A Casual Graphic Goodness-of-fit Assessment for Markov Pharmacodynamic Models

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Background

Markov modeling is a powerful tool for analyzing longitudinal categorical response variables (i.e. chronic disease progression through discrete disease stages), and have gained increasing popularity recently, particularly in the field of population PK/PD modeling and simulation. The Goodness-of-fit assessment of Markov models remains an active on-going research topic[1, 2]. Simulation based model evaluation tools (i.e. visual predictive check, VPC) for Markov models has been used in recent PK/PD publications [3]. Gentleman proposed a goodness-of-fit approach by comparing observed and predicted prevalence, defined as counts/percentages of individuals occupying each state at a particular time, for a time-homogeneous Markov model [4].

Objectives

In PK/PD analysis, the time homogeneity of Markov models usually does not hold because of inclusion of time-dependent covariates. The objective of the analysis was to apply *Gentleman's* approach to PK/PD Markov models that include time-dependent covariates such as drug concentrations or biomarker levels.

Methods

The analysis was done by simulating a hypothetical chronic disease progression process over 1000 days for 250 patients. Let us assume that the disease can be categorized into and ordered with three states (u): stable (u = 1), blast (u = 2), and death (u = 3). Thus, two types of transition are possible for this process: from stable stage to blast stage and from blast stage to death. It is assumed that there is a hypothetical biomarker for this disease, and can be used to predict the disease progression. For simplicity, we assume that the relationship between the transition rates and the levels of the biomarker follows an exponential growth function.

Once the simulated data is fitted with a Markov model, the expected prevalence can be calculated as the product of the total number of subjects under observation at time t and the estimated transition probability $P_{1u}(o, t)$ assuming all subjects are at stable state at t = o. For a time inhomogeneous Markov model, the transition probability, $P_{1u}(o, t)$, can be calculated by multiplying a number of individual transition probability matrices assuming the time-dependent covariate can be approximated as piecewise-constant:

$$P_{1u}(o, t) = P_{1u}(o, t_1)\, P_{1u}(t_1, t_2) \ldots P_{1u}(t_{j-1}, t)$$

Namely, time o to t is split into j equally spaced time intervals and the covariate value is regarded constant within each interval. The goodness of fit can then be assessed by visually or numerically comparing the observed prevalence occupying a disease stage, $O_u(t)$, at time t with the expected number of subjects in that stage, $E_u(t)$, at time t.

Hypothetical Disease Progression Process

$$\lambda_{12}(t) = \lambda_{12}(t=0) \bullet \exp(\beta_{12} x(t))$$
$$\lambda_{23}(t) = \lambda_{23}(t=0) \bullet \exp(\beta_{23} x(t))$$

where $\lambda 12(t)$ and $\lambda 23(t)$ are the time-dependent disease progression rates from stable to blast and from blast to death, respectively; $\lambda 12(t=0)$ and $\lambda 23(t=0)$ are the baseline progression rates; and $\beta 12$ and $\beta 23$ represent the effects of the biomarker process ($x(t)$) on the disease progression. $\beta 12$ = 0.3 and $\beta 23$ = 0.01, suggesting that a positive relationship between the disease progression and the biomarker levels.

Baseline Transition Matrix

$$\begin{pmatrix} -6.24\times10^{-5} & 6.24\times10^{-5} & 0 \\ 0 & -5.29\times10^{-3} & 5.29\times10^{-3} \\ 0 & 0 & 0 \end{pmatrix}$$

Results

The simulated data was analyzed by Markov models implemented in NONMEM®. Two models were fitted: a base model without any covariate and a model with biomarker levels as the time-dependent covariate. Compared to the base model, the objective function value of the covariate model was 129 points smaller.

The observed and predicted prevalence for each disease state were overlaid and plotted over time for each model to assess the goodness-of-fit (Figures 1-2). The uncertainty in the predicted prevalence over time was visualized by constructing 95% confidence intervals around the mean-predicted profiles.

Figure 1 demonstrates that the base model underestimated the prevalence of subjects occupying the stable stage at early times, whereas overestimated the prevalence of subjects occupying the blast stage during this time interval. The expected prevalence across the study time from the covariate ('true') model is much closer to the observed prevalence (Figure 2). The biomarker level in this simulation was assumed to increase as the time increases. Without accounting for the time-dependent covariate, the base model prediction deviates from the data at early times. The prevalence plots clearly showed the superiority of the model with time-dependent covariate.

Figure 1. Observed vs. Predicted Prevalence Based on the Base Model without Covariates

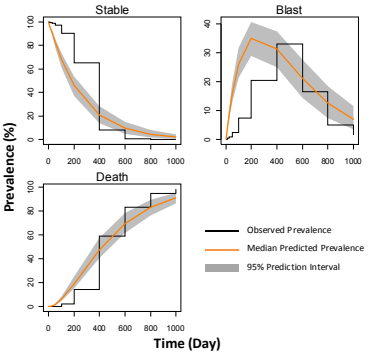
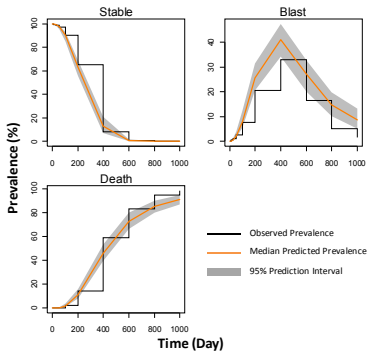


Figure 2. Observed vs. Predicted Prevalence Based on the True Model with Time-dependent Covariates



Conclusions

Gentleman's goodness-of-fit check for prevalence can be used as an alternative graphic assessment for PK/PD Markov models, in which concentrations or biomarker levels serve as time-dependent covariates. However, like simulation-based VPC, the statistical significance of the model deviation cannot be assessed formally by this causal graphic approach.

Reference

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