A Model-Based Meta-Analysis for Treatment-Modified Disease Progression in Multiple Sclerosis.

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Introduction

- Multiple sclerosis (MS) is an autoimmune disease characterized by distinct episodes of acute neurological worsening and formation of brain lesions on MRIs (RRMS) followed by a secondary progressive state (SPMS).
- Biogen has over 15 years of clinical trial data for 5 drugs: natalizumab, dimethyl fumarate, peginterferon beta-1a, interferon beta-1a, and glatiramer acetate.
- In the short term, clinical and radiological outcomes often do not align in clinical practice, e.g.
  - The Expanded Disability Status Scale (EDSS) is a common outcome for clinical trial Data
  - Annualized Relapse Rate (ARR) is the gold standard for relapsing-remitting MS trials
  - MRI data (Gd+ T1 lesions, T2 lesions) is easily measured
- The objective of this work was to extend a previous placebo-only disease progression model [1] to include treatment effects predicting long term clinical outcomes from short-term MRI endpoints.

Methods

- Patient level data was used from 11 clinical trials (Table 1)
- A Bayesian latent variable model [2] was developed with (Figure 1) :
  - **Two latent variables**; one latent variable corresponded to total disease burden and the other corresponded to short term disease activity
  - The disease burden latent variable was estimated as a linear function of time, with patient specific parameters (random effects)
  - The disease activity latent variable was a **Gaussian process** [3]
  - There was an (additive) treatment effect on the latent variables
- Model evaluation focused on **out-of-sample predictive performance**, using a test set of held-out year-two data.
- The model was implemented in Stan using the default No-U-Turn-Sampler with Hamiltonian Monte Carlo method [4].

Figure 1: **Model structure with the covariates, latent variables, and outcomes.** The arrows indicate the structural relationships between different data, parameters, and outcomes in the model. The disease burden latent variable flows across the top of the diagram, and the disease activity latent variable flows across the bottom.

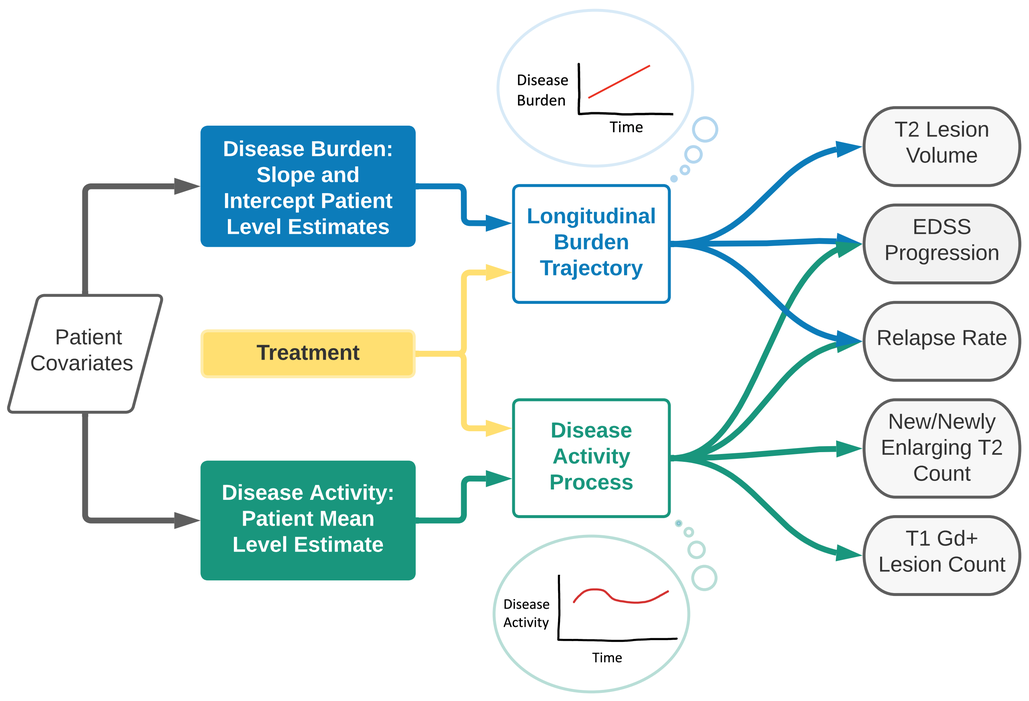
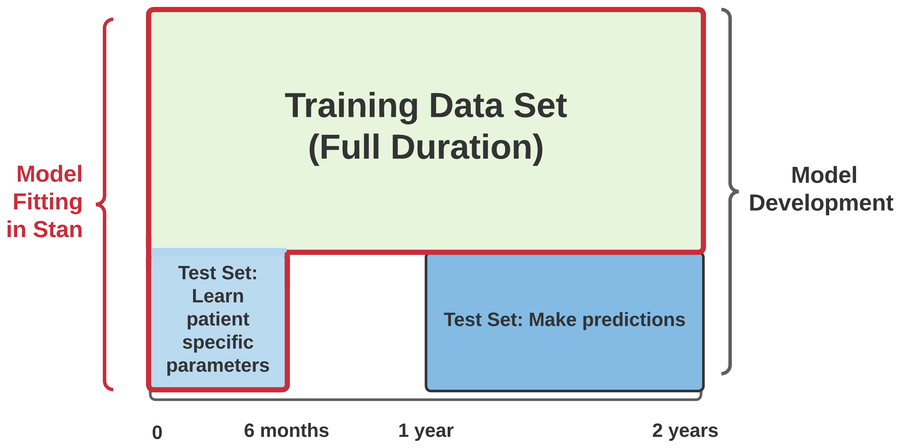


Figure 2: **Model evaluation and test set schematic.** We had sufficient data to look at out-of-sample predictive performance, and focused on model evaluation relevant to the likely model use cases by estimating patient-level random effects using short term data and predicting to longer term data.



Key Components of the Statistical Model

The disease burden was defined as:

$$f_i(t) = f_{0,i} + D_{\text{Drug}}(d_i, t, f) + f_{sl,i}\,t$$
$$\log(\text{T2 Volume}_i(t)) \sim \mathcal{T}(f_i(t)), \sigma_1, \text{df} = 5)$$
$$f_{0,i}(t) \sim \mathcal{N}(\mathbf{x}_i\beta_1, \omega_1)$$
$$f_{sl,i}(t) \sim \mathcal{N}(\mathbf{x}_i\beta_2, \omega_2)$$

The disease activity (acute, inflammatory aspects of MS) was defined as:

$$g_i(t) = g_{0,i} + D_{\text{Drug}}(d_i, t, g) + \text{GP}(t; 0, K(\alpha, \rho))$$
$$\text{T1}_i(t) \sim \text{Neg-Bin}(\exp(g_i(t)), \phi_1)$$
$$\text{New T2}_i(t) \sim \text{Neg-Bin}(\exp(\kappa_0 + \kappa_1 \times g_i(t)), \phi_2)$$
$$\text{Hazard of Relapse}_i(t) = h_0 \times \exp(\kappa_2 \times g_i(t))$$

The treatment effect submodel was defined as, with an EMAX model for dimethyl fumarate and an exponential onset rate for all treatments:

$$\delta_{\text{Dimethyl fumarate}}(d_i, \text{LV}) = \frac{d_i \times E_{\max((LV))}}{d_i + ED_{50}}$$
$$D_{\text{Drug}}(d_i, t, LV) = \delta_{\text{Drug}}(d_i, LV) \times (1 - e^{-\lambda_{\text{Drug}}\,t})$$

- $f_i(t)$ is the latent process for patient i (and directly relates to T2 lesion volume).
- $g_i(t)$ is the short-term disease activity process for patient i (and directly relates to Gd+ T1 lesion counts and new T2 lesions).
- δ is the effect on the latent variable in the structural model of a treatment
- GP is a gaussian process, with mean zero, evaluated at times t with kernel function K. The kernel function had its own parameters which depend on the choice of kernel function. The kernel parameters were not patient specific.

Results

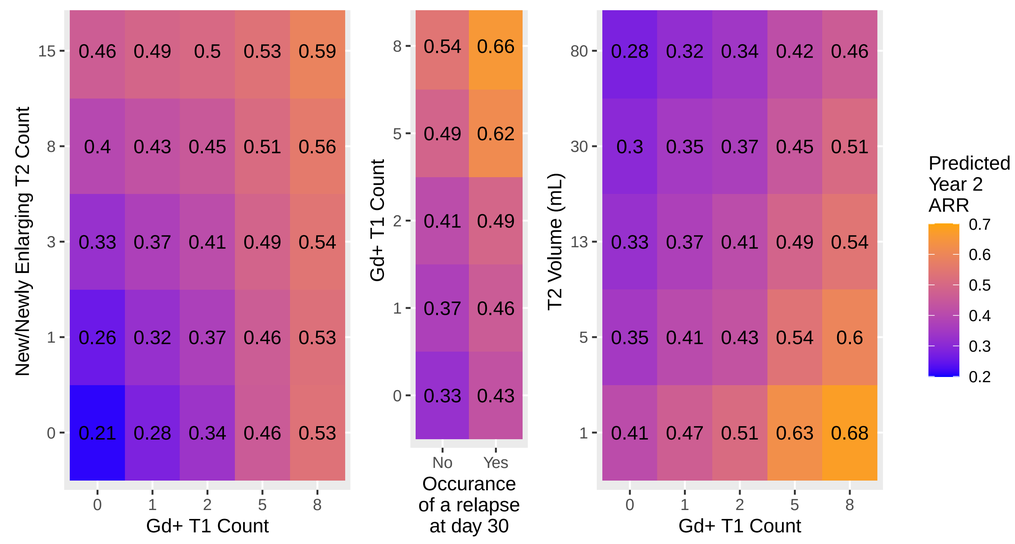
Data

Table 1: **Description of the 11 studies used in the modeling.** Duration is summarized as mean (sd). There were 9 RRMS and 2 SPMS studies included. The studies included both phase 2 studies of a duration of approximately half a year, and phase 3 studies of approximately 2 years in duration. Some of the studies were placebo controlled and others only used active controls.

Study	Study Start Year	Study Population	n	Duration in study (years)
AFFIRM (C-1801)	2001	RRMS	314	1.84 (0.443)
SENTINEL (C-1802)	2002	RRMS	595	1.79 (0.580)
C-1803	2003	RRMS	55	0.373 (0.0539)
C-1900	2004	RRMS	65	0.438 (0.0824)
DEFINE (109MS301)	2007	RRMS	409	1.48 (0.589)
CONFIRM (109MS302)	2007	RRMS	363	1.50 (0.559)
ADVANCE (105MS301)	2009	RRMS	500	0.879 (0.157)
101MS203	2010	RRMS	47	0.366 (0.0679)
ASCEND (101MS326)	2011	SPMS	449	1.66 (0.658)
109MS305	2013	RRMS	113	0.452 (0.0467)
109MS308	2015	SPMS	30	0.184 (0.0913)

Model Fit

Figure 3: **Simulated year-two ARR for different observations at day 0.** Default values were placebo arm, mean values of the covariates, female, T2 volume of 13 mL, 3 N/NE T2 lesions, and no relapse. The observed data was used to estimate subject-level random effects, and the random effects were used to simulate year-two ARR. This simulation was not limited to day 0 and any set of plausible observed values could have been used, e.g. certain observations at day 0, day 30, and 60.



Model Validation

Figure 4: **Out-of-sample prediction calibration (on year-two data) show the model accurately captured treatment effects for predictions.** Patients on placebo had much higher relapse rates than patients on treatment, and natalizumab has the lowest relapse rates.

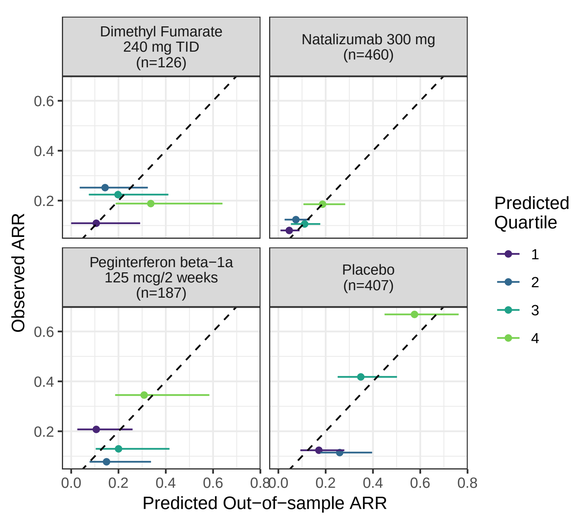
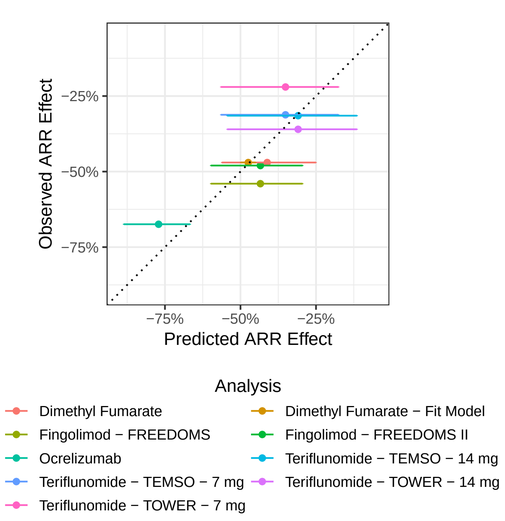


Figure 5: **Ensemble predictions of phase 3 ARR treatment effects were made from phase 2 published results, which show good agreement with observed data.** Phase 2 ARR, Gd+ T1 lesion count, and N/NE T2 lesion count were aggregated to make the phase 3 predictions. Intervals are 80% prediction intervals.



Conclusions

- A Bayesian latent-variable model was developed that characterized placebo data and drug effects across studies, populations, outcomes, and drugs at an individual level.
- The model showed predictive validity of 2-year clinical endpoints (ARR) from 6 month MRI data and was able to predict phase 3 results using phase 2 summary data, leveraging multiple reported phase 2 endpoints in the literature
- The model as a conceptual framework is extensible to include additional study data including clinical outcomes, MRI measures, and pharmacodynamic biomarkers.
- The model serves as the foundation for a platform to guide decision making for future phase II trials of novel compounds in MS.

References

[1] Wiens, M., Maghzi, A.H., Mangal, N., Kandadi Muralidharan, K., Naik, H., French, J. and Gaudreault, F. Quantitative Understanding of the Longitudinal Relationship between Short-term MRI Outcomes and Long-term Clinical Outcomes Measures in Multiple Sclerosis. In *ACoP12 virtual meeting* (2021).

[2] Hickey, G.L., Philipson, P., Jorgensen, A. and Kolamunnage-Dona, R. Joint modelling of time-to-event and multivariate longitudinal outcomes: recent developments and issues. *BMC Med. Res. Methodol.* **16** (2016):117.

[3] C. E. Rasmussen C. K. I. Williams. *Gaussian Processes for Machine Learning* (the MIT Press, 2006).

[4] Carpenter, B., Gelman, A., Hoffman, M., Lee, D., Goodrich, B., Betancourt, M., Brubaker, M., Guo, J., Li, P. and Riddell, A. Stan: A Probabilistic Programming Language. *Journal of Statistical Software, Articles* **76** (2017):1–32. URL `https://www.jstatsoft.org/v076/i01`

Acknowledgements

This work was funded by Biogen Inc.

