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A Dashboard for Latent Class Trajectory Modeling: Application in Rheumatoid Arthritis

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Abstract

A key trend in current medical research is a shift from a one-size-fit-all to precision treatment strategies, where the focus is on identifying narrow subgroups of the population that would benefit from a given intervention. Precision medicine will greatly benefit from accessible tools that clinicians can use to identify such subgroups, and to generate novel inferences about the patient population they are treating. We present a novel dashboard app that enables clinician users to explore patient subgroups with varying longitudinal treatment response, using latent class mixed modeling. The dashboard was developed in R Shiny. We present results of our approach applied to an observational study of patients with moderate to severe rheumatoid arthritis (RA) on first-line biologic treatment.

Keywords:

Precision Medicine, Medical Informatics Applications, Rheumatoid Arthritis

Introduction

Complexity and variability of patients' trajectories in response to treatment poses significant challenges in many medical fields, especially in those requiring long-term care [1-4]. While it is possible to define high-level clinical phenotypes, the prediction of outcomes with respect to interventions is complicated by the high variability in responses [5-7]. One of the main trends in current medical research is a shift from a one-size-fit-all to precision approaches, where the focus is on identifying narrow subgroups of the population who would benefit from a given intervention. In order to achieve this goal of precision medicine, the analysis of longitudinal data in clinical research is becoming increasingly important. Longitudinal analytics methods, their exploitation in the context of clinical decisions, and their translation into clinical practice through accessible tools, represents a potential for enabling precision healthcare [8].

The plethora of rich data routinely collected in clinical practice and in clinical trials captures underlying information that could allow for identification of specific subgroups of patients that may in turn predict if these will benefit from specific treatments. Despite this rapid growth in available data, and advancement in machine learning methods, the application of these in medical research and routine clinical practice is still very difficult and impeded by several factors. One of these issues revolves around the limited involvement of clinicians in the discovery process and a missed link between data-driven discovery and their application in real environments. The development of informatics applications that can introduce data-driven discoveries directly into clinical practice is a current unmet necessity in medical informatics. Precision medicine will greatly benefit from accessible tools that clinicians can use to identify groups of patients that respond differently to therapies, and to generate novel inferences about the patient population they are treating. Source data and visual analytics can improve diseases' management by enacting the implementation of the learning health care system cycle: the introduction of clinical data in outcomes research, together with the translation of research findings into care, can support decision-making with the realization of precision medicine [6].

In rheumatoid arthritis, clinicians already have some classification criteria but are developed using subjective thresholds and typically applied to one or two follow-up time-points. Our approach aims at removing subjectivity and making use of all available data. One approach for subgroup discovery in longitudinal data is latent class mixed modeling (LCMM), a type of latent class analysis that is increasing in popularity as a powerful method for discovering meaningful and differing subgroups with homogeneous patterns of change over time [9-11]. Here we revise the LCMM analysis framework proposed in [12], where authors detail the methodological steps for off-line analysis, adding the necessary steps to allow on-the-fly analysis by clinicians. More specifically, we developed a dashboard tool that allows clinicians to perform several key steps of an LCMM analysis themselves; for example, the clinician can refine and redefine data-driven models, identify which of these models are clinically plausible and relevant, test specific hypotheses, and ultimately translate the results into clinical practice.

We present results of our approach applied to an observational study of moderate to severe rheumatoid arthritis (RA) patients about to commence treatment with a biologic drug. RA is a chronic, systematic inflammatory joint disease of autoimmune nature [13]. RA is a heterogeneous disease that is classified using a set of clinical factors. Patients with similar clinical features in early disease may go on to experience a very different disease course or response to medication [14]. Recently, the treatment of RA was improved by the introduction of biologic disease-modifying antirheumatic drugs which target elements of the immune system, these are typically reserved for those with an inadequate response to non-biologic disease modifying antirheumatic drugs (DMARDs) [13,15]. Clinical responses and efficacy of biologics vary largely among different individuals. Based on experience and observations made in clinic, although defined in a non-methodical fashion, response criteria are accepted (EULAR classification in non/intermediate/poor-response) [16], and clinicians agree on stratifying patients with respect to the response to the therapy as: primary non-responders which never responded or failed to respond within the first 3 months, secondary non-responders who are patients that initially responded but then loose response after 3 months, and good responders. Secondary noon-response

is seen in a significant minority of primary responders. Reasons for this could include: patients stop taking drug (i.e. feel better and are less motivated), patients develop anti-body against the therapeutic (immunogenicity), as the TNF/TNF pathway is brought under control a second inflammatory pathway may kick in and cause the disease to flare. In RA, a precision medicine approach will allow better understanding of which patients respond to specific therapies within a given time window, as well as improved disease monitoring. In order to understand the underlying mechanisms of response, well powered biomarker discovery studies are needed. A first step is to this process is to better define the phenotype so that biomarkers can be contrast across meaningful patient groupings and include all patients across multiple time-points.

Here we describe an accessible tool to perform LCMM analysis in RA. The goal is to provide clinicians and medical researchers with the possibility to automatically identify different responders to biological treatments over time. The tool relies on a dashboard-based approach to translate the data-driven retrieved models into medical inference and practice [17,18].

Methods

Latent Class Trajectory Modeling

We applied LCMM with the goal of identifying subgroups of RA patients with distinct responses to different types of biological treatment over time. The implementation of the dashboard is based on the framework proposed in [12], which includes eight steps: 1: definition of a scoping model; 2: refinement of the number of classes; 3: refinement of the model structure on the basis of fixed-effects through random-effect specification; 4: model adequacy assessment; 5: graphical presentations; 6: classes discrimination; 7: clinical characterisation and plausibility; and, 8: sensitivity analysis. Our developed dashboard implements the framework as an interactive tool aimed to give the possibility to clinicians to carry out, independently, each step of the analysis. In particular, clinicians can perform steps related to graphical representation, classes' discrimination and clinical plausibility, independently from the first steps of the analysis. Indeed, for this application we initially performed steps 1 through 4 to retrieve a *favoured model*, which we used as the default model in the dashboard. Dashboard's users can exploit this favoured model to perform the last steps of the analysis (i.e. visualize classes trajectories and compare clinical characterises in the classes), but they can also change the model parameters (e.g. the number of classes, fixed-effects) and re-run the whole analysis. Below we describe in detail the steps that we implemented in the dashboard.

Step 1: Scoping Model

We used a maximum likelihood approach to fit the model through the 'lcmm' function from the R package lcmm [19]. The function estimates mixed-effect models and latent class mixed-effect models for different types of longitudinal outcomes. We built models for the entire cohort, using all the possible combination of the available variables. While the scoping model is based on the entire cohort, the dashboard provides the option to stratifying patients on the basis of the class of treatments and perform the analysis on these subsets separately.

Step 2: Number of Classes

We tested the scoping model to determine the optimal number of classes K: 1-10 number of classes. The lcmm function provides Akaike (AIC) and Bayesian information criterion (BIC) as model fit indices. The K number of classes chosen was primarily based on BIC as suggested in [12]. AIC was considered to confirm or clarify the empirical solution. The dashboard presents as a default parameter the number of classes with the lowest BIC and gives the option of changing this number from a fixed range (1-10 classes).

Step 3 Model Refinement

We further refined the model using the model with the lowest BIC derived in step 2, considering the possibility of using linear or quadratic specification of time (days) as the random-effect, logarithm transformed values of our outcome measure, and linear or quadratic link functions to model the longitudinal outcome. The dashboard allows to perform the LCMM analysis with linear or quadric time, transforming or not the outcome and with different link functions.

Step 4 Model Adequacy Assessment

For each subject, we calculated the posterior probability of being assigned to each trajectory class and exclusively assigned the individual to the class with the highest probability. Average maximum posterior probability of assignments above 70% in all classes was considered acceptable. We ensure that each class includes at least 10% of the initial population, otherwise the model is discharged.

Steps 1-4 allow a favoured model structure to be selected using the lowest BIC value and satisfactory values from the model adequacy assessments. The favoured model is used to set the default parameters. Although, as already specified, the dashboard allows to modify the parameters and perform the analysis from scratch.

Step 5 Graphical Presentations and Class Separation

We assessed the design choices according to the clinical relevance for the specific application in RA. Severity RA is estimated using the Disease Activity Score in 28 joints (DAS28). It is an index which combines different scores: the count of the 28 swollen joints and 28 tender joints, the C-reactive protein (CRP) which levels rise in blood in response to inflammation, and the Visual Analog Scale (VAS) of patient's general health. The results of the model are visualized with the DAS28 trajectories of classes over time as well as with all four DAS28 components' individual trajectories. Differently from the original LCMM framework, where classes' discrimination was assessed by degrees of separation, this step is embedded in the graphical representation of the trajectories to simplify the tool usability by final users. The trajectories of the subjects belonging to each discovered latent class are represented with locally weighted scatter plot smoothing method (LOESS) and include confidence intervals. This step allows clinicians to independently clarify the meaning of the presented solutions and to revise the assumptions in performing latent class mixed modeling that might be context dependent.

Step 6 Clinical Characterisation and Plausibility

To assess the clinical meaningfulness of the resulting trajectories/classes, the dashboard allows for comparison of relevant clinical characteristics in the discovered latent classes through a graphical representation with violin plots (for continuous variables) and bar plot (for categorical variables).

Cohort and variable description

The data we used to perform the analysis were derived from a prospective cohort study, BRAGGSS (Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate). BRAGGSS is a UK based study including over 50 recruiting centres. Patients participate in the BRAGGSS study are followed for 12 months, during which they are assessed at baseline and three follow-up visits, at 3, 6 and 12 months [20]. From the entire cohort, we selected 1,531 patients with at least one measure of DAS28 recorded. The baseline characteristics of the total patient population are shown in Table 1. Considering the

different types of treatment, patients are stratified to three groups: biological drugs, biological drugs plus DMARDs (excluding Methotrexate), and finally biological drugs plus DMARDs (including Methotrexate). Methotrexate (MTX) is the first-line therapy for RA.

Table 1 – Cohort characteristics

Treatment group	Only Bio	Bio and DMARD	Bio and MTX
Number of subjects	275	248	1006
Gender (%)			
Male	21	21	26
Female	79	79	73
Age at baseline	65,5	65,2	62,7
(Mean and SD)	12,6	11,2	12,6
DAS 28 at baseline	4,19	4,38	4,18
(Mean and SD)	1,22	1,23	1,24
BMI at baseline	29,8	29,2	30,0
(Mean and SD)	19,7	10,8	15,2

Dashboard Implementation

The dashboard was built in response to the interest of clinicians and medical researchers for having a tool that they can independently use to identify different response trajectories of DAS28 during the first 12 months of treatment with biological drugs. To assess the usability of the tool and the clarity of the analysis to end-point users, we organized biweekly meetings with RA specialist clinicians, during which we discussed each step of the analysis and design of the dashboard according to clinicians' needs.

Dashboard Architecture

We implemented the dashboard using Shiny [https://shiny.rstudio.com]. Shiny is an open source R package to build interactive web application on the basis of R scripts. Shiny applications have two components, a user interface (UI) object and a server function, which are passed as arguments to the shinyApp function that creates a Shiny app object from this UI/server pair. The user interface object controls the layout and appearance of the application (in our case the Dashboard graphical user interface (GUI)). The server function contains the instructions to run the analyses (The Analysis Engine that performs the LCMM analysis). Finally, the shinyApp function creates Shiny objects from an explicit UI/server pair.

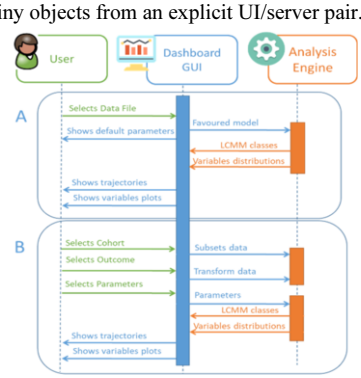

Figure 1 – UML Sequence Diagram.

Dashboard Functionalities

Figure 1 describes the system's functionalities along with the main actions of a user, dashboard GUI and analysis engine. Panel A shows the actions needed to run the favoured model, panel B depicts the actions needed to refine and re-run the model. The first user's action is to select a properly formatted text file (see Supplementary), the default parameters shown in the dashboard GUI are the ones used to run and present the favoured model. The analysis engine perform the LCMM on the basis of these parameter, assign each subject to the most probable class and sends back the results to the dashboard as DAS28 trajectories and variables values in the classes. The dashboard GUI shows the graphs of the trajectories and variables distributions. The user can re-run the whole analysis selecting a different cohort of patients (i.e. only patients treated with a specific drug regiment), outcome (i.e. log transformed DAS28) and different parameters, for example a different number of classes, as shown in Figure 1, panel B. The last set of actions to needed perform the analysis and present the results are then identical as in the approach in presented in panel A.

Results

LCMM model

In RA, clinicians expect to encounter three types of patients: primary non-responders (flat trajectories), secondary non-responders (trajectories with decreasing trends followed by increasing trends), and good responders (trajectories with decreasing trends). The favoured model selected within the first four steps of the analysis identified four classes. This is the default model shown by the dashboard, which has been discussed by clinicians on the basis of different clinical characteristics and DAS28 components. Our LCMM analysis was able to recognize a fourth group of responders: secondary good responders (trajectories with increasing trends followed by decreasing trends)

Dashboard Interface

Figures 2 and 3 depict the Dashboard GUI's results pane: DAS28 trajectories and their components in Figure 1, and demographic and clinical values distributions in Figure 2.

The main page of the Dashboard contains a panel where the user can choose the input dataset. The "View Data" button allows to visualize the dataset on which we are going to run the analysis. If the user doesn't modify any parameter, the favourite model parameters are set by default. The user starts the analysis by pressing the "Best model" button and receives a message when the analysis is complete. The same panel allows users to select a different subset of the dataset with the dropdown menus "Choose the outcome" and "Choose the treatment group", and to preview the filtered and transformed dataset. The rest of the dropdown menus and check boxes allow to set the lcmm parameters: covariates of the model, time effect, number of classes and link function. Pressing the "Start the analyses" button, the lcmm analysis starts. If all the required variables have been correctly selected, the user receives feedback that the analysis has started, otherwise he/she receives an error message which advises to complete the form in the correct way.

The first panel (Figure 2) visualizes the trajectories of the Das28, and their components. The second panel is accessible via the "Compare classes" tab and shows the variables distributions. Continuous variables: age, BMI and the health assessment questionnaire disability index (HAQ score), are presented with violin plots; categorical ones are presented with bar plots. By clicking the "Reset form" button, the user can reset the dashboard to the initial state and restart the analysis.

Qualitative Assessment of the Tool

The qualitative assessment of the dashboard's functionalities and usability has been carried out through 13 meetings where we discussed the analyses, functionalities and interface of the dashboard. We organised bi-weekly meetings with clinicians and separately, 4 meetings with a technical group composed of

experts in medical informatics. The first bi-weekly meetings consisted in preliminary sessions where we defined the key functionalities for the dashboard. First of all, we clarified the interest of clinicians in having a tool to perform this type of analysis. Secondly, we discussed expectations from the dashboard. Over several weeks, we refined the dashboard according to the feedback we received. For example, one request was to be able to visualize the trajectories of DAS28 and its components, especially for VAS and the count of tender joints. This is because RA has significant implications for patient quality-of life and increased psychological symptoms. Depression and anxiety have implications for disease activity primarily due to their influence on tender joints and patient global assessment. In addition, the capability to visualize the distribution of the type of biological drugs in each sub-group was also requested. This is because anti–tumor necrosis factor (anti-TNF) is the most common biologic therapy, but sometimes patients fail to respond on this initial anti-TNF therapy. For clinicians it is important to visualize the distribution of the type of biologic drug in each subgroup, in order to better assess the trajectories of DAS28. When we finalized the tool, we presented it at our internal meeting. We received positive feedback in terms of usability and the results of the lcmm analysis. The main refinement suggested was to add the option of visualizing the number of patients for each class, in order to create awareness in the classification that we obtained from the analysis; this has now been implemented within the dashboard.

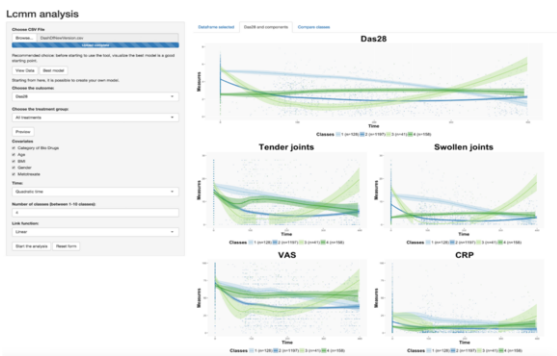

Figure 2 – Latent Classes' Trajectories: Das28 and its Components

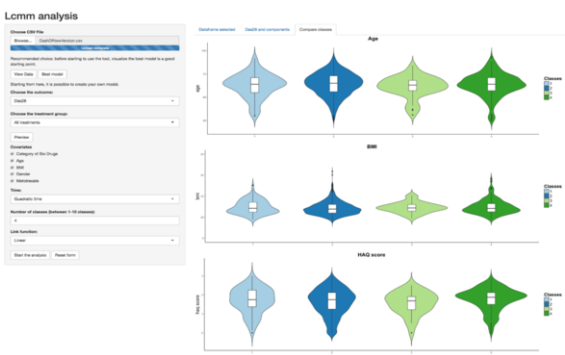

Figure 3 – Variable Distribution in the Latent Classes

Discussion

We present here a dashboard for performing latent class mixed-modeling analysis in the context of RA. The presented results and application case study are based on data from the BRAGGS multi-center study. To the best of our knowledge, this the first example of an accessible tool that enables lcmm analyses to be carried out, along with graphical representation of the results, specifically intended for a clinician and medical research user base. The dashboard provides clinicians the possibility of generating novel hypotheses regarding treatments responses, identify subgroups of patients that respond differently over time, and to assess results by comparing the mined groups with demographic and clinical features. The dashboard presents an initial, but crucial step towards enabling the translation of data-driven approaches into medical practice bettering the definition of phenotypes and supporting precision medicine.

Alongside the aforementioned contributions, several limitations of the study need to be recognised. While the graphical comparison of clinical characteristics and covariate serves to assess the clinical plausibility of the discovered classes, they might be biased. Additional methods like multinomial regression or corrections for measurement error in the classification of individuals to reduce bias could reduce potential biases. The dashboard has been evaluated by qualitative assessments through meetings with clinicians and medical informatics experts. While this approach contributes to implement a tool that responds to real-world and practical needs, a structured and quantitative usability validation is likely to further benefit the development and implementation of such a tool. Once the usability of the tool is assessed, further technical and methodological enhancements can be applied. In future versions, it may be beneficial to create a direct link between the dashboard and the BRAGGS database. Discriminative and sensitivity analysis can also be added as final steps for analyses. The BRAGGS dataset includes data on adherence to treatments and proteomics analysis performed on a subset of the cohort. Future work could focus on including these and other data, as an additional approach for subgroup validation and biomarker discovery.

Conclusions

While the initial goal of developing a tool to perform lcmm for precision medicine is situated within the scope of the current dashboard, the functionality scope can be extended. The application of lcmm analyses has shown promising results in several medical fields [9,10], and the system can be extended, generalised, and applied in any of these. Furthermore, this approach would also facilitate public and patient involvement/engagement in medical research. Accessible results will encourage involvement in study design and interpretation/dissemination of study findings through various patient groups. While more work is needed to determine the real impact of the use of such systems in medical practice, dashboard frameworks [17,18] can work as a bridge between different clinical fields, machine learning approaches and precision medicine, creating the possibility of real improvement in clinical research and practice.

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