A DeepNLME framework for modelling ordinal data to describe disease progression in patients with Alzheimer's disease.

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DeepPumas

Introduction: CDR Scores

- The Clinical Dementia Rating (CDR) scores are commonly used clinical instruments for assessing the degree of dementia severity.
- CDR Scores are used to assess:
  - Three domains of cognition (memory, orientation, judgment/problem solving).
  - Three domains of function (community affairs, home/hobbies, personal care).
- A range from 0 to 3 is used to assess each score through structured interviews of both the study subject and a companion/informant.

Table 1. Clinical dementia rating scale (CDR).

Impairment	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight	Consistently slight forgetfulness	Moderate loss; marked for recent events	Severe loss; new material rapidly lost	Severe loss; only fragments remain
Orientation	Fully orientated	Fully orientated except for time relationships	Orientated only for place at examination	Disorientated with time and place	Orientated to person only
Judgement and Problem Solving	Solves everyday problems; judgement good	Slight impairment in judgement	Moderate difficulty in judgement	Severely impaired in judgement	Unable to make judgements, solve problems
Community Affairs	Independent function at usual level	Slight impairment in activities	Unable to function at all these activities	No pretence of independent function outside home	
Home and Hobbies	Life and interests well maintained	Interests slightly impaired	Mild but definite impairment	Only simple chores preserved	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, etc.	Requires much help

Source: The Table is an abbreviated version of the one in Morris (1997), op. cit.

Presentation Outline

Motivation was initially to model the sum of the scores – or the Sum of Boxes- to describe disease progression.

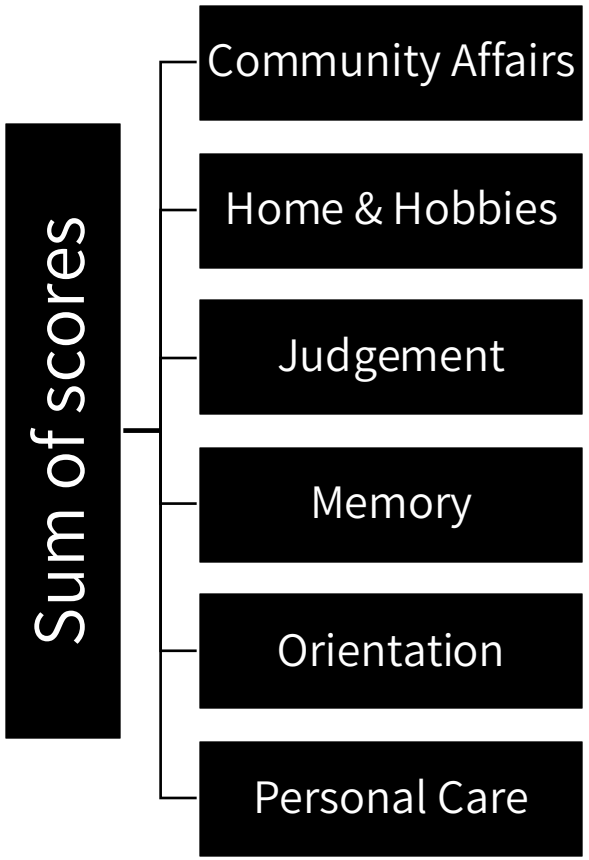
We conducted sequential covariate modeling to enhance the model with covariates.

Examined each Sub-Score individually to enable accurate predictions within specific functional domains. We implemented a streamlined workflow that allowed for efficient modeling across all Sub-Scores.

We examined how covariates can be utilized to improve individual score prediction.

We concluded our analysis by comparing the two modeling approaches through the Sum of Boxes predictions versus the sum of the Sub-Scores .

Motivation: Modeling the Sum of Boxes



Model the CDR sum of Boxes.

This can be used to describe disease progression in patients with Alzheimer.

What is the gain in generalization performance we obtain by including the covariates in the model?

However, underlying mechanism is unknown.

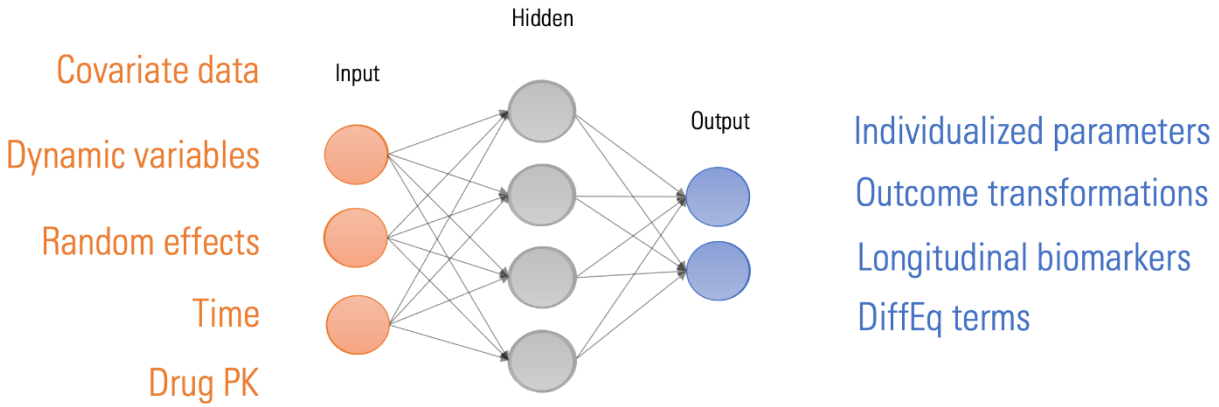
Introduction: DeepNLME

- We can use a DeepNLME model through **DeepPumas** to leverage Scientific Machine Learning (SciML) models to describe the unknown dynamics in our system.
- A simple example of Universal Differential Equations (UDEs):

$$\frac{dDepot}{dt} = -k_a Depot$$

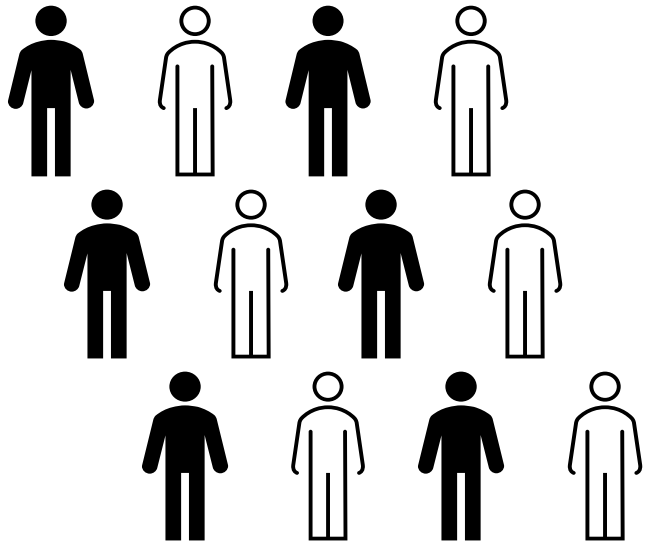
$$\frac{dCentral}{dt} = k_a Depot - k\ Central$$

$$\frac{dR}{dt} = NN(Central, R, \eta, Cov)$$

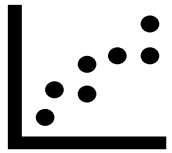


Data

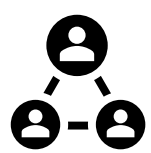
- The analysis is based on placebo group data from two-phase III clinical studies (**GRADUATE I and II**) [1].
- After filtering, a total of 326 (**GRADUATE I**) subjects were used as a training population and 352 (**GRADUATE II**) for testing.

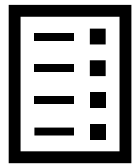


- Time profiles for each CDR sub-score spanned for **1000** days with up to **7** observations per subject for both test and train sets.



- Covariates related to demographic information, patient physiological characteristics and other cognitive score such as FAQ, MMSE, and ADAS-Cog where available.





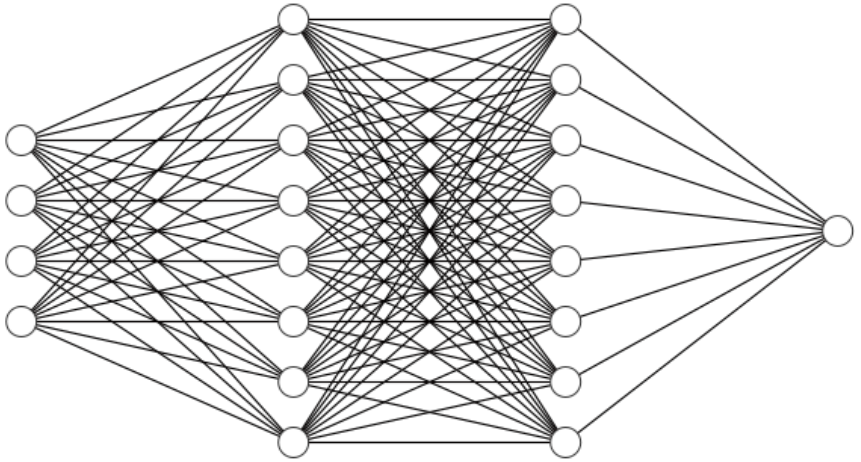
1. Bateman RJ, Smith J, Donohue MC, Delmar P, Abbas R, Salloway S, et al. Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease. N Engl J Med. 2023;389:1862–76.

Methods: Modeling the Sum of Boxes

DNLME model :

$$\frac{dCDR_{SB}}{dt} = NN(t, \eta, CDR_{SB}),$$
$$CDR_{SB}(0) = CDR_{SB,baseline} e^{\eta_{baseline}}$$

Input Layer :
- *Explicit Time*
- *CDR-SB Value*
- *Random Effects*



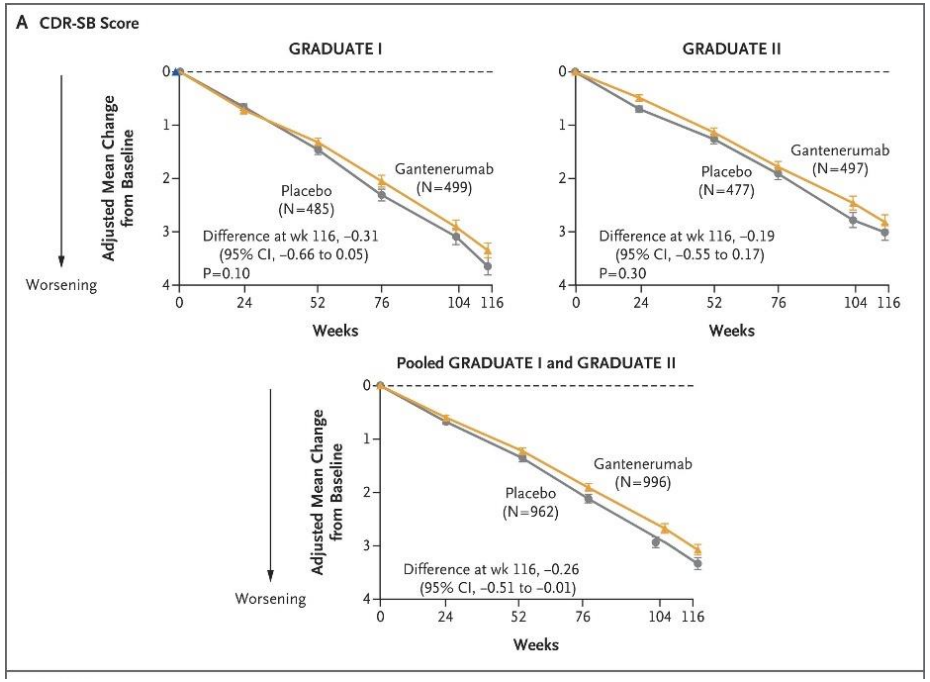
Output Layer :
CDR Sum of Boxes

Methods: Modeling the Sum of Boxes

Reference model :

$$CDR_{SB} = a_0 + a_1 * t + t * \beta_1 * Covariate_1 + \cdots + t * \beta_n * Covariate_n$$

- Reference model was chosen based on exploratory data analysis from the original publication [1] that showcased the clinical trials.
- The changes from baseline in the CDR Sum of Boxes exhibited a moderately linear trend.



1. Bateman RJ, Smith J, Donohue MC, Delmar P, Abbas R, Salloway S, et al. Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease. N Engl J Med. 2023;389:1862–76.

Methods: Covariate Modeling

- Sequential covariate modeling was performed to map baseline covariates to the empirical Bayes estimates of the fitted DeepNLME model.
- The **augment** workflow available in **DeepPumas,** is used for this purpose.
- The goal is to capture more individual variability through covariates and thus to improve longitudinal predictions.
- The steps summarizing this workflow are shown in the following diagram:

1. Fit an NLME model to describe individual time courses using random effects.
2. Extract an approximation of the posterior distribution of the random effects for each subject in the training data.
3. Fit a machine learning model to predict these posterior distributions from covariates.
4. Augment the original NLME model with the machine learning prediction of the random effect value.

Methods: Sensitivity Analysis

- Covariate and baseline biomarker significance was assessed based on sensitivity analysis using the Jacobian matrix of the function neural network f with respect to the baseline covariates.
- For a neural network with an input vector x and an output vector y, the Jacobian matrix J is defined as the matrix of all first-order partial derivatives of the output with respect to the input

$$\mathbb{J} = \begin{bmatrix} \frac{\partial \boldsymbol{f}(\mathbf{x})}{\partial x_1} & \cdots & \frac{\partial \boldsymbol{f}(\mathbf{x})}{\partial x_n} \end{bmatrix} = \begin{bmatrix} \nabla^T f_1 \\ \vdots \\ \nabla^T f_m \end{bmatrix} = \begin{bmatrix} \frac{\partial f_1(\mathbf{x})}{\partial x_1} & \cdots & \frac{\partial f_1(\mathbf{x})}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_m(\mathbf{x})}{\partial x_1} & \cdots & \frac{\partial f_m(\mathbf{x})}{\partial x_n} \end{bmatrix}$$

- The Jacobian matrix was computed for each subject, and the mean of the absolute values was then calculated across all subjects.
- For the sensitivity analysis, all the available baseline covariates were used.
- The final model incorporated only those covariates that consistently demonstrated high influence across all EBEs, as evidenced by their ranking and comparative test log-likelihood performance in the presence and absence of other covariates.

Results: CDR Sum of Boxes

- The ***DNLME*** model can also generate subjects which are more representative of the data which is evident from the minimal outlying regions in the VPC.

Model	Test -LL
DNLME	-2449
Reference	-2312

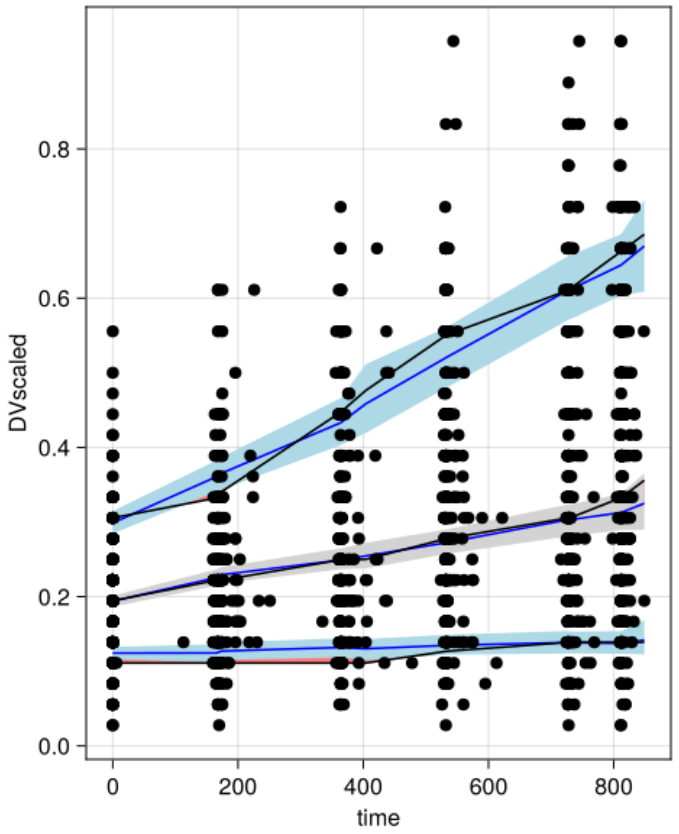


*Figure 1: VPC for the **DNLME Model***

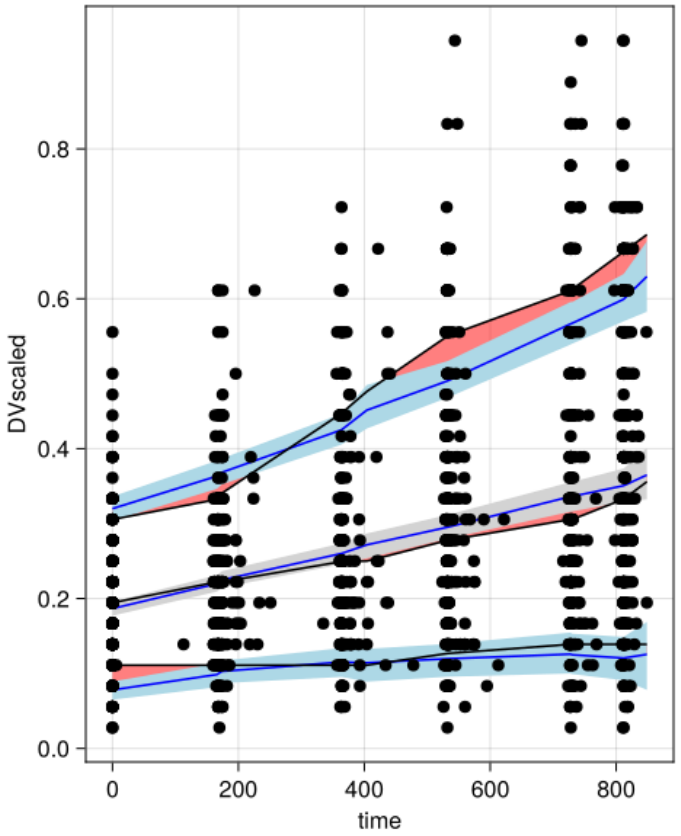


*Figure 2: VPC for the **Reference model***

Results: CDR Sum of Boxes

- Although the linear model is able to make decent predictions, we can see that some subjects have non-linearities in their profiles, which are better captured with the neural-ode model.

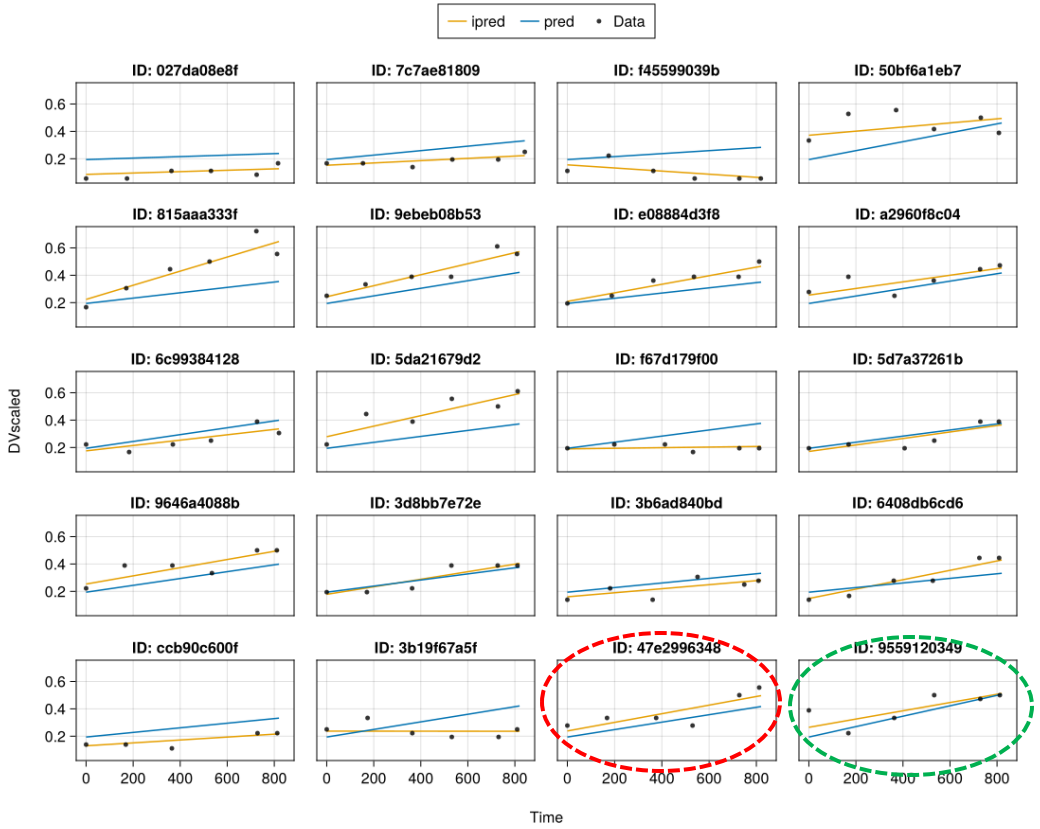


*Figure 3: IPREDs and PREDs vs Time for the test population - **Reference model***

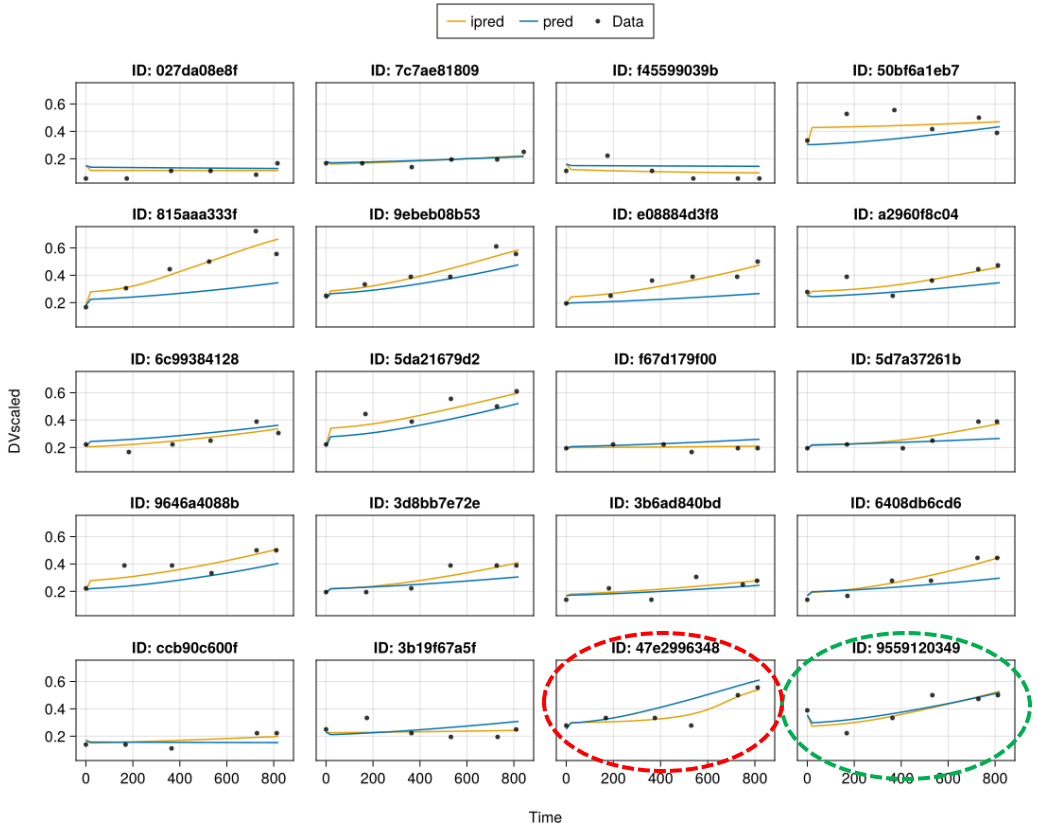


*Figure 4: IPREDs and PREDs vs Time for the test population - **DNLME model***

Results: Covariate Analysis

- In most sub-scores, the baseline values that dominated importance, were the **Adas-Cog**, **Mini-Mental State Examination**, **FAQ** scores and **CDRSB baseline** .
- The same covariates were used for both the reference and DNLME models.
- For both reference and DNLME cases, the same covariate modeling approach was used i.e. using a Neural Network to map covariates to EBEs.

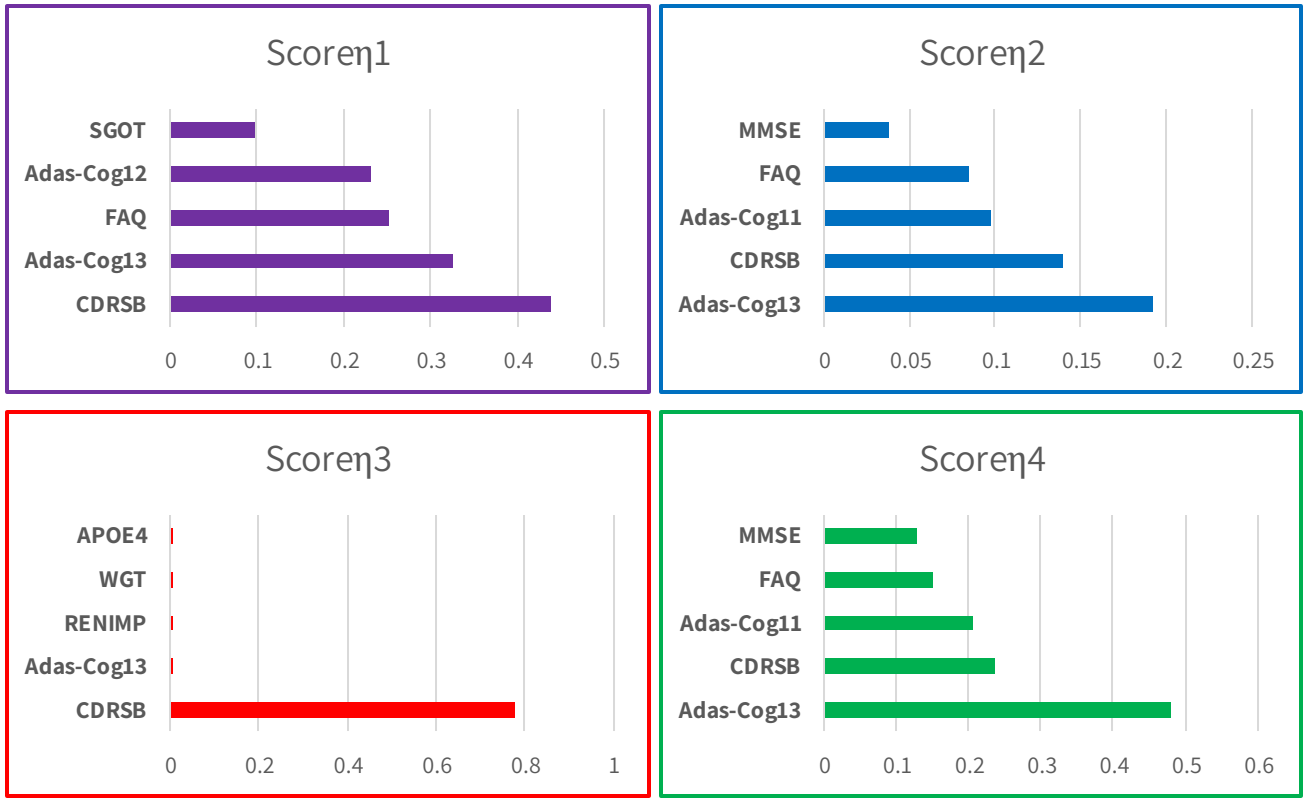


Figure 5: Covariate rankings for each EBE

Introduction: Ordinal Regression

- Regression model for **discrete** data where the dependent variable values have a **natural order.**
- Unlike typical linear regression, equidistance between the possible values is not presumed.
- Observed Data are finite set of categories $\{c_1, c_2, \dots, c_k\}$ which are ordered $c_1 < c_2 \dots < c_k$
- We use the Cumulative Density Function for predicting each possible outcome.

$$logit\big(\mathbb{P}(y_{ij} \leq\ c_k\big) = \gamma_k$$

- The most common approach for choice of γ is the ***proportional odds*** model:

$$\gamma_\kappa = \alpha_\kappa + \beta * X$$

where ***X*** is any predictor (in our case, time ***t***).

- The main assumption of the proportional odds is that β is the same across all possible outcomes.
- We use an ordinal model as **Reference** model to compare performance
- Though useful, this approach is restrictive in terms of finding non-linear relations between γ and the predictors.

Methods

- In this work, we propose to use the **DeepNLME** framework to describe the γ_k functions.
- This means that they can be any non-linear function so long as it satisfies the necessary CDF conditions.
- The mathematical formulation is summarized as follows:

$$\gamma_k = \gamma_0 + \sum_{m=1}^{k} \Delta\gamma_m \quad (1)$$

$$\Delta\gamma_k = \text{softplus}(g_k) \quad (2)$$

$$\frac{dg_k(t;\psi_{ik}{}^{NN})}{dt} = NN_k(t, g_k(t;\psi_{ik}{}^{NN});\ \psi_{ik}{}^{NN}) \quad (3)$$

where $\psi_{ik}{}^{NN}$ describe the individual neural network model parameters describing the sub-score time profiles for the ith individual and NN is a neural network with corresponding inputs $t, g_k(t;\psi_{ik}{}^{NN})\ and\ \psi_{ik}{}^{NN}$.

Results: CDR Sub-Scores – Memory

- We present the results for the **Memory** CDR sub-score which was used to build the model. The same model with minor tweaks in the neural network architecture was used to model the rest of the scores.

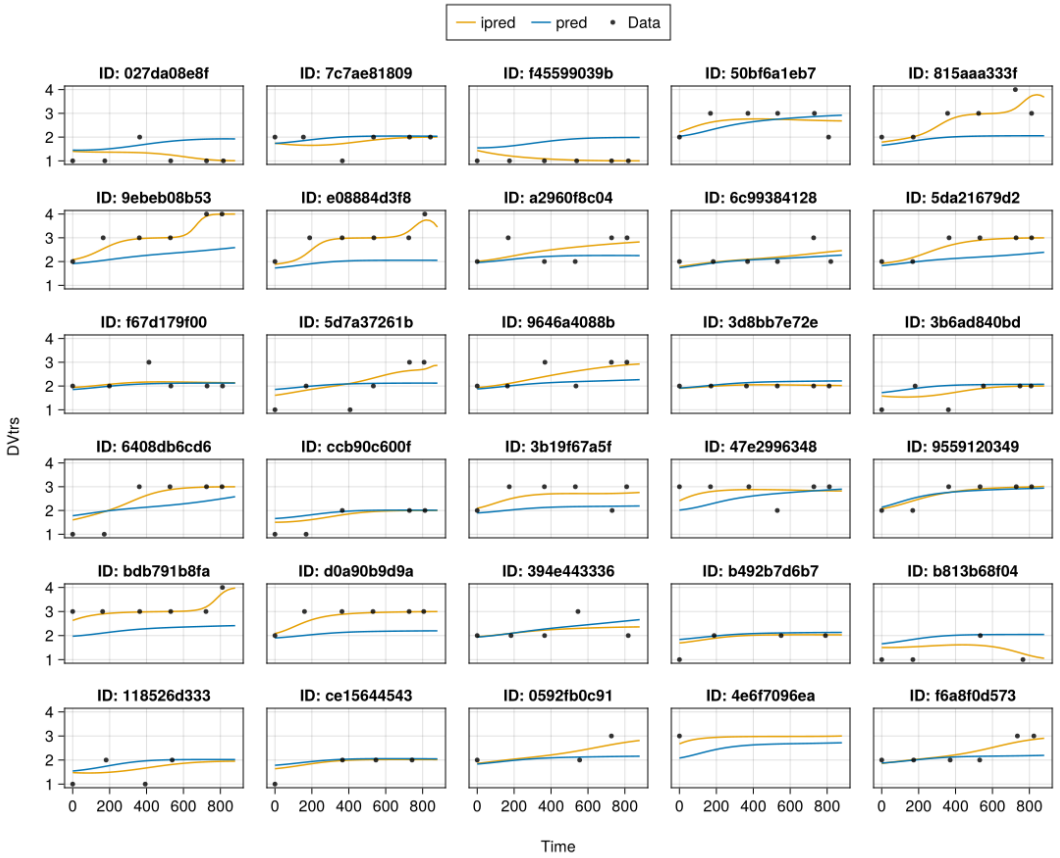


Figure 6: IPREDs and PREDs for test population – **Memory** sub-score.

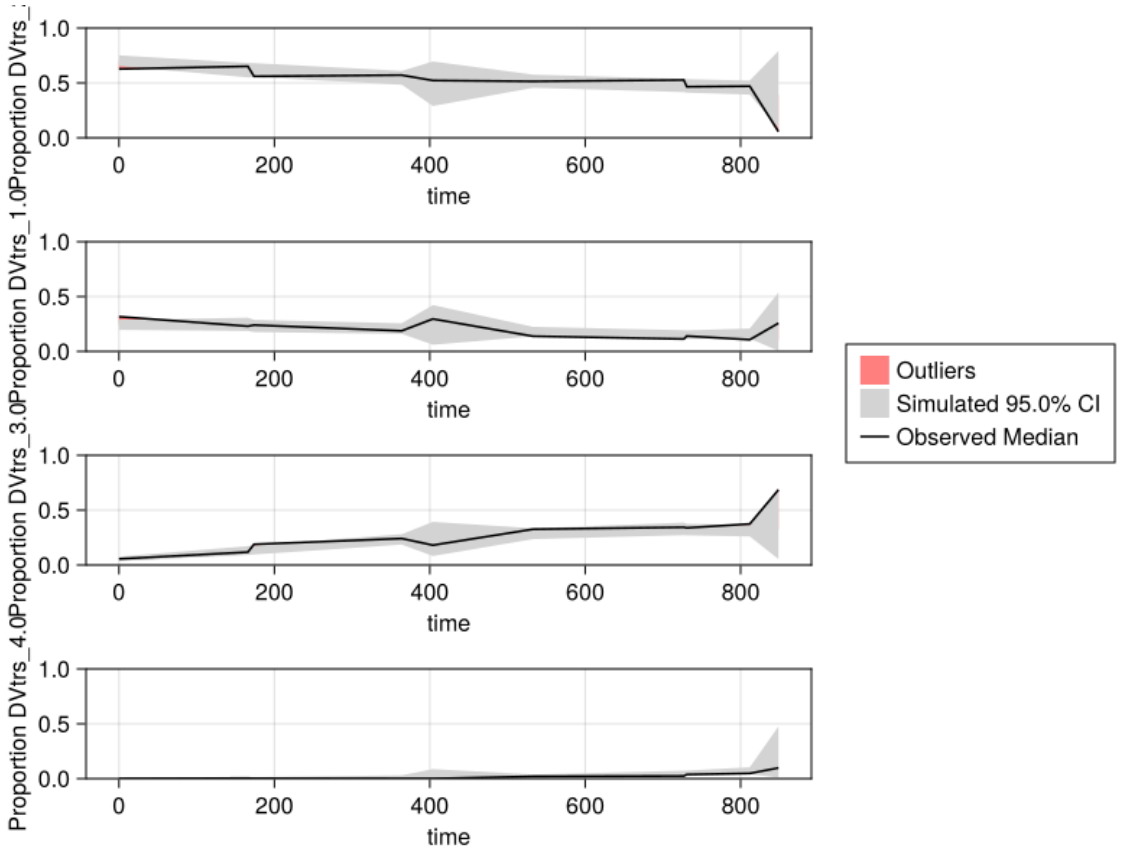


Figure 7: Visual Predictive Check for **Memory** sub-score.

Results: Covariate Analysis

- In most sub-scores, the baseline values that dominated importance, were the **Adas-Cog**, **Mini-Mental State Examination**, **FAQ** scores and **CDRSB baseline** .
- In order to reduce model complexity, only these covariates were used in the final models.
- For both reference and DNLME cases, the same covariate modeling approach was used i.e. using a Neural Network to map covariates to EBEs.

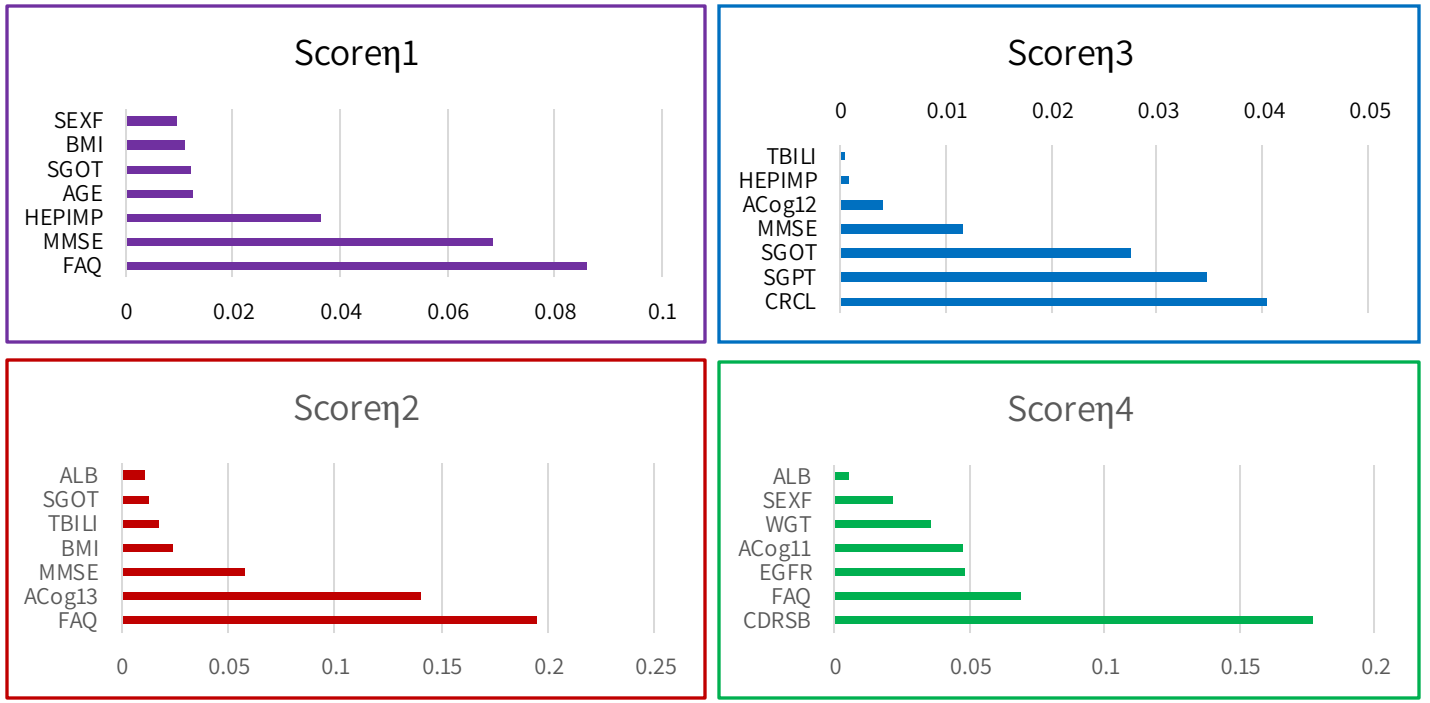


Figure 8: Covariate rankings for each EBE – **Community Affairs** score

Results: DNLME vs Reference

- Comparison is shown between a proportional odds model and the DNLME approach for the **Memory** sub-score.

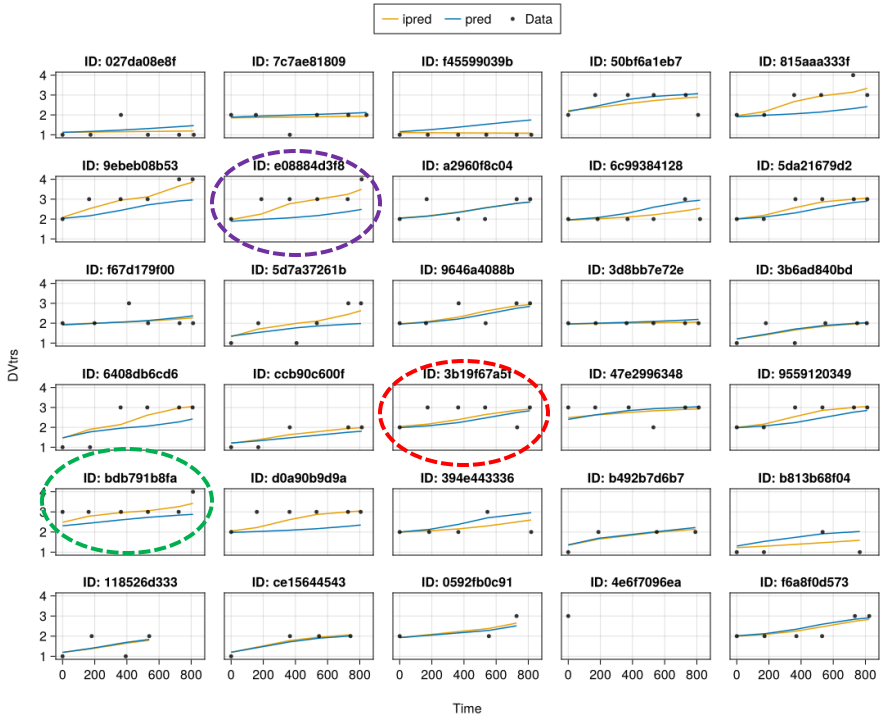


Figure 9: IPREDs and PREDs for test population – **Reference** model.

- A side-by-side comparison of individual predictions (IPREDs) and population predictions (PREDs) shows the DNLME model is superior in fitting the data.

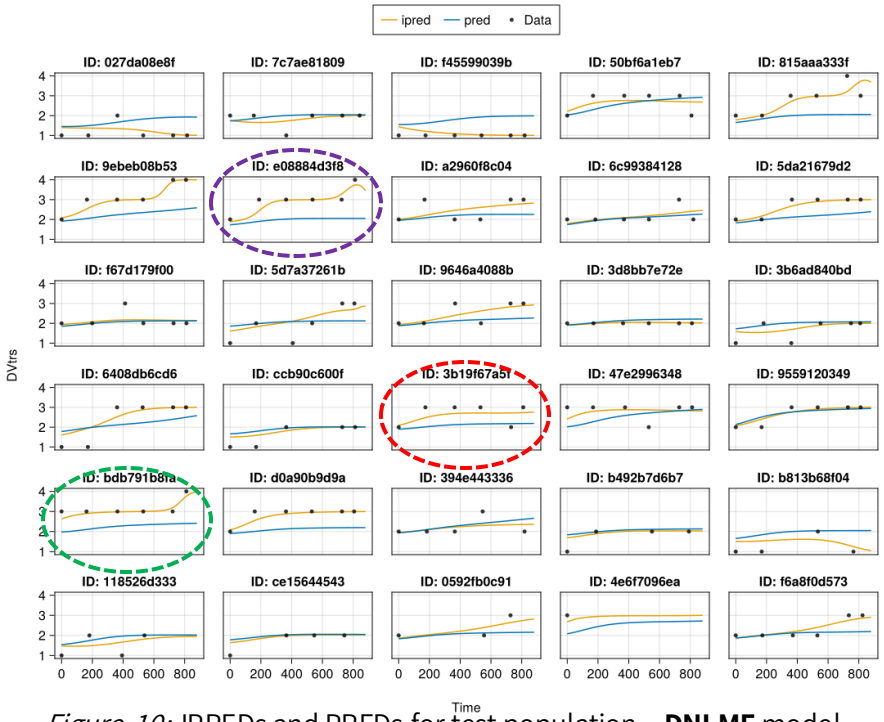


Figure 10: IPREDs and PREDs for test population – **DNLME** model.

Results: DNLME vs Reference

- Comparison is shown between the proportional odds model and the DNLME approach for the **Community Affairs** sub-score.

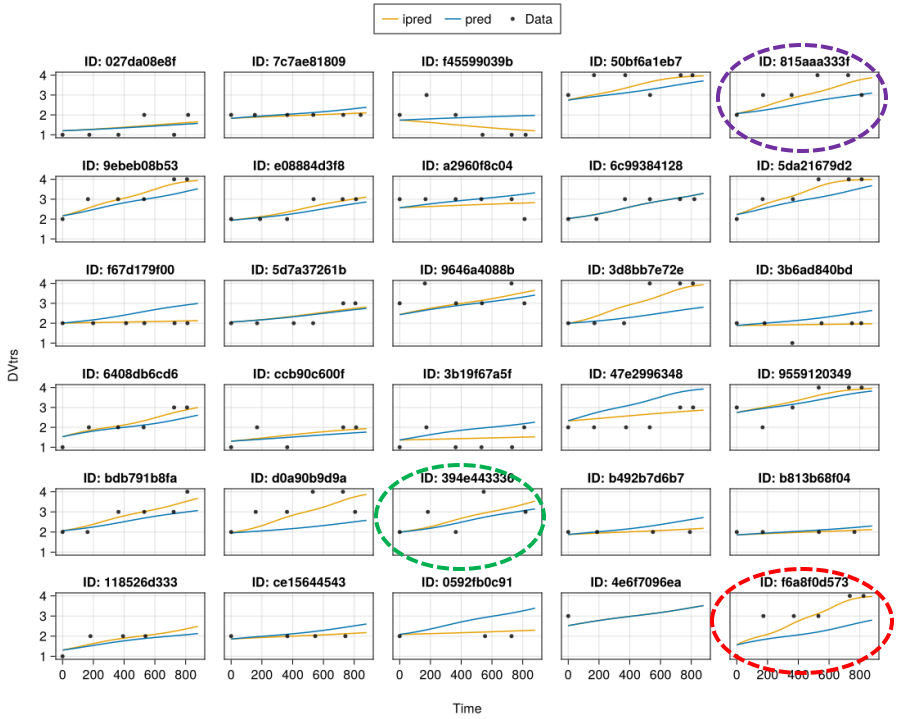


Figure 11: IPREDs and PREDs for test population – **Reference** model.

- A side-by-side comparison of individual predictions (IPREDs) and population predictions (PREDs) shows the DNLME model is superior in fitting the data.

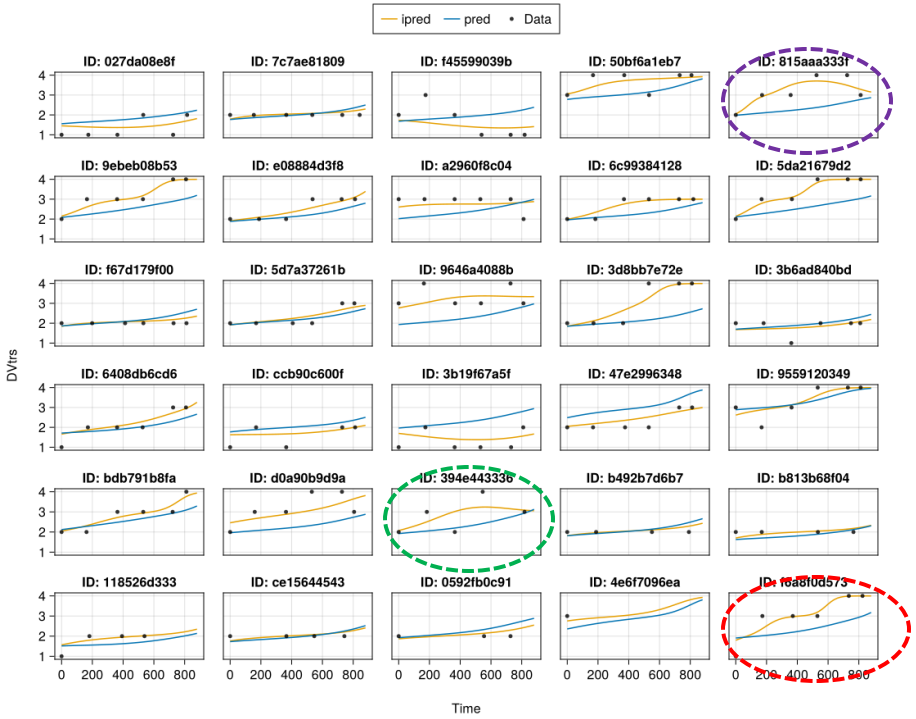


Figure 12: IPREDs and PREDs for test population – **DNLME** model.

Results: DNLME vs Reference

- **DNLME** model can assume non-linear shapes in γ values, as opposed to the proportional odds model.

Figure 13a : **γ** values for the possible outcomes of the **Reference model**

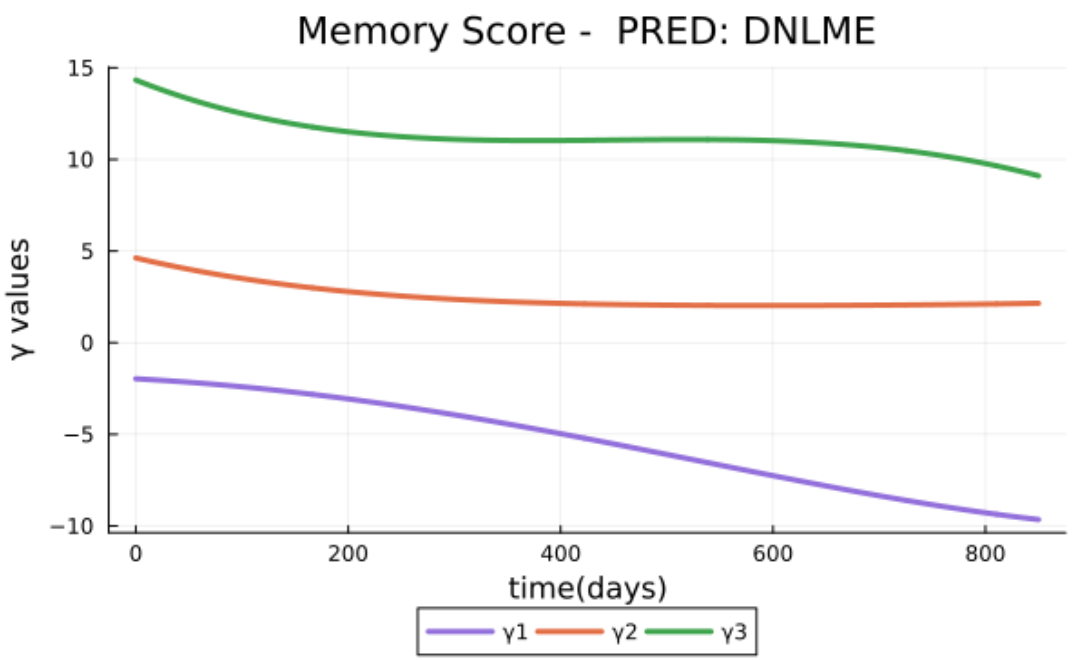


Figure 13b : **γ** values for the possible outcomes of the **DNLME model.**

Results: DNLME vs Reference

- **DNLME** model can assume non-linear shapes in γ values, as opposed to the proportional odds model.

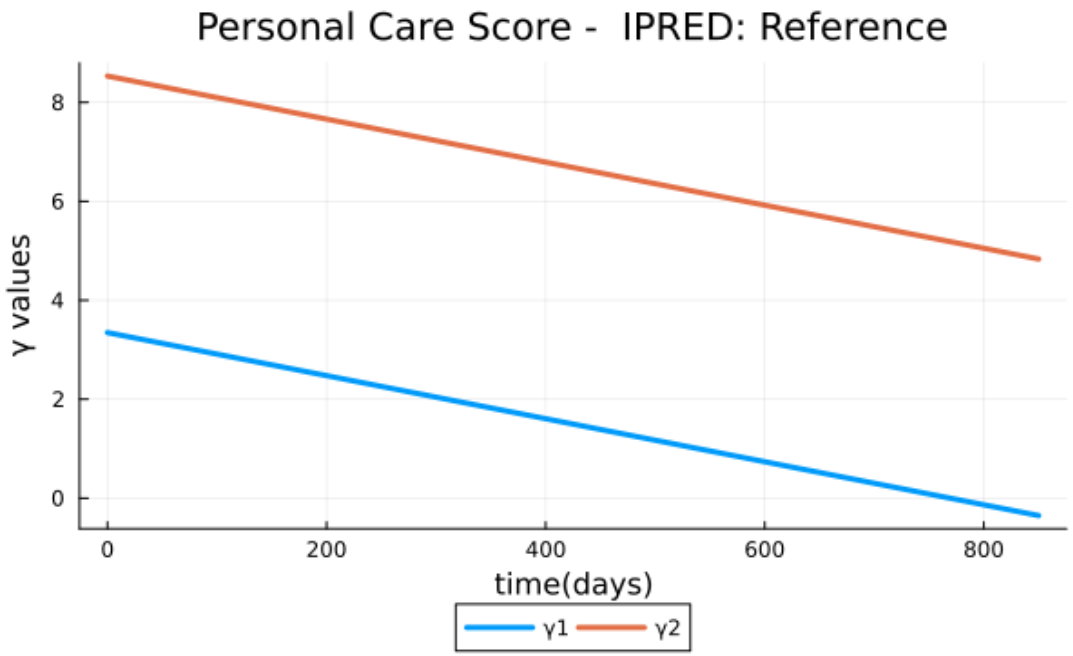


Figure 14a : **γ** values for the possible outcomes of the **Reference model**

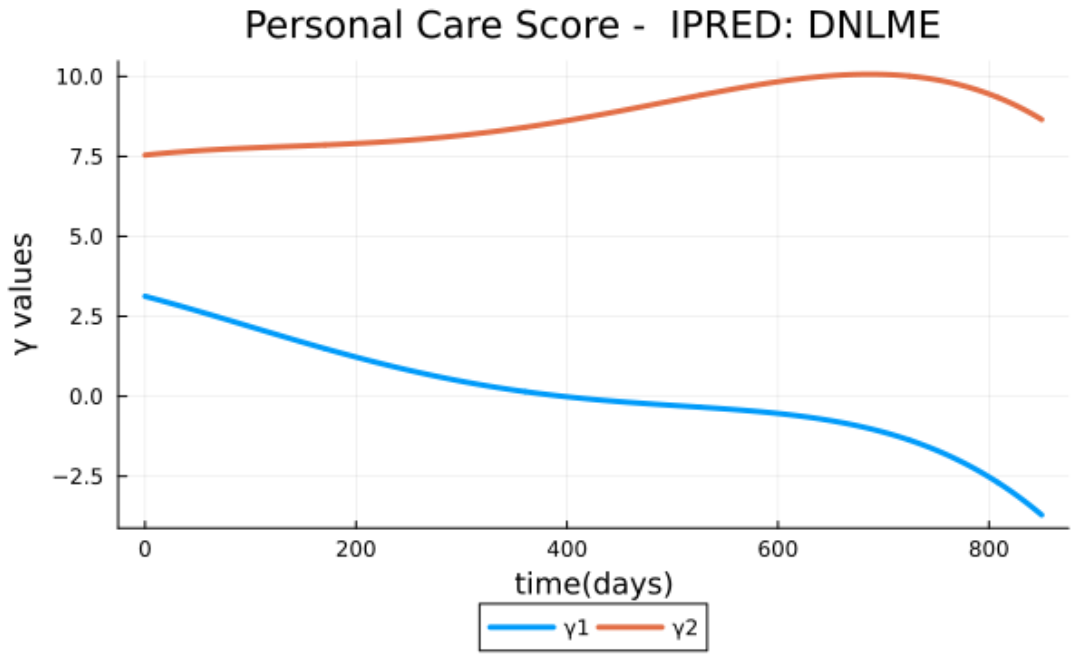


Figure 14b : **γ** values for the possible outcomes of the **DNLME model.**

Results: DNLME vs Reference

- We can examine those subjects whose log-likelihood is greatest for the DNLME model over the reference i.e. when the following is max:

$$\Delta LL_{cond} = ll_{DNLME} - ll_{Ref}$$

- We can see that for these subjects the linear model is not able to properly describe the entire profiles.
- The DNLME model is clearly more flexible in these cases and can fit the data more accurately.

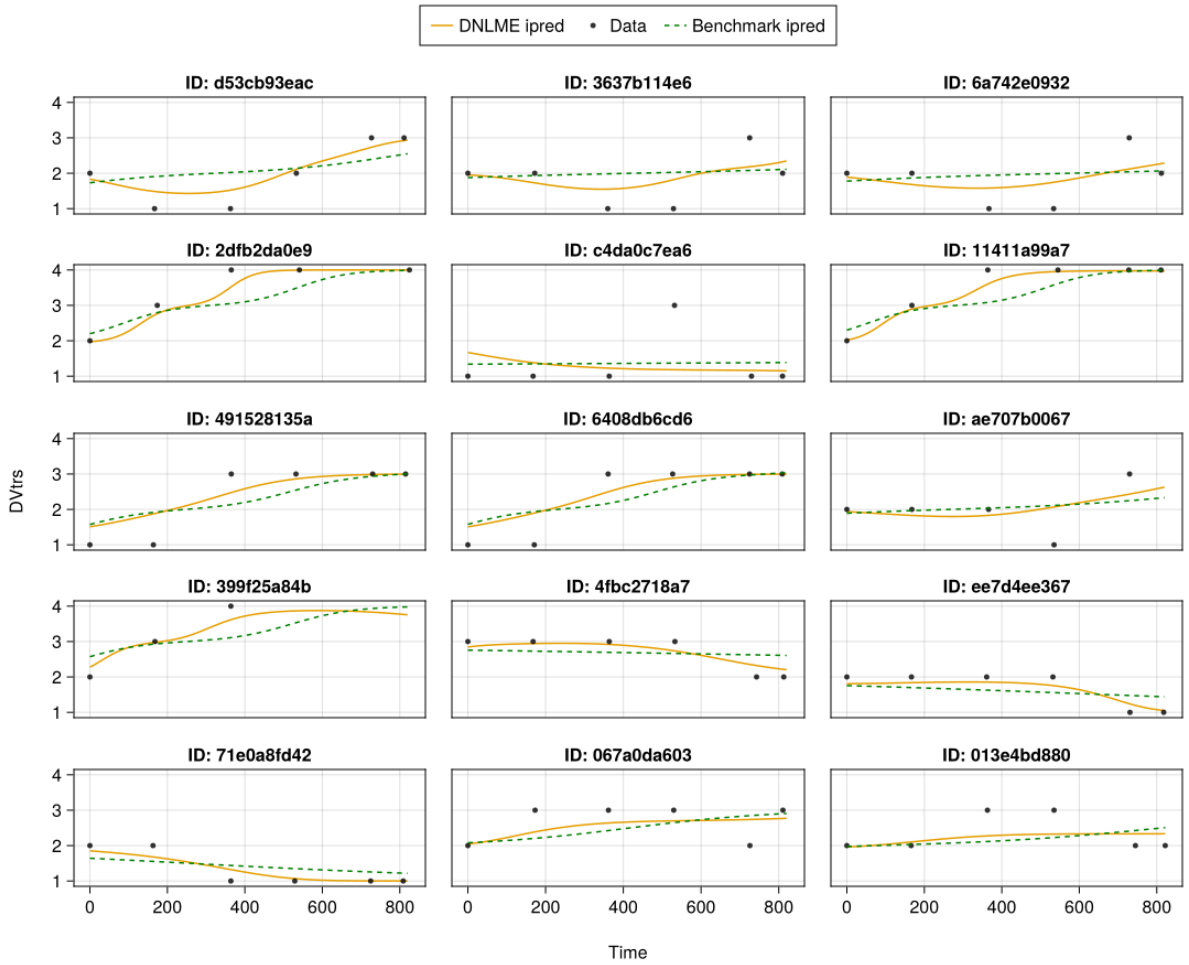


Figure 15: Subjects with max value for $\Delta LL_{cond} = ll_{DNLME} - ll_{Ref}$ for the **Memory** sub-score

Results: CDRSB vs Sum of CDRSS

Finally, we demonstrate a head-to-head comparison between the two modeling approaches.

We compare individual predictions from the CDR Sum of Boxes model vs the predictions of the individual sub-scores summed up for the test set.

The CDRSB model seems to be a superior choice for studying the total CDR score in this case.

However, the individual score models can be very useful for inference on specific domains and clinical decisions.

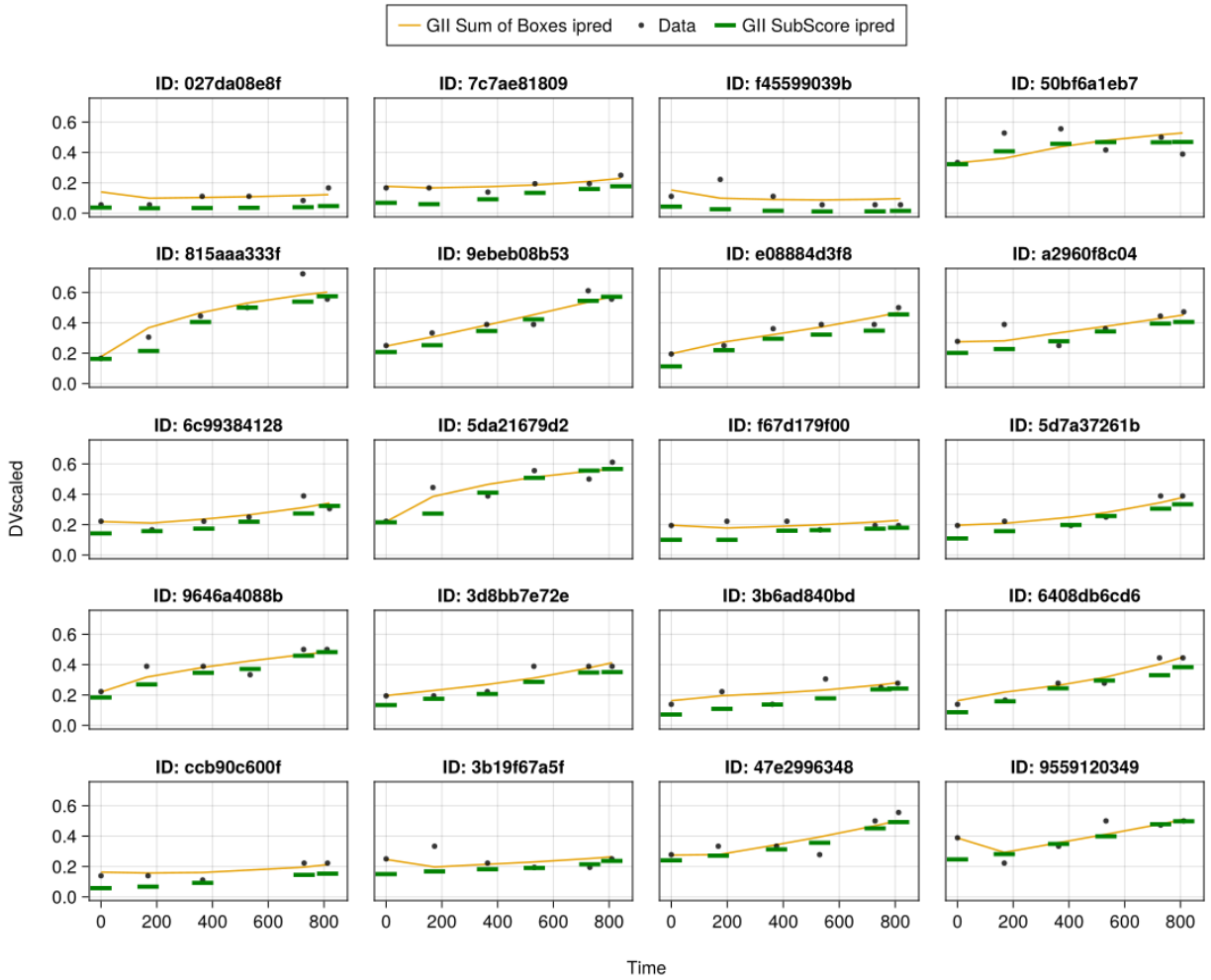


Figure 16: Comparison between the two modeling approaches **CDRSB vs Sum of CDRSS.**

Conclusions

We applied **DeepNLME** to ordinal data and describe disease progression in subjects with Alzheimer's.

The proposed model was developed on a single CDR sub-score and extended to others with minimal modification.

Sequential covariate modeling identified key baseline covariates, through sensitivity analysis.

Our model's predictions are superior to a reference model commonly used for ordinal data.

The workflow can be generalized easily and support MIDD through comprehensive multi-dimensional modeling of domain scores.

Thank you !