A Longitudinal Dose-response Model for the Progression of Alzheimers Disease, Based on a Combination of Summary-level and Patient-level Data

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Background and Objectives

Previously published statistical models for the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-cog) have elucidated key features of the longitudinal progression of this endpoint [1, 2, 3, 4, 5, 6]. While these models perform well with respect to characterization of the population mean profile, they have not enabled the simulation of realistic individual patient profiles, since the predictive distribution of these models is not constrained to the defined range of the ADAS-cog (0–70 for the commonly used 11 item version of the instrument). Moreover, the covariance structures employed in previous efforts do not allow for probabilistically correct synthesis of summary-level meta-data with individual patient data. Our proposed model builds on previous work to redress both of these issues.

Data Sources

Our general intent is that our model correctly characterize all publicly available data on the progression of ADAS-cog scores in the mild to moderate AD population. As such, our current iteration of the model is based on a simultaneous fit to the following data sources.

- **The literature meta-data set assembled and analyzed by Ito et al. [5, 6].** These data consist of summary means by treatment arm for 52 placebo controlled trials of acetylcholinesterase inhibitors in patients with mild to moderate Alzheimer's Disease, and represent approximately 19,972 patients. Data were collected and compiled based on prospective search and acceptance criteria, as described by Ito *et al.*
- **Individual longitudinal data from the Alzheimer's Disease cohort of the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI).** The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). The Principal Investigator of this initiative is Michael W. Weiner, M.D., VA Medical Center and University of California - San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research – approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For up-to-date information see www.adni-info.org.
- **Individual longitudinal data from patients randomized to placebo arm in several (interventional) trials.** These include data from the LEADe study [7] and study SC-58635, made available by Pfizer Global Research and Development.

Model Specification

Likelihood for individual patient scores

- $ADAS_{ipk}$ denotes the observed ADAS-cog score on the i^{th} occasion in the p^{th} patient in the k^{th} study;
- t_{ipk} denotes the time of the observation relative to the randomization time for that patient,
- D_{ipk} denotes the dose assigned to the patient at time t_{ipk}, expressed as a multiple of a reference dose (with reference dose varying by drug).

We specify the residual distribution of scores for patient p as:

$$ADAS_{ipk}/70 \,|\, \text{patient } p \sim \text{Beta}\left(\theta_{ipk}\tau_k,\ \left(1-\theta_{ipk}\right)\tau_k\right). \tag{1}$$

Note that this distribution is parameterized such that:

$$\text{E}[ADAS_{ipk}/70 \,|\, \text{patient } p] = \theta_{ipk} \tag{2}$$

$$\text{V}[ADAS_{ipk}/70 \,|\, \text{patient } p] = \frac{\theta_{ipk}(1-\theta_{ipk})}{\tau_k+1} \tag{3}$$

Thus, θ_{ipk} is the conditional expectation for patient p. We model this conditional expectation using the logit link function:

$$\log\left[\frac{\theta_{ipk}}{1-\theta_{ipk}}\right] = \eta_{pk} + \alpha_{pk}t_{ipk} + I_{\text{INTRV},ipk}E_{\text{PBO}}(t_{ipk}) + E_{\text{DRG}}(t_{ipk}, D_{ipk}), \tag{4}$$

where η_{pk} and α_{pk} are the (random) patient-specific intercept and slope, $I_{\text{INTRV},ipk}$ is an indicator for whether patient p is receiving an intervention (either active or placebo; in terms of the current data sources, the value of this indicator is 0 only for patients in the ADNI study and 1 otherwise), $E_{\text{PBO}}(t_{ipk})$ is the effect of placebo (nonlinear with respect to time, but assumed to be fixed across patients), and $E_{\text{DRG}}(t_{ipk}, D_{ipk})$ is the effect of drug (nonlinear with respect to both time and dose, but assumed to be fixed across patients). The placebo and drug effects are modeled as

$$E_{\text{PBO},ipk} = \beta\left(e^{-k_{el}t_{ipk}} - e^{-k_{eq}t_{ipk}}\right) \tag{5}$$

$$E_{\text{DRG},ipk} = (D_{ipk})^{\gamma_{d(p)}}\frac{E_{\Delta,d(p)}t_{ipk}}{ET_{50,d(p)}+t_{ipk}}. \tag{6}$$

The patient-level random effects are modeled as

$$\eta_{pk}|\ \text{study } k \sim \text{N}\left(\mu_{\eta,k}+\lambda_\eta(BMMSE_{pk}-21),\ \sigma^2_{\eta,k}\right) \tag{7}$$

$$\alpha_{pk}|\ \text{study } k \sim \text{N}\left(\mu_{\alpha,k}+\lambda_\alpha(BMMSE_{pk}-21),\ \sigma^2_{\alpha,k}\right), \tag{8}$$

where $BMMSE$ denotes baseline MMSE score. An additional level of the hierarchy (not shown here) corresponds to inter-study random effects.

Operational likelihood for summary statistics

Following the approach of Gillespie *et al.* [8], we model the summary-level data by directly specifying likelihoods based on approximate sampling distributions. We invoke the approximate linearity of the logit function over the range of primary interest to derive the approximate mean and variance of the sampling distributions. Beta distributions that are matched to these means and variances are employed as the "operational likelihoods".

$$\overline{ADAS}_{ijk}/70 \,|\, \text{arm } j \sim \text{Beta}\left(\overline{\theta}_{ijk}(n_{jk}\tau_k+n_{jk}-1),\ \left(1-\overline{\theta}_{ijk}\right)(n_{jk}\tau_k+n_{jk}-1)\right).$$

As discussed above, the exact distribution of $\overline{\theta}_{ijk}$ is not analytically available. However, invoking the approximate linearity of the logit transformation over the range of interest, we have:

$$\text{logit}[\overline{\theta}_{ijk}] \approx \overline{\alpha}_{jk}t_{ijk} + \overline{\eta}_{\text{intercept},jk} + E_{\text{placebo},ijk} + E_{\text{drug},ijk}$$

Priors

Ranges based on clinical plausibility (specified on the original scale) were converted to parametric constraints. In general, Uniform priors were specified on modest supersets of these ranges. Non-Uniform distributions for certain parameters were employed for mathematical and/or computational convenience.

Missing Data Mechanisms

For the purpose of posterior predictive checks only (not for model fitting), we consider a missing at random (MAR, but not missing completely at random, MCAR) missing data mechanism in which expected time to dropout is a function of baseline MMSE:

$$T_{pk} \sim \text{Exponential}(\exp(-(\zeta_0+\zeta_1 * BMMSE+\zeta_{\text{STUDY},k}))),$$

Posterior Predictive Checks

Shorter duration studies

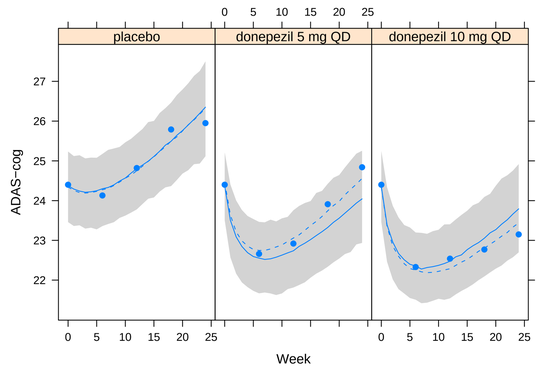

Figure 1: Posterior predictive checks for sample means from the study described in Burns *et al.*[9]. The solid line and grey region represent the median posterior prediction and the 90 percent posterior prediction interval respectively, conditional on study level random effects but unconditional with respect to patient level random effects, and the dashed line represents the median posterior prediction conditional on subject level random effects. Solid points represent simple arithmetic means based on observed cases.

Longer Duration Studies

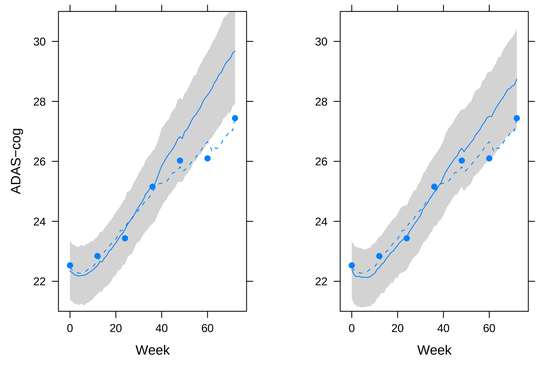

Figure 2: Posterior predictive checks for LEADe sample means, based on incorporation of an MCAR MDM (left panel) and the "working assumption" MAR MDM (right panel). The interpretation of the lines and shaded region are as in Figure 1.

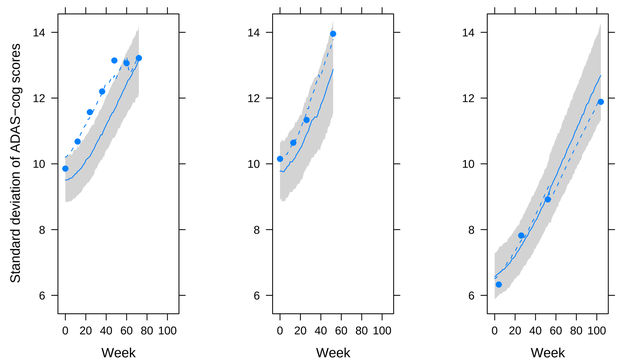

Figure 3: Posterior predictive checks for sample standard deviations for LEADe study (left panel), SC-58635 (center panel), and ADNI AD cohort (right panel). As predicted by the model, standard deviations for the ADNI AD cohort are smaller than time-matched values from the other two studies, primarily as a result of the more restrictive baseline MMSE criteria.

Applications

Simulations from the fitted model have been used to assess operating characteristics for a number of candidate trial designs. Two such examples are indicated in Figures 4 and 5.

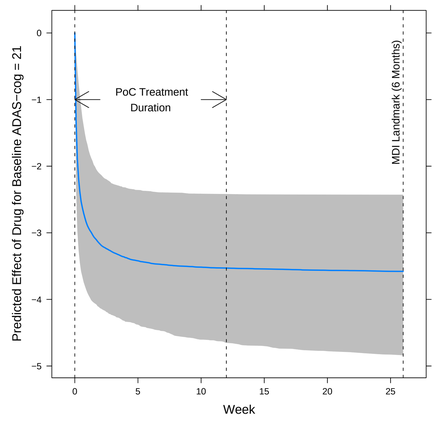

Figure 4: Assuming donepezil-like onset of effect, a proof of concept trial with 12 week duration and assessments every three weeks (and using model-based analysis) is sufficient to support reliable extrapolation to six months.

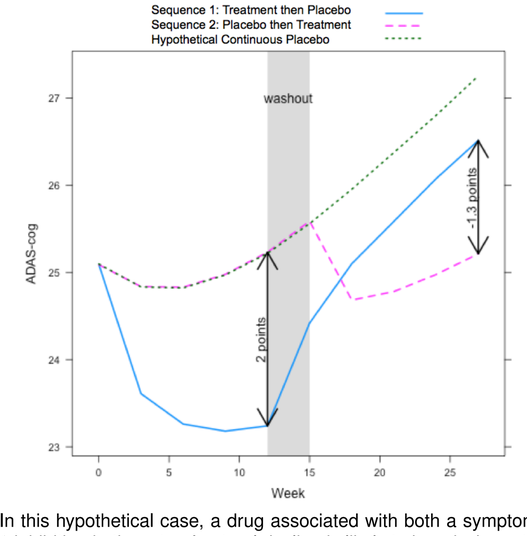

Figure 5: In this hypothetical case, a drug associated with both a symptomatic effect and a 50% inhibition in the rate of natural decline is likely to be mischaracterized by a cross-over trial (assuming a conventional non-model based analysis): the bias in the estimate of the treatment effect will be non-negligible (and negative).

References

References are provided in a two-page version of this poster available at www.metrumrg.com.

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