Web-based Software for Real-time Simulation-assisted Trial Design in Alzheimer’s Disease

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Introduction

Rates of endpoint progression and conversion in Alzheimer’s Disease populations are known to depend to a significant degree on prognostic factors that may be assessed during the screening phase of a clinical trial. While there is a degree of consensus on which prognostic factors are qualitatively important, there is still considerable uncertainty regarding the quantitative implications of these associations, particularly for trials in prodromal and “combined” (prodromal AD + AD dementia, taken together) populations. Our goal was to develop a model-based web application that allows rapid simulation-based estimation of rates of progression as a function of user-selected trial entry criteria, and to deploy platform-independent software for these simulations in a manner that would allow easy use by drug development team members, including individuals with no specific training or expertise in modeling and simulation.

Methods: Data

The proposed software is based on a statistical model that was fit to the Early Mild Cognitive Impairment (EMCI), Late Mild Cognitive Impairment (LMCI) and Alzheimer’s Dementia (AD) cohort data published by ADNI. Individual CDR items (“box scores”) were treated as the response of interest.

A schematic presentation of the statistical model is shown below.

The input form for the developed application allowed end-user specification of upper and lower inclusion/ exclusion limits for the following baseline prognostic factors: MMSE, CSF A-beta 42, FAQ, and age. The user interface (input form as well as output) is displayed below.

The run time required to simulate two specified populations and return output to the user was approximately one minute. The application tested successfully on both Google Chrome and Safari web browsers.

Methods: Model

The statistical model employed by the software is similar in nature to the ADAS-cog progression model developed by Ueckert et al. An extended form (extended with additional endpoints) of our CDR progression model has been schematically represented elsewhere. This model hypothesizes that expected CDR scores are a function of a latent (unobserved) disease status, and that this latent status progresses as function of the following baseline covariates: MMSE, CSF A-beta 42, FAQ, Age.

The model was implemented as a Bayesian model, fit using Markov Chain Monte Carlo (MCMC), using OpenBUGS version 3.2.2. Diffuse prior distributions were specified. Model fitting executed prior to the runtime of the web-based software produced samples from the joint posterior distribution, to be used in simulation. Standard Bayesian model diagnostics, including posterior predictive checks, were used to verify that the model was fit for the intended purpose.

Methods: Software Architecture

R code to simulate from the model and associated user interface code (also written in R) were then configured to work in conjunction a Shiny Server web server layer on an expandable grid cluster in Amazon’s Elastic Compute Cloud (EC2). Computations were parallelized over a 32 core server with on demand bursting in order to reduce the amount of time needed to simulate and return results to end users.

Results

Model validation diagnostics indicated that the model was fit for the purpose of predicting endpoint progression rates in the subpopulations of interest. An example posterior predictive check, evaluated in the general LMCI population, is provided below.

Table showing simulation-based estimates of changes in CDR-sob.

Discussion

We have proposed a technical solution to allow fuller and more practical use of modeling and simulation in the context of Alzheimer’s Disease clinical trial design. This technical solution represents the coalescence of multiple advances in scientific computing, software architecture, and the statistical modeling of Alzheimer’s Disease.

• The statistical model employed by the software leverages modern Bayesian techniques to relate trial entry criteria to longitudinal multivariate outcomes (CDR “box scores”), in this case that are nonlinear in time.

• The scientific computing solution utilized here is essentially a matter of parallelization, which in itself is not novel in the context of pharmacometric modeling and simulation. However, the availability of relatively inexpensive, on-demand, scalable computing resources via the Amazon cloud presented a new practical opportunity for parallel computation that was critical to the success of our application.

• Our use of Shiny Server to serve out webforms rendered by the shiny R package leverages new advances in the practical ease with which customized statistical computations can be surfaced to users over the web in a platform independent manner.

By leveraging easily-customized and easily-deployed web server technology in conjunction with scalable high performance cloud computing resources, simulations from complex statistical models can be rapidly surfaced to drug development team members to aid in decision making. This in turn can be expected to lead to the selection of Alzheimer's Disease trial designs that have more secure quantitative justification and are therefore more likely to detect anticipated treatment effects.

References

