Modeling Huntington's disease progression using a bounded integer approach

Luke Kosinski[1], Lauren Quinlen,[1] Nathan Cunicelli[2], Terina Martinez[3], Christopher Mezias[3], Yi Zhang[1]

[1]Critical Path Institute, Quantitative Medicine, [2]Critical Path Institute, Data Collaboration Center, [3]Critical Path Institute, Huntington's Disease Regulatory Science Consortium

Introduction/Objectives

Huntington's disease (HD) is a rare, fatal, and progressive neurodegenerative disorder that has been challenging to develop disease modifying therapies for. Disease progression modeling of HD has potential to help inform new trials and de-risk drug development, but disease progression in HD is typically assessed using clinical rating scales which are integer in nature. Modeling strategies that treat endpoints as continuous violate the integer nature of the data, while ordered categorical approaches require a large number of parameters for larger scales. We apply the bounded integer model [1, 2] to the total motor score (TMS) subsection of the composite Unified HD Rating Scale (cUHDRS) [3] and compare its performance to logistic and beta regression model structures. The bounded integer model divides a normal distribution into equal-area bins corresponding to each integer possibility of a given rating scale, preserving the integer nature of the data, and uses a latent variable to estimate the probability of a rating, keeping the number of parameters low. Note that we do not test ordered categorical models as TMS has over 100 possible values, requiring excessive numbers of parameters for categorical approaches.

Table 1: Model structures

TMS = Total Motor Score
r = rate of progression
u, l = Upper and lower bounds
μ, τ = mean and dispersion parameters for beta distribution
ϕ = Cumulative distribution function for the standard normal distribution
$Z_{\frac{k}{n}}$ = Cutoff for the kth category of the n equal-sized area divisions of the normal distribution.

Model name	Equation
Generalized logistic, fixed bounds	$\frac{d\text{TMS}}{dt} = r\text{TMS}\left(1 - \frac{\text{TMS}}{\max(\text{TMS})}\right)$
Generalized logistic, model-fit bounds	$\frac{d\text{TMS}}{dt} = r(\text{TMS} - l)[1 - \frac{\text{TMS} - l}{u - l}]$
Beta with logit link	$Beta(\mu\tau, (1-\mu)\tau)$; $\ln\left(\frac{\mu}{1-\mu}\right) = \text{TMS}_0 + rt$
Bounded integer	$P(k) = \phi\left(\frac{Z_{\frac{k}{n}} - f(\text{TMS})}{\sigma}\right) - \phi\left(\frac{Z_{\frac{k-1}{n}} - f(\text{TMS})}{\sigma}\right)$; $f(\text{TMS}) = \text{TMS}_0 + rt$

Methods

Aggregated data from four clinical trials – 2CARE [4], CREST-E [5], AMARYLLIS [6], and First-HD [7] – and four observational studies – Enroll-HD [8], Predict-HD [9], TRACK-HD [10], and TRACK-ON [11] – comprising over 16,500 HD patients from the Critical Path Institute database was leveraged for modeling. The data selection criteria are: A) complete cases analysis for TMS , B) at least 40 CAG repeats, the cutoff for 100% likelihood of developing the inherited disease [12], and C) a baseline prognostic score index [13] of at least zero. The analysis set post-data selection contains over 12,500 patients. Four base models (Table 1) of TMS over time were compared: a generalized logistic model, a generalized logistic model with model-fit bounds, a beta regression model with a logit link function, and the bounded integer model. Error structures (Table 2) and patient-level random effects for both intercept and slope terms were included. Models were fit in NONMEM version 7.5, PsN 5.4, and Pirana 24.9.2, and compared using mean squared error (MSE) and mean absolute error (MAE) from a 5-fold cross validation. Visual predictive checks (VPCs) were built to evaluate model fit. One additional bounded integer model utilizing the HD integrated staging system (HD-ISS) [14] as a covariate was built to visualize covariate effects using a VPC.

Table 2: Error structures $y_{ij}, \hat{y}_{ij}, \epsilon_{ij}$ = Observed, fitted, and error values for ith patient and jth visit. μ_{ij}, τ = beta parameters

Error model	Structure	Scenario
Additive	$y_{ij} = \hat{y}_{ij} + \epsilon_{ij}$	Appropriate when the variability is assumed to be constant across a range of values.
Proportional	$y_{ij} = \hat{y}_{ij}(1 + \epsilon_{ij})$	Appropriate when the precision of measurement is dependent on the magnitude of measurement itself.
Combined Error	$y_{ij} = \hat{y}_{ij}(1 + \epsilon_{1ij}) + \epsilon_{2ij}$	Appropriate when the variability is proportional to the dependent variable and an assay specific variability.
Beta Regression	$y_{ij} \sim beta(\mu_{ij}\tau, (1-\mu_{ij})\tau)$	Appropriate for bounded measurements for which floor or ceiling effects are significant.

Figure 1: Visual Predictive Checks (VPCs)

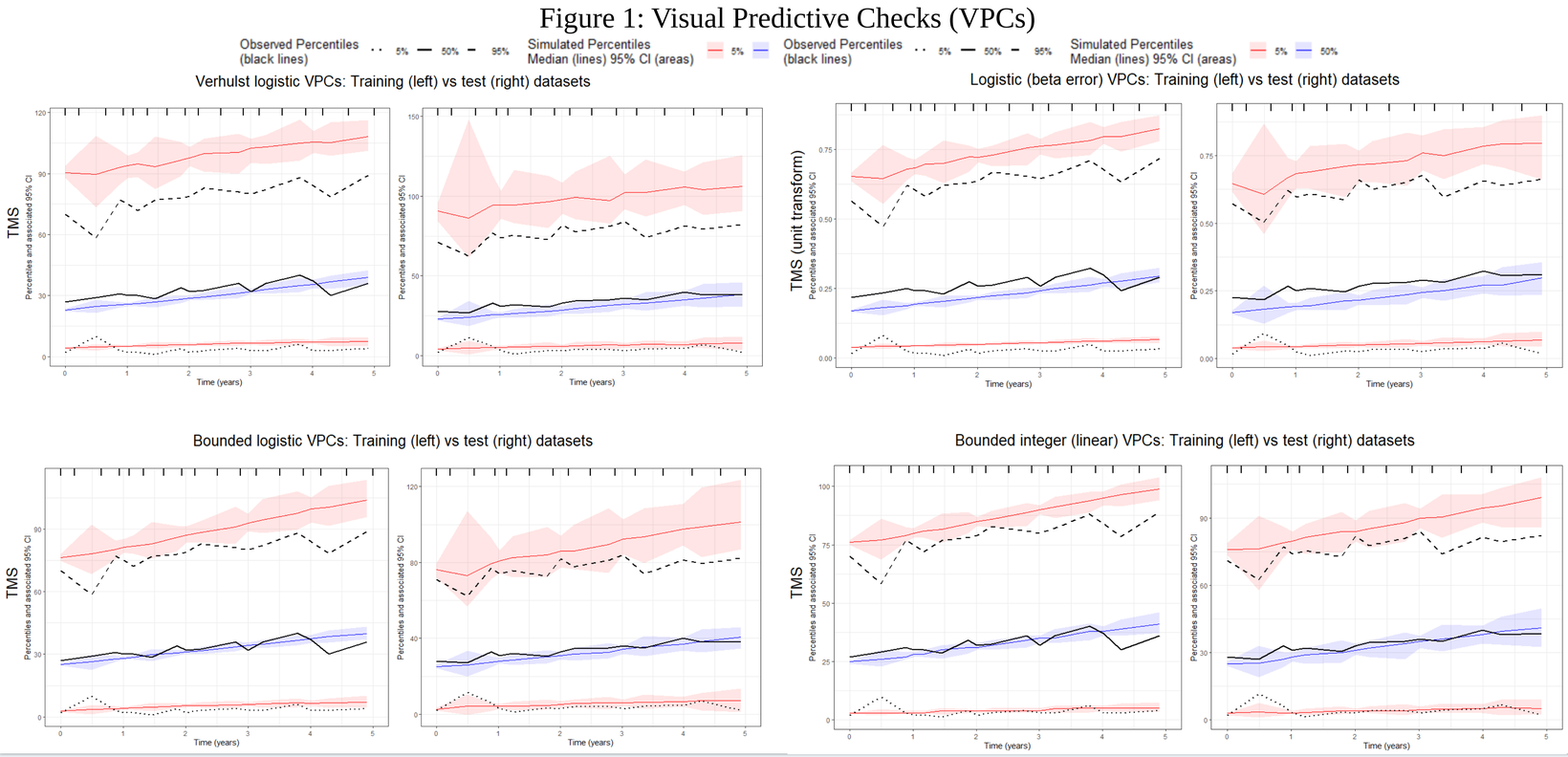


Figure 2: Model diagnostics

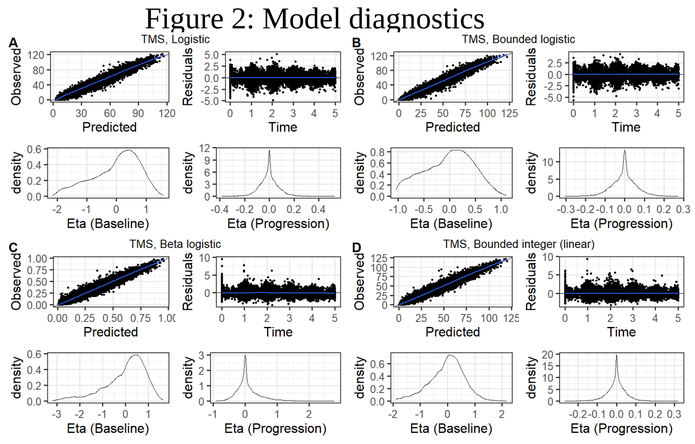
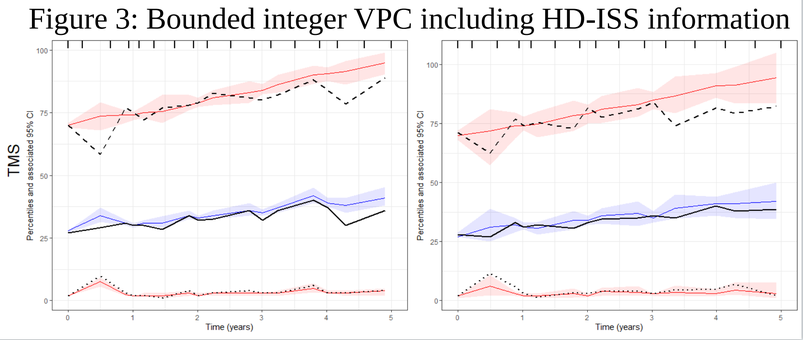


Figure 3: Bounded integer VPC including HD-ISS information



Results

VPCs (Figure 1) and diagnostic plots (Figure 2) were explored. All models demonstrated reasonable performance based on diagnostic plots (Figure 2). VPCs indicated slightly improved performance for the bounded integer model relative to the other models (Figure 1), with good performance at the lower and mid ranges but overestimation at the upper range. The 5-fold cross validation results indicated the best performance for the bounded integer model (Table 3). These results indicate better performance for the bounded integer model compared to the other models. To observe whether the upper range fit could be improved by adding a covariate, the HD-ISS was added to the model and a VPC was made showing reasonable fit at all data ranges (Figure 3).

Table 3: 5-fold cross validation results, where $k = 1, \ldots, 5$ indicates partition

Model	Sum of MSE $\sum_{k=1}^{5} \text{MSE}_k$		Sum of MAE $\sum_{k=1}^{5} \text{MAE}_k$	
	Training	Test	Training	Test
Generalized logistic	94.15	90.57	16.02	15.58
Generalized logistic with model-fit bounds	96.96	93.35	15.88	15.37
Beta with logit link	97.49	92.27	16.21	15.49
Bounded integer	93.13	88.27	15.50	14.82

Conclusions and References

The bounded integer model captures TMS in our HD data better than the logistic and beta regression approaches explored here. With the addition of HD-ISS information, the VPC suggests good model fit for the bounded integer model at all data ranges for approximately four years (Figure 3). These results suggest that disease progression models in HD, which are useful in their ability to help understand the disease and plan clinical trials, may benefit from modeling TMS or other cUHDRS subsections using a bounded integer approach.

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Contact

For more information:

- C-Path: https://c-path.org/

Luke Kosinski

Scientific Director, Quantitative Medicine

lkosinski@c-path.org

Acknowledgments: The Critical Path Institute is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) and is 56% funded by the FDA/HHS, totaling $23,740,424, and 44% funded by non-government source(s), totaling $18,881.611. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.