition, the trained model generates posterior probability distribution over states for each visit.

The models are trained in an unsupervised manner. There are several decisions for users to make prior to training: 1) the number of states; 2) a set of observed attributes used for training; 3) constraints on progression steps (e.g., forward-only, forward-backward, no-skip). The number of states are often determined based on the model fitness (e.g., log-likelihood measure) after multiple training phases. The set of observed attributes are determined based on domain knowledge and refined via multiple training iterations. Users can also set constraints on the type of progression based on the disease. For more information on Markov models, please see [5]. Our goal is to help users understand the results of a trained model’s predictions on patients’ status that can lead to better modeling decisions and clinically useful insights.

3.5 Tasks: Disease Progression Pathways

This section reports our target users’ tasks. We identified our target tasks based on iterative discussions with domain experts, including physician scientists and statisticians. We initially generated a variety of low-level analytic questions and then abstracted to more generalizable, high-level visualization tasks by following a design study methodology [58, 60]. The following list shows the main user tasks.

T1: Understand the overall state transition patterns of all subjects: Users gain an overview of state transition patterns. This includes, but not restricted to, T1.1. viewing frequently occurring state transitions; T1.2. viewing unexpected, infrequent state transitions; T1.3. viewing state transition pathways (e.g., dwell time, progression pathways, sink states); T1.4. viewing state-to-state bipartite transition network.

T2: Understand the characteristics of the states: Users seek to understand the average distributions over the observed variables, both used and unused for training, per state. Understanding the characteristics helps them interpret the states in a clinical perspective.

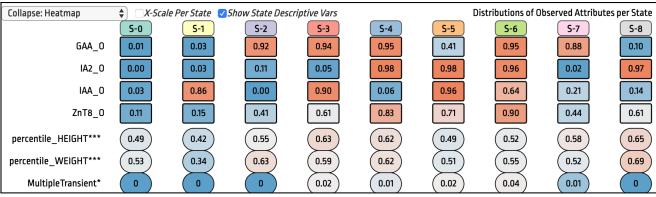


Fig. 3: Feature Matrix shows mean values (blue to red; red being higher values) for observed variables (rows) of states (columns). Users can duplicate and fix the position for a set of variables (GAA_0, IA2_0, IAA_0, ZnT8_0 at the top) by using the 'stick to the wall' function.

T3: Construct and refine cohorts based on observed measures and state transitions: Users want to build multiple cohorts by setting filters with respect to various observed measures. They also want to refine cohorts gradually by using state transitions and onset time.

T4: Compare multiple cohorts: Users want to quickly test hypotheses about the relationship between onset time, observed measures, and state transitions by building and comparing corresponding cohorts.

T5: View individual patients' state transitions: Users want to view and compare patients' state sequences over a timeline. They want to learn how similar or dissimilar selected subjects are in detail.

T6: View uncertainties in the model: Users want to understand disease progression pathways with their uncertainties. Users not only want to understand the most probable sequence but also want to check the posterior distributions over states per visit.

T7: Save and load intermediate analysis results: Experts often spend days, weeks, and months interacting with the models, and discuss results with their colleagues. Therefore, users want to save their intermediate results, such as cohorts, view settings, and sorting order for views, so that they can resume their analyses from the last session.

Based on the derived tasks, we iteratively designed and assessed multiple views. In the following section, we introduce the design of DPVis and how each view and feature supports user's analytic tasks.

4 DESIGN OF DPVIS

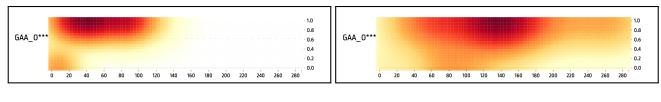
DPVis consists of seven view areas as Fig. 1 shows, and each has a different role. In particular, we developed multiple visualizations for two main view areas in Fig. 1 (B) and (C): 1) Panel for Observed Attributes and Panel for State Transitions. Users can toggle between visualizations depending on their tasks. All visualizations are connected, so users can set filters using any view to update all views and the currently selected cohort. In the following sections, we introduce each view of DPVis and how these views can help users solve their tasks.

4.1 Static Variables Distribution View

Static Variables Distribution View shows a list of selected measures that do not change over time in horizontal bar charts. Users can use this view to show the general summary of subjects in terms of their static measures, such as gender, race, and family history status. Using this view, users can build cohorts based on factors related to subjects' genetic characteristics and/or various environmental factors (T1). As an example, for T1D, researchers hypothesize that children who are breastfed have lower risk of developing the disease [15, 24]. Users can click on the bar with 'Y' label on the 'bfever' bar chart to create a cohort with subjects who were breastfed (see Fig. 1 (A)). To investigate further, users can add another filter by clicking on 'Mother' on 'T1D_reln2', which refines the cohort to represent subjects who received breastfeeding from diabetic mothers. Users can remove individual filters by clicking on a specific bar, and they can remove all by clicking an empty area in the background.

4.2 Distribution Views in Panel for Observed Attributes

Panel for Observed Attributes contains various views that present the distribution of observed attributes that change their values over visits (time). In this view, users can gain various insights from overview and details about interaction between features, states, and time. Importantly, this view can also visualize variables associated with a visit but was



(a) Distribution of GAA_0 in State-2 (b) Distribution of GAA_0 in State-7

Fig. 4: Feature Heatmap over Time shows density of attribute values over time. Above is an example for glutamic acid decarboxylase autoantibodies (GAA_0) for states 2 and 7 in the T1D model.

not used for training the disease progression model. This enables users to understand the characteristics of states based on all observed data.

4.2.1 Feature Matrix

Feature Matrix shows a grid layout in which a row represents an observed attribute and a column represents a state learned by the model. Each cell in this layout represents the mean of the attribute (row) values of the visits that were predicted as the corresponding state (column). The diverging color map is used to map the range of minimum-maximum values of each measure to the blue-red scale across the states. This view is primarily used to understand distinctive characteristics of different states with respect to the distribution over observed attribute values (T2). During the design process, users requested the ability to fix the heatmap of a set of selected measures below the state title ('stick to the wall' as shown in Fig. 3). In this way, users can glance at the fixed heatmap to understand the characteristics of states based on the variables selected while interacting with other views. For instance, in the nine-state model shown in Fig. 3, the states captures various combinations of autoantibodies observed during patients' visits. Users can readily find that State-0 shows the state without any autoantibodies present (low values in blue for all four attributes on top), and single-autoantibody states (states 1,2,7,8). In addition, they can also see four states with multiple autoantibodies (States 3 through 6). With these in mind, users can interpret states in other views with respect to the existence of single or multiple autoantibodies easily.

4.2.2 Feature Distribution

Users can choose to expand Feature Matrix to Feature Distribution, which shows the distribution of each observed attribute in more detail. Once expanded, the view shows a histogram in addition to mean and standard deviation per cell in the grid layout. As Fig. 1 (B) shows, the view repeats the same scale for all histograms for the same attribute in order to enable comparison across states. Users can switch and toggle back to fit the scale for each cell. The view also shows a dotted line which represents a global mean value of the corresponding attribute across states. In addition, users can check the number of missing values per cell with a shaded bar above each cell. Users can also mouseover on bars for distribution, bars for missing values, and dots for means to read the numbers in a pop up. By leveraging the distributions shown in this view, users can set a filter by drawing and moving brushes per cell. By using this feature, users can interactively build more sophisticated cohorts based on state-feature interactions. Once users set filters, Feature Distribution overlays orange bars on top of the bar chart, which indicate the distribution over attribute values per state for the selected cohort. For instance, users may want to set a filter for percentile BMI higher than 50% in State-0 in order to check if the group shows any distinctive pathway trajectories in other views (T3).

4.2.3 Feature Heatmap over Time

Feature Heatmap over Time shows the trend of observed attributes over time instead of states. We used 2D Kernel density estimation with Gaussian kernel in order to compute the values for each cell over 20×100 grid pixels; each cell size of the grid is determined in proportion to users' browser dimension and screen resolution. We map attribute values to the RGB scale of white, yellow, and red so that the darkest red represents the densest area in the plain of time (x-axis) and the corresponding attribute (y-axis). The initial view shows an overview of attributes values over time. Users can filter this view by each state and compare the densities between multiple states. Users can find interesting similarities between State 2 and State 7 over the "stuck to the wall" Feature Matrix of the two states. As Feature Matrix

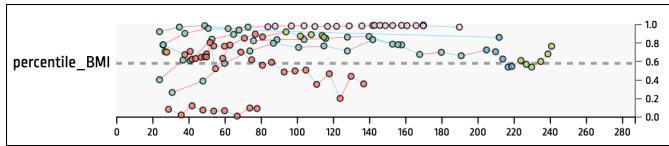


Fig. 5: Feature over Time shows scatter plot of each visit’s (dot) value of an observed variable (Y-axis) over time (X-axis). Above example shows the trajectories for percentile_BMI of a cohort, whose subjects were breastfed with family history of diabetic mothers.

in Fig. 4 shows, users can find that these two seemingly similar states represent two different states in terms of subjects’ age, where State 2 is highly dense at the age in early ages around 40-50 months while State 8 is captured at ages between 120 and 160 months.

4.2.4 Feature over Time

Users can further investigate the details of the temporal trends of the observed attributes using Feature over Time. This view shows a scatterplot, with optional connecting lines per subject, per attribute. Each dot in a scatterplot represents a visit’s time (x-axis), attribute value (y-axis), and state (color). The connecting lines between visits represent the trajectories of subjects over the attribute value range, and each line segment connecting two dots are colored based on the slope of the progression (red for positive; blue for negative). Using the previously created cohort (breastfed children with family history of diabetic mothers), users can discover that subjects in this cohort show higher-than-average BMIs, where a couple of subjects have obesity above 85th percentile. This observation implies that these subjects were relatively taller and/or heavier, throughout long-lasting observation periods. We can also see hard cut-offs at month 24 because there is no agreed BMI index for children under 24 months in clinical practice [14].

4.3 Pathway Views in Panel for State Transitions

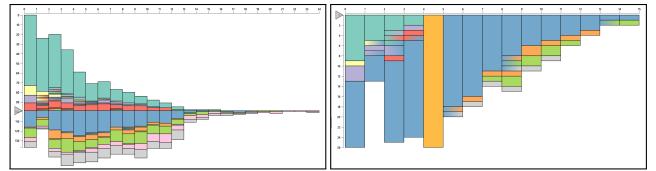
Pathway views show various representations of state transition patterns over sequences of visits or over time. In Panel for State Transitions, users can choose among four views depending on the time intervals of visits in observational data and their analytic goals.

4.3.1 Pathway over Observation

Pathway over Observation shows state transition patterns of multiple subjects using the stacked sankey diagram approach. As Fig. 7 shows, the view consists of two visual elements: nodes and paths. Nodes are vertically stacked for each visit (x-axis), where each stack’s height represents the number of subjects with the corresponding state at the visit. Paths are drawn horizontally between two consecutive visits, where each path connects a state (State-A) of the previous visit (Visit-0) to another state (State-B) of the current visit (Visit-1). The thickness of each path represents the number of subjects who transitioned from State-A to State-B over the visits between 0 and 1. For an N -State model, the view presents N nodes per visit and N^2 paths between every consecutive visit. Pathway over Observation allows users to gain an overview of transition patterns by comparing the height of stacks over visits first (**T1**). Then, users can check more details like incoming subjects and outgoing subjects with respect to each stack or each visit.

We added multiple interaction techniques to the view so that users can interactively ask questions related to state transitions more intuitively. First, we implemented Alignment Handle, which enables users to vertically align stacked bars over visits with respect to a break point between states per visit (e.g., between States 1 and 2 over all visits). This view reconfigures the vertical arrangement of stacks so that users can temporarily divide multi-state transitions into binary ones—above and below Alignment Handle as Fig. 7b shows. For instance, users can place Alignment Handle between two states, where the transition from one state to another indicates irreversible progression from benign to malignant clinical stages that can result in permanent disabilities. Users can quickly glance over how stacks above Alignment Handle decrease their length and in which visit the trend shows a significant progression.

Users can also turn Pathway over Observation into a bipartite sankey diagram. This view has only two stacked bars with paths between



(a) Pathway by Time Unit shows stacked bars aligned at an anchor point between (highlighted in orange) with State 4 at subjects’ age between 4 and 5 years old.

(b) Users set a filter by clicking on a node

them (see Fig. 7c). This configuration simplifies the transition by only showing the cutover from a start to an end. By using this view, users can follow the state pathways between two nonconsecutive visits, and answer questions like “what happen to 30 State-A subjects after 30 visits?” Users can reconfigure and switch to the new start and the end visits to observe patterns between them during their analysis.

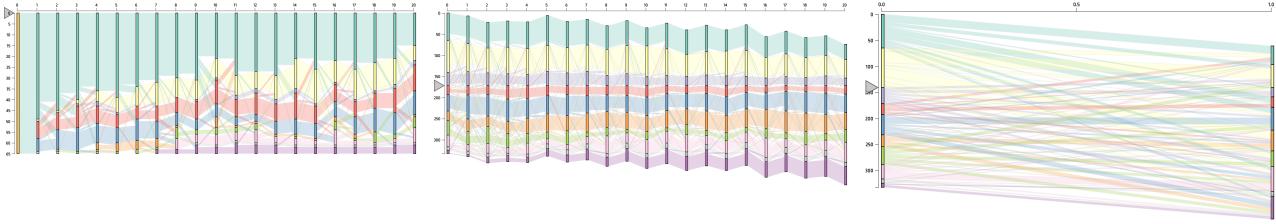
Users can also use Pathway over Observation to build cohorts. Users can click a stack per visit and/or state transition paths between states to filter subjects as Fig. 7a shows. This action propagates to all other views; users can choose either to refresh Pathway over Observation itself with the filtered subjects or to keep the current view. Regardless of the choice, users are able to keep the current selection of node or path highlighted in orange for their reference.

While the view is generally useful, Pathway over Observation is best suited for clinical studies with regular visits separated by a consistent interval between them. Some clinical studies start with a screening visit, followed by weekly or bi-weekly sessions that assess patient status using various lab tests. In this case, Pathway over Observation reveals state sequences and allows researchers to view the development of diseases in multiple cohorts. On the other hand, some other clinical studies observe clinical sessions that are conducted in irregular visits. In this case, Pathway over Observation may misguide or obscure patterns because patients’ visits occur in irregular, inconsistent fashion; we cannot align and aggregate state transitions by visit sequences. Therefore, we need additional views that can be applied more generally to clinical observations with irregular study visits.

4.3.2 Pathway by Time Unit

Pathway by Time Unit shows state transitions aggregated for a user-selected time unit (e.g., hour, week, month). The visualization appears as a counterpart to Pathway over Observation minus paths drawn between nodes. In Pathway by Time Unit, stacked bars are drawn over a timeline. The width of each bar indicates a time unit, where it shows a year in Fig. 6. The height of each stack in a bar represents the number of subjects who were captured with the state during the time period. Instead of paths drawn between nodes in Pathway over Observation, Pathway by Time Unit shows state transitions with color gradients on nodes. A node stack of the linear gradient of green (State-0) to red (State-3) over a time unit (between ages 2 and 3) indicate the subjects transition from 0 to 3 in their ages between 2 and 3. Using Pathway by Time Unit, users can understand the prevalent states and their development over time in subjects’ age or years preceding a certain medical event by examining the stacked bars over time. Users can gain insights into the general trend of when subjects start showing multiple autoantibodies by aligning Pathway by Time Unit between State 3 and 4 as Fig. 6a shows. In ages between 4 and 5, users can observe a significant decline in zero or single autoantibodies (States 0, 1, 2, 3) and an increase in multiple autoantibodies (State-4). Users can also easily observe study attrition for participants over 4 years old.

As Pathway over Observation provided, Pathway by Time Unit also allows users to align state node stacks with respect to a break point using Alignment Handle (see Fig. 6a). In addition, Pathway by Time Unit also allows users to switch between user-defined time units. The time variable can be defined various ways depending on analytic goals and disease types. For instance, time can be defined as subjects’ biological ages when users believe that the growth of biological development can act as a significant confounding factor for disease progression, such as T1D. In other cases, we can use years preceding each subject’s onset of



(a) Pathway over Observation shows pathways for subjects who started their first visit with State 0 (green); the first respect to a new anchor point (between states 3 and 4), nodes and the path between the two nodes, showing where node is highlighted in orange after users click to filter. (b) Alignment Handle rearranges nodes and paths with respect to a new anchor point. (c) Users converted the view to only show start and end nodes and the path between the two nodes, showing where subjects starting with each state land in their final visits.

Fig. 7: Pathway over Observation uses the sankey diagram approach to summarize state transition pathways for subjects over observed visits.

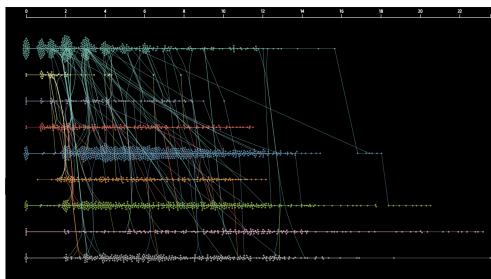
motor impairment and/or cognitive disabilities in case of Huntington’s disease. Users can also click on a node stack to set a filter based on subjects’ state at a particular age (see Fig. 6b). As Fig. 6b shows, subjects who were at State 4, showing multiple autoantibodies, tend to maintain their status over time.

4.3.3 Pathway Waterfall

Pathway Waterfall shows subjects’ state transition patterns using parallel beeswarm visualizations overlaid with individual subjects’ trajectory lines. As Fig. 8 shows, we first divide the space into N vertical spaces, each of which is dedicated to show a timeline for visits with N -th state. Individual dots, colored corresponding to its state, are placed over the timelines, and we preserve the timestamp without overlaid dots using the beeswarm algorithm [13]. Then, we visualize trajectory lines for individual subjects that follow the state transition pathways over time. To reduce the clutter while maintaining the vertical position, we used a modified version of force-edge bundling technique [25], where we only bundle trajectories with the same state-to-state transitions at similar times. To contrast the visual patterns of the trajectories more vividly, we used a dark background color. A participant commented about the intuitive pattern of Pathway Waterfall, “it looks like Mardi Gras beads hanging on the wall. Easy to see where (in which state) they hook and tangle up (congested departing edges) within the time period, which implies the rapid development of various autoantibodies.”

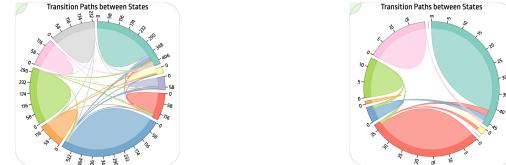
Using this view, users can view the distribution of visits over time per state. In addition, they can also gain insights into the heterogeneous state transition patterns over time by viewing bundled paths and following the trajectories. As Fig. 8a shows the overview of state transition pathways and the characteristics of states. The last three states appear to be “sink states”, in which subjects tend to stay once they enter. The major transition patterns occur between ages of 1 and 4, as one can see from congested departing edges within the time period, which implies the rapid development of various autoantibodies.

Using Pathway Waterfall, users can set filters on each timeline of a state so that they can filter subjects that follow and stay at the states within the user-defined time periods. This view is particularly useful to disease progression pathways of subjects that share the same starting and ending states but follow distinctive pathways. Fig. 8b shows disease progression patterns of subjects who started with no autoantibodies (State 0) before the age of 3 but ended up with all autoantibodies (State 6). Some subjects show drastic, rapid progression at their early ages, but some others went through single- and double-autoantibodies states



(a) Pathway Waterfall shows state transition patterns of all subjects over 25 years.

Fig. 8: Pathway Waterfall shows state transition pathways using parallel beeswarm plots and trajectory lines tied with force edge bundling. Each beeswarm represents visits (dots) and their assigned states (color) over time (x-axis); paths show transitions between consecutive visits.



(a) State Transition Chord Diagram shows state transition patterns of all subjects. (b) Users set filters for a cohort of subjects who were breastfed by diabetic mothers.

Fig. 9: State Transition Chord Diagram shows a summary of state transitions between all pairs of consecutive states.

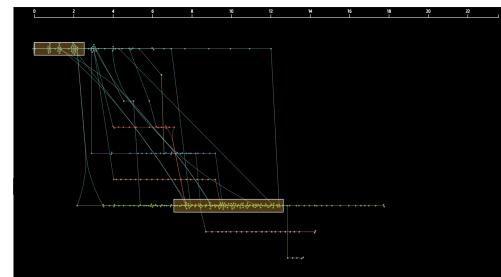
in the middle. Interestingly, it also shows two outliers, who passed State-6 and transitioned back to single-autoantibody states (7 and 8).

4.3.4 State Transition Chord Diagram

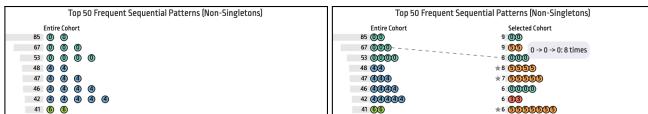
State Transition Chord Diagram shows the overall state-to-state transition patterns over all consecutive pairs of observations from subjects using a radial network diagram. The view can be used to understand the overall frequency of state transitions. This view serves as an explanatory summary of the state transition learned from the particular setting of HMMs. It allows users to compare the number of visits per state by viewing the size of the nodes (states) on the circular layout and to compare the transitions between two states by the size of arcs connecting two nodes inside the circular layout. In case of forward-only progression models, one arc is drawn per a pair of different states. As Figure 9a shows, the current model interprets that state transition occurs rarely as the majority of transitions are no change shown as self-directed arcs. On the other hand, a cohort with subjects who were breastfed by diabetic mothers, as shown in Fig. 9b shows a greater amount of States 1 and 3 and less States 4 and 8.

4.4 Frequently Occurring State Transition Pattern View

Frequently Occurring State Transition Pattern View shows a list of frequently occurring state transition patterns mined from all consecutive observations. By running the BIDE algorithm [66] on subjects’ state sequences, we first generate the most frequently occurring state sequence patterns. To avoid filling up the list with fine granular patterns, we filtered top 50 patterns in terms of the number of unique subjects with the corresponding pattern; we also do not take into account any single-state patterns. Then, we list all patterns, where each pattern is a row of state circles, in a vertical order, as shown in Fig. 10a. Inspired



(b) Users filtered Pathway Waterfall by drawing two rectangular regions of interest



(a) The view shows the top-50 most occur- (b) A new list of patterns from a cohort with ring state sequence patterns. any siblings with diabetes.

Fig. 10: Frequently Occurring State Transition Pattern View shows the result of pattern mining algorithm (BIDE) [66].

by Peekquence [34], we also visualized the frequency of the patterns as a bar chart next to each pattern. Users can click on each pattern to filter subjects who included the particular state transition patterns.

The view expand and introduce yet another list of patterns once users set filters on any views as Fig. 10b shows. Then, the initial list is squeezed to the left in order to make space for the new list of pattern mining results on the right. The parallel lists of patterns show differences in the ranked order of patterns mined from all subjects (left) and selected cohort (right). If there are any patterns which were not included in the initial list but occurred in the new list, we add a star symbol to the left of each pattern to show the difference. For patterns that exist in the initial list, users can hover the pattern to show a dotted line between the same pattern in two different lists to check how the rank of the pattern differs in two subject cohorts.

4.5 Subject Timeline

Subject Timeline shows individual subjects' observations over time. In this section, we introduce two components of the view: 1) Subject List View; and 2) Dual Kernel Densities View.

4.5.1 Dual Kernel Densities View

Dual Kernel Densities View shows the two independent 1-D Kernel Density (KD) diagrams, each with increasing y-axis (density) in the opposite direction, upward and downward, respectively, as Fig. 11 shows. The KD above the timeline shows the density of time at the onset (e.g., diagnosis of Chronic Obstructive Pulmonary Disease (COPD)). Subsequently, the KD below the timeline can be freely chosen by users, with the dropdown menu on the top-right corner, among the secondary onset variables (e.g., the first failure in motor, cognitive, functional tests for Huntington's Disease). Each KD includes an arrow indicating the mean age of its onset for subjects. Once users set filters, the KDs introduce and overlay brighter KDs inside, which indicate KDs for the selected cohort. Dual Kernel Densities View also introduces additional dotted lines, indicating the mean values of the cohort. Users can also draw a rectangular region over the timeline, which sets a filter for subjects who had the onset at the age between the user-defined range. Fig. 11 suggests that the subjects' mean diagnosis age is at 8-9 years old with a peak around age 12 and a long tail towards older ages. By looking at the dual KDs, it seems that the mean difference between the diagnosis (red KD above) and the first onset of seroconversion (light purple below) is about three years; the difference increases for a cohort (dotted lines, darker purple below, and orange above) with being breastfed, which is consistent with the prior studies [15, 24]

4.5.2 Subject List View

Subject List View provides a list of subjects' observations as dots (visits) over a timeline. Each dot represents a visit, which are color-coded based on the corresponding state. For each subject, we draw a narrow, red rectangle below a dot for a visit with the onset of the disease and an asterisk symbol above a visit with the onset of the secondary variable (e.g., initiation of medication in Parkinson's disease). The initial order of subjects are in the order of patient index code, but the list brings patients within a selected cohort to the top once users set filters. In Subject List View, users can view the posterior distribution over N states as a pie chart. By observing how slices of pies change their values over time, users can inspect the detailed disease progression of a subject including the model's confidence of state assignment (T6). Users can hover to open a popup view that shows the posterior distributions of all visits for a specific subject. Fig. 11 shows the selected list of patients who were never breastfed. Most dots present full circles

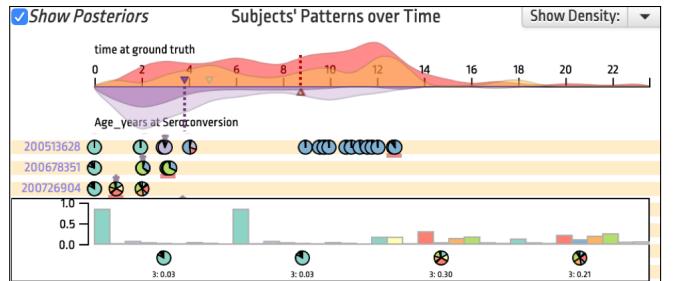


Fig. 11: Subject Timeline shows 1) Dual Kernel Densities View and 2) Subject List View. Dual Kernel Densities View overlays additional dual Kernel Density Diagrams for a selected cohort, and Subject List View highlights subjects in the cohort. Users open a popup to view posterior distributions over 9 states for a subject with three visits.

(dominant with a slice), which show model's confidence in the state assignments. However, a subject on the popup shows evenly-spread posterior distributions over nine states for the last two visits, which signify uncertainties of state assignment for those visits. As it turns out in the view, the subject shows seroconversion (purple star above pie) and diagnosis (red underline below pie) at the same time under 1 year old, which is why the model thinks of the visits as uncertain or outliers.

4.6 State Sequence Query Builder

State Sequence Query Builder is a way users can freely define and refine queries to create a cohort based on state transition patterns (T3). Using a drag-and-drop interaction, users can freely build, edit, and remove patterns. The view initially shows an empty canvas with horizontally arranged state nodes with an additional dummy node (in total, $N+1$ nodes). As users start dragging a node, a green area appears, which indicates an area in which users can drop the node to build a pattern. Once the number of nodes on canvas increases above one, links are drawn connecting the nodes. Every node and edge has its own properties shown with labels, which can also be edited on a popup window. Each node has three properties: 1) time, 2) node_at, and 3) posteriors. Using these three properties, users can further refine a search query per node with respect to the time range of the node, whether the node is at the beginning, middle, end, or anywhere, and the top-2 posterior distributions. Each edge between two nodes has two properties: 1) the maximum time between nodes and 2) the sequential order of the two nodes. Users can set the maximum allowed time between two nodes and determine whether the two states need to be consecutive, not consecutive, or either. The dummy node is used when users do not intend to specify any state for the visit. Once users are satisfied with the configuration of patterns to search for, users can hit the "Filter by Pattern" below to filter based on the pattern. Users can continue to refine patterns after observing the results. Fig. 12 shows a pattern with two nodes: State-2 and State-5. The pattern includes specific configuration: 1) State-2 occurs between age between 0 and 85 months as the beginning state for the subject; 2) State-3 occurs between age between 114 and 287 months as the ending state for the subject; 3) both states are assigned with posterior probabilities greater than .75 at least.

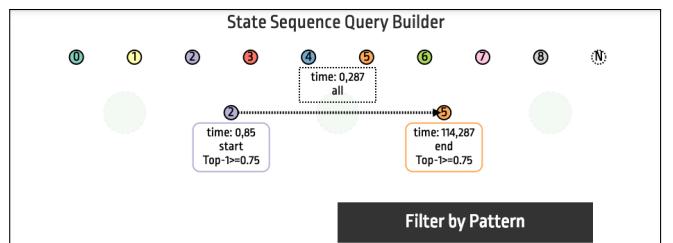


Fig. 12: State Sequence Query Builder allows users to build and refine state transition patterns. Users can adjust filtering criteria (e.g., time of visit) for each node and edge by opening context menu.

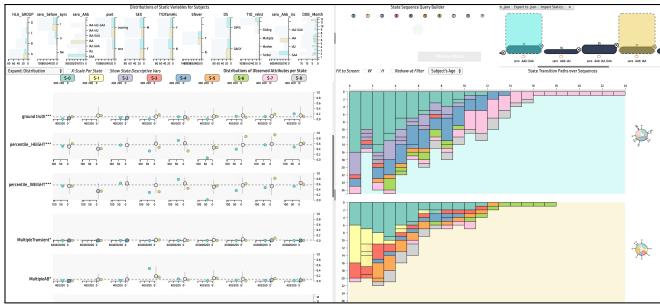


Fig. 13: Comparison Mode shows comparison between two cohorts: 1) subjects who were seroconverted with GADA (glutamic acid decarboxylase autoantibodies; light blue) and 2) those who were seroconverted with IAA (Insulin Autoantibodies; light yellow).

4.7 Cohort View and Comparison Mode

In this view, users manage cohorts built during their analysis. They can also trigger Comparison Mode between selected cohorts from this list.

4.7.1 Cohort View

Cohort View shows a list of subject cohorts that have been built and kept by the user (see top right corner in Fig. 1). Using this view, users can easily switch between cohorts. The height of each bar corresponds to the relative number of subjects within each cohort. The title can be modified with free text so that users can keep short description about the cohort. As users hover each bar, a popup view shows the description of filters, namely a list of pairs of an attribute name and its value range, used to create the corresponding cohort. The small icon below each bar allows users to ‘clone’ the set. Using this function, users can branch out new analytic path from an existing cohort while keeping its original. Users can also import cohorts from existing static variables by choosing one variable on the dropdown menu at the top-right corner. Users can also save the cohorts as a file along with other configurations like the sorting order of observed variables in views of Panel for Observed Attributes. They can save the current progresses or load previously created cohorts anytime to continue their analyses in another day or to share their progresses with other colleagues (T7).

4.7.2 Comparison Mode

Once users have more than two cohorts in Cohort View, users can trigger Comparison Mode with selected cohorts. As Fig. 13 shows, this selection turns all views into Comparison Mode. Static Variables Distribution View changes the existing bars transparent in the background, and introduces additional bars per category or bin of each bar chart; the newly introduced bars, each representing a cohort with assigned color as shown as light blue and light yellow in Fig. 13. It also opens Feature Distribution in Panel for Observed Attributes. Feature Distribution removes all existing bars for distributions, except for the mean dots and error bars. It introduces additional dots, color-coded for corresponding cohorts, separated horizontally at the vertical position for the mean values of the corresponding states per cohort. Comparison Mode disables Frequently Occurring State Transition Pattern View and Subject Timeline while maximizing the viewport of Panel for State Transitions. Pathway by Time Unit show cohorts in a vertical list so that users can compare multiple cohorts’ state transition trajectories. Using Comparison Mode, users can compare state transition pathways and their interaction with various static and observed attributes for multiple cohorts (T4). Fig. 13 shows Comparison Mode between subjects seroconverted with GADA against subjects seroconverted with IAA, where GADA and IAA are two distinct antibody types. They show distinct pathways as users can view the prevalence of State 1 (yellow stacks in Pathway by Time Unit) in the IAA cohort (yellow background). The IAA cohorts show higher-than-average percentile height and weight particularly for States 6 and 7 in Feature Distribution, which occur at ages after 10 years old in Pathway by Time Unit; the accelerated growth pattern is supported by Lamb et al. [35].

5 CASE STUDY: CLINICAL STUDIES OF TYPE 1 DIABETES

In this section, we introduce a case study that demonstrates how DPVis can help users explore disease progression pathways. Together with two physician scientists, we developed the following use case of DPVis by analyzing observational data from clinical studies of T1D. We illustrate this story with a fictitious character, Amy, a clinical investigator in T1D research who seeks to understand the disease progression patterns from 168 subjects, who were diagnosed with T1D, using observations from clinical studies: DIPIS [28] and DAISY [56].

Amy decided to model the subjects’ progression data using CT-HMM. Since there is no prior research in using DPM for subjects with T1D, she trained models with a range of parameters, primarily the number of states, from 2 to 20. She had a hypothesis about which variable sets could best characterize T1D development: autoantibodies. For training the autoantibody model, she used three observation variables, all markers of disease progression: glutamate decarboxylase autoantibody (GADA), insulin autoantibody (IAA), and islet autoantigen-2 autoantibody (IA2A) (More studies on autoantibodies can be found [64]). To test her hypothesis, she trained the two different models respectively with a range of states ($N = [2, 20]$). After testing the models with multiple rounds of cross-validations, she narrowed down to the best performing model based on the log-likelihood scores on the validation dataset: the 9-state autoantibody (AAB) model.

Amy started exploring the 9-state autoantibody model (see Fig. 1), first considering the overview provided by Feature Matrix, Pathway by Time Unit, and State Transition Chord Diagram. She found that the model provides balanced distribution over 9 states, according to State Transition Chord Diagram. She opened Feature Matrix in Panel for Observed Attributes to interpret the list of observed attributes that distinguish one state from another. Using the ranked order of measures, she found that the model accurately captures the development of all three autoantibodies over time as seen in Fig. 1. She also found it very interesting to see zinc transporter 8 autoantibodies (ZnT8A) tended to correlate with state assignment, even though it was not included as an observed variable used for the model training. She checked the data collection and learned that ZnT8A was measured only if another autoantibody (GADA, IAA, and IA2A) was positive: a measurement bias. She used the ‘stick to the wall’ feature, selecting GADA, IAA, IA2A, and ZnT8A to be always on top below the state column in Panel for Observed Attributes for easy reference. This view summarizes the states’ characteristics with respect to the three observation variables (GADA, IAA, and IA2A), starting from no autoantibody (State-0), to single autoantibody (States 1, 2, 7, and 8), to double autoantibodies (States 3, 4, 5), and triple autoantibodies (State 6), as Fig. 3 shows. Amy found that the states represent unique combinations of the three autoantibodies, except States 2 and 7, which are single-autoantibody states with GADA. She turned Feature Matrix to Feature Heatmap over Time to compare states, 2 and 7, and found that State-7 occurs at older ages (140 months) than State-2, as Fig. 4 shows.

With the 9-state model, Amy started exploring the disease progression patterns of 168 subjects. It is known that T1D follows three clinical stages: Stage 1, two or more autoantibodies but normal blood glucose; Stage 2, two or more autoantibodies and high blood glucose; Stage 3, clinical diagnosis of diabetes (see more details in Insel et al. [27]). Amy started with the following questions. Can we observe similar trends from subjects? Are there unexpected, extraordinary subjects who do not follow the three-stage progression? Can we find pre-stage patterns even before subjects develop two or more autoantibodies in Stage 1? What are the characteristics of the patterns?

To follow state transition patterns of subjects with two or more autoantibodies at one point, Amy created three cohorts by filtering based on States 3, 4, and 5, which have two unique autoantibodies. Using Frequently Occurring State Transition Pattern View, Amy checked the most frequent patterns of subjects after States 3, 4, and 5; then, she opened Pathway Waterfall to understand their pathways. For the State-3 cohort, there were 31 subjects in total. Among 31 subjects, 17 subjects stayed in double autoantibodies (States 3, 4, 5), and 10 subjects progressed to triple autoantibodies (States 6); the rest of 4 subjects evolved to a single antibody state (State 7 or 8). Among 56 subjects in the State-

4 cohort, 49 subjects stayed in double (States 4,5, or 6) or transitioned to triple autoantibodies; 7 subjects went to a single antibody state (State 8). Among 20 subjects in the State 5 cohort, 15 subjects stayed in double or triple autoantibodies (States 5 or 6); 5 subjects went to a single autoantibody state (State 8). In conclusion, DPVis allowed her to visually confirm that subjects generally follow the three-stage model, where they maintain multi-autoantibody status and showed increasing trends in HbA1c (reflecting elevated blood sugar levels) toward the last visit, where the subject is diagnosed, in Feature over Time. There were also notable exceptions who went from multiple to single autoantibody states (16 subjects). Furthermore, she also finds that State 3 and State 5 cohorts are relatively young at diagnosis (mean age = 7.2 and 7.9 years old) in comparison to State 4 cohorts (mean age = 9.9 years old). This led Amy to believe that there seems to be heterogeneous progression patterns that follow the 3-stage model, but there are also exceptions. She further set a filter using a static variable, called ‘seroconverted after 6 years old’, on top of the State 4 cohorts. She realized that all subjects who ended up at State 8 (single-antibody) showed a sharp increase of ZnT8A after 6 years old. Amy speculated that ZnT8A will be another observed variable for a new CT-HMM model if she can collect more observations on ZnT8A without measurement bias.

Following subjects’ trajectories, Amy found that there are many subjects who were continuously assigned State 0 (no autoantibodies) for all visits, yet they were diagnosed with T1D. To investigate the cohort closer, she searched using a visit sequence pattern starting and ending with State 0 with no time restriction in State Sequence Query Builder. The query returned seven subjects, who were diagnosed around 90 months (7.5 years) old, according to Dual Kernel Densities View. Among those seven, four appeared to have seroconverted before six years old in Static Variables Distribution View, so she clicked to set a filter based on “seroconverted before six.” In Feature over Time, four out of seven subjects did not show any presence of GADA or IA2A throughout their observation periods, but showed brief presence of IAA in one visit which disappeared in the subsequent visit. Amy speculated two interpretations. First, the negative autoantibody at the last visit may be measurement error. Second, the subjects may represent an endotype characterized by factors that are not captured in our data [2]. Amy was intrigued and decided to request more information about them.

6 DISCUSSION

In this section, we discuss implications of DPVis, lessons learned from our study, and provide our thoughts for future work.

6.1 Design Study Reflection: Working in a Triad on DPVis

An important key to success of design study is to effectively facilitate communication between experts in their domains, mainly health professionals, statisticians, and visualization experts. By combining the pieces from the triad of experts, we can build an effective visual analytics application. Though it is essential for the experts to carefully evaluate each other’s inputs, it is very challenging due to the knowledge gaps between domains. What facilitates effective communication between experts in different fields can be the visualization itself [33]. Throughout meetings, experts discussed over DPVis, which resulted in several changes to try out in the next phase. Therefore, what makes a visual analytics tool interpretable and engaging for users is how effectively the representations facilitate communication and new insights among the team. DPVis was used to translate a fundamental question from health professionals about HMMs, “what is a state and how does it differ from clinical stages?” As Section 5 revealed, DPVis allowed our team to understand how multiple states may fit a clinical stage and to hypothesize more granular states that can describe within and outside clinical stages. An expert also reported that Pathway Waterfall allowed him to make sense of the overall scale and dimension of patients’ visits over time. In the meetings, we gained numerous insights into the data aided by the various visualizations presented in this paper.

6.2 Cohort Building Using Multiple Views

Our goal for this study is to help physician scientists to discover heterogeneous disease progression patterns and their interaction with various

patient factors. Thus, it is inevitable to include multiple views that provide different perspectives of state transition. We provided four different views in Panel for State Transitions. Each view shows its unique visual interpretation of subjects’ trajectories. Given heterogeneous conditions of observational data, multiple views can avoid unwanted bias from a view with its specific aggregation of diverse patterns.

Physician scientists often test hypotheses by comparing different patient cohorts. The cohorts are often challenging to describe when using sophisticated criteria for grouping patients; DPVis provides various ways to build cohorts using all views and allows direct construction and refinement of queries using State Sequence Query Builder, setting intuitive filtering actions on any views. The flexible methods for constructing filters was useful for our experts to formulate and test their hypotheses. The features blends well with users’ analytic workflow, where they define and express cohorts and test their hypotheses by comparing the patterns out of those cohorts. Cohort View enables users to maintain and share such cohorts with colleagues as they iteratively refine their analysis. Using these features, we generated clinically useful insights for potential future publication in clinical journals. A future work is to investigate intuitive ways to build cohorts, which include drawing expected patterns over visualizations like AxiSketcher [32].

6.3 Embracing HMMs for Visual Analytics

In our study, we find that HMMs provide various outcomes that can be useful for visual analytics applications. In particular, HMMs allow us to discover latent (hidden) states that are associated with observed attributes in an unsupervised manner. Clinical researchers desire to learn about how diseases go through various states (stages), to discover biomarkers (observed attributes) that can affect or characterize the progression, and to use them to detect disease earlier in patients. HMMs provide us with the explainable states and their transitions with posterior probabilities—which informs users of the model’s confidence. More importantly, it is essential to use visual analytics for users to explore and compare various modeling options and outcomes. Our case study demonstrates that users can intuitively make sense of the model outcomes and make informed decisions on what actions they need to take, e.g., gather more data, change the number of states, or choose a new set of observed attributes for modeling. A future direction is to build visual analytics applications that enable users to compare multiple training instances with different parameter combinations.

7 CONCLUSION

In this work, we conducted a design study with physician scientists, statisticians, and visualization experts to develop a visual analytics application for exploring disease progression pathways and their interaction with various measures. As a result, we developed DPVis, which seamlessly incorporates HMMs and provides intuitive views and interactive features that facilitate users to develop and test hypotheses by iteratively constructing multiple cohorts based on state transitions and distributions over multiple measures. With a case study, we demonstrate the usefulness of the application to derive clinically useful insights using HMMs on observational data from clinical studies of T1D. Our collaborators have been continuously researching disease progression patterns for Huntington’s disease and Parkinson’s disease. In future work, we plan to extend DPVis to observational data from clinical studies of other chronic diseases (e.g., Alzheimer’s Disease).

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