A meta-analytic model for Alzheimer’s Disease progression incorporating both summary-level data and patient-level data

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1. Background on Alzheimer’s Disease (AD) Clinical Trials

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Key features of clinical trials in Alzheimer’s Disease (AD)

- **Co-primary endpoints:**
  - A cognitive endpoint, typically the ADAS-cog.
  - A “global” endpoint reflecting overall clinical condition, e.g. the Clinical Dementia Rating Scale.

- **Population:**
  - Most therapies under development target mild to moderate severity.
  - Increasing interest in milder and “pre-AD” populations, however mild population is near cusp of dynamic range of ADAS-cog.

- **Study duration:**
  - Registrational trials for e.g. Donepezil were 26-30 weeks, but 18 month trials are now standard.
  - To differentiate a purely “disease modifying” (DM) drug from placebo, need to wait for cognitive decline in placebo group.
Estimated and Hypothesized Drug Effects Over Time

![Graph showing the progression of ADAS-cog scores over time for Placebo, Donepezil 10 mg QD, and Hypothetical DM treatment.](image-url)
Why use modeling and simulation?

**Modeling:**
- Avoid subjective selection of historical data that support our preconceptions.
- Formal articulation of basic assumptions so they can be debated.
- Honest, data-driven assessment of uncertainty.
- More (good) data → more precise estimates (especially relevant in estimating variance components)
- A model is prerequisite to simulation . . .

**Simulation:**
- More realistic models can be explored
- Larger class of trial designs can be explored
- Larger set of operating characteristics can be explored (e.g. probability of a significant result at the “best” dose after multiplicity adjustment).
- Predictive power is more honest than conditional power [1].
Summary data from literature

Data from systematic review of literature, assembled and published by Kaori Ito et al [2, 3], from which this is taken:

Step 1: Literature Search Criteria
- Sources: all available clinical trials in National Institute for Clinical Effectiveness ("NICE"), Medline, Embase, SBAs at FDA's CDER website (years 1990-2008)
- Key search terms: AChE inhibitor names, endpoints names (ADAS-cog, MMSE, CIBIC, etc.), and clinical trials definitions (double-blind, randomized, etc.)

Step 2: Literature Acceptance Criteria
Accept:
Literature with ADAS-cog reported if placebo group data is available from non-AChE study (i.e. Vitamin E study), keep only placebo data from that literature
Exclude:
- any duplicated literature (the same clinical data)
- duplicated data points reported with different analysis methods (selected OC over LCOF if available)
- an exploratory study (open study with number of patients <= 20)

Step 3: Further Refinement
One Study was removed from the analysis:
- only week 52 result (change from baseline) was reported, baseline ADAS-cog was not reported, and the drop-out rate was high [n=173 (baseline) to n=95 (week 52)], open study (rivastigmine)
Patient-level data

- Alzheimer’s Disease Neuroimaging Initiative (ADNI)
  http://www.adni-info.org/
  - Non-randomized, non-treatment study.
  - 2–3 year follow-up (depending on baseline status), with assessments roughly every 6 months (schedule depends on baseline status).
  - Primary endpoints are imaging and biomarker endpoints, but ADAS-cog is assessed as well.

<table>
<thead>
<tr>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>MCI</td>
</tr>
<tr>
<td>Mild AD (MMSE 20-26)</td>
</tr>
</tbody>
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- Proprietary clinical trial data sets.
Brief History of Published AD Progression Models

- Disease progression model published by Holford and Peace [4, 5, 6].

\[
E[S(t)] = S(0) + \alpha \times t + E_{PBO}(t) + E_{DRUG}(Conc)
\]

- Ito et al [2, 3] developed a meta-analytic version of this model (based on summary statistics) and applied it to substantial new body of evidence. Modifications:
  - inclusion of new covariates, notably baseline severity
  - modeled drug effect directly as a function of time and dose, not using concentration as an intermediary.

\[
E[S(t)] = S(0) + \alpha \times t + E_{PBO}(t) + E_{DRUG}(t, Dose)
\]
Gillespie et al (*) derived an error structure that allows simultaneous modeling of summary-level data and patient-level data.

- Statistically sound “weighting” of residuals and random effects based on sampling theory.
- Accurately predicts:
  - observed correlations between time points (important in simulating adaptive trials or trials where primary analysis uses longitudinal data)
  - changes in marginal variance over time (important in simulating any clinical trial).

Where We Are Today

- In progress: “fusion” of models by Ito et al. and Gillespie et al.:
  - Adapting Gillespie et al. model to respect the 0–70 constraint on the ADAS-cog (described in detail in subsequent slides).
  - Incorporating research on key covariates by Kaori Ito.
  - Application of this model to summary-level literature data and ADNI data (simultaneously).
Let $ADAS_{ipk}$ denote the observed ADAS-cog score on the $i^{th}$ occasion for the $p^{th}$ patient in the $k^{th}$ study.

Where it is convenient, we will use the following subscripts in place of $p$:
- $j = j(p)$, denoting study arm
- $d = d(i, p)$ denoting drug (not applicable for placebo)
- For example, $t_{ijk}$ denotes the time of the $i^{th}$ visit for all patients in arm $j$ in study $k$. 
Distribution of Individual Patient Scores

\[ ADAS_{ipk}/70 \mid \text{patient } p \sim \text{Beta} \left( \theta_{ipk}, (1 - \theta_{ipk}) \tau \right). \]

This distribution is parameterized such that:

\[
\begin{align*}
\mathbb{E}[ADAS_{ipk}/70 \mid \text{patient } p] &= \theta_{ipk} \\
\mathbb{V}[ADAS_{ipk}/70 \mid \text{patient } p] &= \frac{\theta_{ipk}(1 - \theta_{ipk})}{\tau + 1}
\end{align*}
\]

We then model the conditional expectation as:

\[
\log \left[ \frac{\theta_{ipk}}{1 - \theta_{ipk}} \right] = \alpha_{pk} t_{ipk} + \eta_{\text{intercept}, pk} + E_{\text{placebo}, ipk} + E_{\text{drug}, ipk}
\]
Fixed Effects for Placebo and Drugs

\[ E_{\text{placebo},ipk} = \beta \left( e^{-k_{el}t_{ijk}} - e^{-k_{eq}t_{ijk}} \right) \]

\[ E_{\text{drug},idk} = \left( \frac{D_d}{D_{\text{ref},d}} \right)^{\gamma_d} \frac{E_{\Delta,d}t_{idk}}{ET_{50,d} + t_{idk}} \]
Hierarchical Random Effects

- Inter-study random effects

\[ \alpha_{\text{study},k} \sim N \left( \mu_\alpha, \psi_\alpha^2 \right) \]

\[ \eta_{\text{intercept,study},k} \sim N \left( \mu_{\text{intercept}}, \psi_{\text{intercept}}^2 \right) \]

- Inter-patient random effects

\[ \alpha_{pk \mid \text{study } k} \sim N \left( \alpha_{\text{study},k}, \omega_\alpha^2 \right) \]

\[ \eta_{\text{intercept},pk \mid \text{study } k} \sim N \left( \eta_{\text{intercept,study},k}, \omega_{\text{intercept}}^2 \right) \]

- As shown by Gillespie *et al*, this covariance model correctly predicts the growth of the marginal variance over time.
Distribution of Sample Statistics

\[
\begin{align*}
\overline{ADAS}_{ijk}/70 \mid \text{arm } j & \sim \text{Beta} \left( \overline{\theta}_{ijk}(n_{jk}\tau_k + n_{jk} - 1), \left(1 - \overline{\theta}_{ijk}\right)(n_{jk}\tau_k + n_{jk} - 1) \right), \text{ where,} \\
\overline{\theta}_{ijk} & = \frac{1}{n_{jk}} \sum_{p:j(p)=j} \theta_{ipk}
\end{align*}
\]

Now define these “shorthand” random effects:

\[
\begin{align*}
\overline{\alpha}_{jk} & \equiv \frac{1}{n_{jk}} \sum_{p:j(p)=j} \alpha_{pk} \\
\overline{\eta}_{\text{intercept},jk} & \equiv \frac{1}{n_{jk}} \sum_{p:j(p)=j} \eta_{\text{intercept},pk} \\
\overline{\text{logit}}[\theta]_{ijk} & \equiv \overline{\alpha}_{jk} t_{ijk} + \overline{\eta}_{\text{intercept},jk} + E_{\text{placebo},ijk} + E_{\text{drug},ijk}.
\end{align*}
\]

And invoke the approximate linearity of the logit over the range of interest:

\[
\text{logit}[\overline{\theta}]_{ijk} \approx \overline{\text{logit}}[\theta]_{ijk}
\]
Linear Approximation to Logit

Points shown are observed sample means from 4 studies; all time points and all study arms are shown.
Distribution of Sample Statistics (cont’d)

Our model for $\overline{ADAS}_{ijk}/70$ results in approximately the correct gain in conditional precision, relative to a single observation:

$$\sqrt{\text{V}[ADAS_{ijk}/70 | \text{arm } j]} = \frac{\bar{\theta}_{ijk}(1 - \bar{\theta}_{ijk})}{n_{jk}(\tau_k + 1)} \approx \frac{\sqrt{\text{V}[ADAS_{ipk} | \text{patient } p]}}{n_{jk}}$$

We also get the correct gain in marginal precision by modeling the average random effects as:

$$\bar{\alpha}_{jk} | \text{study } k \sim \mathcal{N}(\alpha_{\text{study},k}, \omega_\alpha^2 / n_{jk})$$

$$\bar{\eta}_{\text{intercept},jk} | \text{study } k \sim \mathcal{N}(\eta_{\text{intercept,study},k}, \omega_{\text{intercept}}^2 / n_{jk})$$
Draft Priors (sensitivity analysis still needed)

\[ E_{\Delta,\text{drug}} = \frac{(1 + b_{\text{drug}}) E^*_{\text{drug}}}{b_{\text{drug}}} \]

\[ \log(E^*_{\text{drug}}) \sim \text{N}(0, 0.1) \]

\[ ET_{50,\text{drug}} = \frac{t^*}{b_{\text{drug}}} ; \ t^* = 12 \text{ weeks} \]

\[ b_{\text{drug}} \sim \text{U}(0, 100) \]

\[ \gamma_{\text{drug}} \sim \text{U}(0.01, 10) \]

\[ \mu_\alpha \sim \text{N}(0, 100) \]

\[ \mu_{\text{intercept}} \sim \text{N}(0, 100) \]

\[ AUC_{\text{placebo}} \sim \text{U}(0, 100) \]

\[ \beta = -AUC_{\text{placebo}} / \left( \frac{1}{k_{el}} - \frac{1}{k_{eq}} \right) \]

\[ k_{el} \sim \text{U}(0, 2) \]

\[ k_{eq} - k_{el} \sim \text{U}(0, 2) \]

\[ \psi_{\text{intercept}} \sim \text{U}(0, 10) \]

\[ \omega_{\text{intercept}} \sim \text{U}(0, 10) \]

\[ \psi_\alpha \sim \text{U}(0, 10) \]

\[ \omega_\alpha \sim \text{U}(0, 10) \]

\[ \mu_\sigma \sim \text{U}(0, 1000) \]
Example Posterior Predictive Checks

**Individual Predictions:**
- Study 1 arm 1
- Study 1 arm 2
- Study 1 arm 3
- Study 2 arm 4
- Study 2 arm 5
- Study 2 arm 6

**Population Predictions:**
- Study 2 arm 4
- Study 2 arm 5
- Study 2 arm 6

- Donepezil 5
- Donepezil 10
- Placebo 0
Transparent and Public Vetting of Models

Welcome to OpenDiseaseModels.org

Please read this page and the Overview section before doing anything else.

OpenDiseaseModels.org is an open-source disease/systems model development project. Analogous to open-source software development projects, the goal of this effort is to develop better, more useful models in a transparent and public collaborative forum.

Motivation

The motivation for OpenDiseaseModels.org is driven by the following principles:

1. Development of disease/systems models is an extremely resource-intensive effort.
2. Pre-competitive insight and resources shared across companies/institutions will lead to better systems models than could be developed by a single institution.
3. Open models, which are transparently developed and publicly vetted, will be more widely accepted and will be better positioned to impact the entire scientific/biomedical/health community.
Closing Thoughts: Statisticians and Modeling

- Most statisticians wanting to get more involved in modeling work should focus on learning three things:
  - computing
  - computing
  - computing

- On the other hand, we don’t want to become computer technicians. Don’t lose sight of the special body of knowledge and insight that has developed in the statistics discipline.
  - Think carefully about variances and correlations (they do matter!)
  - Think carefully about the data that aren’t there (missing data; selection effects; confounding).
  - Think carefully about how data will ultimately be analyzed to make decisions.
Spiegelhalter, D.J., Freedman, L.S. and Blackburn, P.R.
Monitoring clinical trials: conditional or predictive power?

Ito, K., Rosario, M., Ahadieh, S., Corrigan, B.W., French, J., Fullerton, T., Zhang, R., Lockwood, P., Zhao, Q., Qiu, R., Russell, T. and Tensfeldt, T.
A disease progression meta-analysis model for cognitive deterioration with alzheimer's disease.

A disease progression meta-analysis model in Alzheimer's disease.
*Alzheimer's & Dementia* (Accepted May 13, 2009).

Holford, N.H. and Peace, K.E.
Methodologic aspects of a population pharmacodynamic model for cognitive effects in alzheimer patients treated with tacrine.

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Results and validation of a population pharmacodynamic model for cognitive effects in alzheimer patients treated with tacrine.

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