A Bayesian Nonlinear Mixed-effects Disease Progression Model

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Abstract

A nonlinear mixed-effects approach is developed for disease progression models that incorporate variation in age in a Bayesian framework. We further generalize the probability model for sensitivity to depend on age at diagnosis, time spent in the preclinical state and sojourn time. The developed models are then applied to the Johns Hopkins Lung Project data and the Health Insurance Plan for Greater New York data using Bayesian Markov chain Monte Carlo and are compared with the estimation method that does not consider random-effects from age. Using the developed models, we obtain not only age-specific individual-level distributions, but also population-level distributions of sensitivity, sojourn time and transition probability.

Keywords: Cancer screening; Nonlinear mixed-effects models; Sensitivity; Sojourn time

Introduction

The disease progression model introduced by Zelen and Feinleib [1] assumes that disease progresses through three states: where So corresponds to the disease-free state, Sp the preclinical disease state when an asymptomatic individual unknowingly has the disease that a screening exam can detect, and Sc the clinical state when the disease manifests itself in clinical symptoms. In addition, if one enters the preclinical state (Sp) at time t₁ and the clinical state (Sc) at time t₂, the time difference (t₂ - t₁) is called sojourn time. The length of the time (t₂ - t₁) is called lead time if one is offered a screening exam at time t₁ within the preclinical state (t₁ ≤ t ≤ t₂) and the disease is diagnosed.

Screening aims to detect disease in the preclinical state before symptoms appear, which may greatly increase the chances for effective treatment. The disease progression model has been used to analyze the screening data with three key components [2,3]: sensitivity of the screening modality, the sojourn time distribution, and the transition probability density from the disease-free to the preclinical state. These three parameters are building blocks for screening modeling, because all other parameters of interest can be expressed as a function of these key parameters. In particular, the sensitivity of the screening modality is critical for evaluating the predictive performance of a screening program. Note that the sensitivity is defined as the conditional probability that a screening test is positive when one is in the preclinical state (Sp).

Screening sensitivity may depend on a variety of factors, such as position, location and size of the tumor, experience of the radiologist, age, etc. Wu et al. [2] modeled the sensitivity as a function of age with an age-dependent transition probability density and then applied the model to the Health Insurance Plan of Greater New Yorker (HIP), a breast cancer screening study, and later to the Mayo Lung Project data, a lung cancer screening study [3]. However, sensitivity of mammogram increases as a woman’s age increases, while screening sensitivity of chest X-ray for lung cancer does not depend on age. In later developments, sensitivity was modeled as a function of the time spent in the preclinical state along with age at diagnosis [4], but sensitivity was influenced by the proportion of time in the preclinical state to the sojourn time more than by age for breast cancer screening. For this reason, Kim and Wu [5] recently modeled sensitivity as a function of the sojourn time and time spent in the preclinical state and then applied the model to the Johns Hopkins Lung Project data. Nevertheless, it still remains unclear which of these models describes sensitivity more appropriately.

Besides, the progress of disease can vary by age. In particular, it is well known that human cancer incidence depends on age, and the risk of being diagnosed with cancer increases with age [6]. Therefore, it is desirable to estimate the results of disease (e.g., cancer) screening for overall summaries as well as for age-specific summaries. To our knowledge, disease progression models have not considered variation in age.

The main objectives of this study were to resolve the two aforementioned issues: (i) finding a proper sensitivity model and (ii) estimating the disease progression models by considering variation in age. To this end, we generalize sensitivity as a function of age at diagnosis, sojourn time, and time spent in the preclinical state and a nonlinear mixed-effects model is developed for disease progression models from a Bayesian framework. We then applied our models to the Johns Hopkins Lung Project (JHLP) data and the Health Insurance Plan for Greater New York (HIP) data. All simulations were run by using the statistical software R (R Development Core Team), and the algorithms described in this study can be obtained upon request from the authors.

The remainder of the paper is organized as follows. In Section 2, we introduce a disease progression model and our generalized sensitivity model. A Bayesian nonlinear mixed-effects model is developed based on a trinomial distribution in Section 3. In Section 4, the developed models are applied to JHLP and HIP data. Concluding remarks are found in Section 5.

A Disease Progression Model

Suppose an individual begins the screening exams at the
where $N_i$ is the number of screenings. As a result, the overall likelihood function for all the study groups is the product of the age-specific contributions across all age groups

$$L_i(\theta) = \prod_{i=1}^{K} L_i(\theta).$$

The conventional parameter estimation ignores the age-specific effect since its likelihood function is based on Equation (3). One approach to incorporating the age-specific effect into a model is to use a mixed-effects model. In the next section, a nonlinear mixed-effects model is developed with the age-specific effect as a random-effect.

### A Bayesian Nonlinear Mixed-Effects Model

The three-stage hierarchical nonlinear mixed-effects model is developed for disease progression models from a Bayesian framework. The first-stage model has the form of

$$[s_{ij, t_j} | \theta] \sim \text{Tri}(n_{ij, D_{ij}}, l_{ij} | \theta), 1 \leq i \leq K; 1 \leq j \leq N_i,$$

where $D_{ij}$ is the probability of an individual correctly diagnosed at the $j$th scheduled exam given at the $i$th age group; $l_{ij}$ is the total number of the individuals examined at $t_{ij}$ at the $i$th age group; $S_{ij}$: the number of cases diagnosed at $t_{ij}$ at the $i$th age group; and $\theta$ is a $p$-dimensional age-specific parameter vector, where, in this project, $p=7$ and $\theta = (\log(c_{ij}), \beta_j, \log(\gamma_j), \alpha_j, \log(\sigma^2), \log(\kappa_j), \log(x_i)).$ Note that $\text{Tri}$ stands for a trinomial distribution. The second-stage is structured based on a multivariate normal distribution (MVN) and is given by

$$[\theta | \theta, \Sigma_p] \sim \text{MVN}(\theta, \Sigma_p),$$

where $\theta$ is the population-average parameter vector, and $\Sigma_p$ is the between-age covariance matrix. The third stage of the model describes the prior distributions

$$\theta \sim \text{MVN}(c, C_p) \left[ \Sigma_p^{-1} - W \cdot \alpha_p \cdot [\text{orP}_p]^{-1} \right],$$

for given $c, C_p$ , and $\text{orP}_p$, where $W$ is a Wishart distribution. The posterior distribution for $(\theta_1, \ldots, \theta_K, \Sigma_p)$ is proportional to

$$\prod_{i=1}^{K} \prod_{j=1}^{N_i} \text{Prob}(s_{ij, t_j}) \cdot \text{Prob}(l_{ij} | \theta_0, \Sigma_p) \times \text{Prior}(\theta, \Sigma_p).$$

The previous published results in Kim and Wu and Wu et al. are utilized as the starting point for the analysis. The posterior distribution is given by

$$\theta \sim \text{MVN}(c, C_p) \left[ \Sigma_p^{-1} - W \cdot \alpha_p \cdot [\text{orP}_p]^{-1} \right].$$

The model is then fit to the data using Markov Chain Monte Carlo (MCMC) methods. The posterior distribution is used to make inferences about the age-specific effects and the overall likelihood function is used to make inferences about the population-average parameter vector.

## References

1. Kim S, Jang H, Wu D, Abrams J (2015) A Bayesian Nonlinear Mixed-Effects Disease Progression Model. J Biom Biostat 6: 271. doi:10.4172/2155-6180.1000271

2. Note that the sojourn time in $S_p$ and $O(x) = \int q(t) \, dt$ is the survivor function of the sojourn time. The log-logistic distribution was used to model the sojourn time [2].

3. $\gamma = \eta/\rho = \left[ \begin{array}{c} \eta_1 \\ \vdots \\ \eta_N \end{array} \right]$ is the average age at entry in the entire study group and $\eta_i$ ordered screening exams starting at age $t_i$, where $D_i$ is the fixed follow-up time after the last examination. The $j$th screening interval is $(t_i,j-1, t_i,j)$, $j = 1, 2, \ldots, N_i$ at the $i$th age group. The following notation is used: the $j$th annual screening exam occurs at age $t_{i,j} = t_{i,0} + j - 1$, for $j = 1, 2, \ldots, N_i$. Let $t_{i,0} = 0$, $n_i$ is the total number of individuals examined at $t_{i,i}$. The number of cases diagnosed and confirmed at $t_{i,i}$ is $n_i$.

4. For each age group, we model sensitivity to vary with three factors, which are screening age $t$, sojourn time $T$, and time spent in the preclinical state. Note that $W(x)$ is the probability density function for transition $S_p$, and $\text{Tri}$ stands for a trinomial distribution. The second-stage is structured based on a multivariate normal distribution (MVN) and is given by

$$[\theta | \theta, \Sigma_p] \sim \text{MVN}(\theta, \Sigma_p),$$

where $\theta$ is the population-average parameter vector, and $\Sigma_p$ is the between-age covariance matrix. The third stage of the model describes the prior distributions

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The model is then fit to the data using Markov Chain Monte Carlo (MCMC) methods. The posterior distribution is used to make inferences about the age-specific effects and the overall likelihood function is used to make inferences about the population-average parameter vector.
al. were used for selecting of the hyper-parameters (i.e., prior information) of the JHLP and HIP data, respectively. That is, we used the following estimates of mean and standard deviations for the hyper-parameters (a, b, y, μ, α², k, p), respectively, (1.676 ± 1.338, 0.085 ± 0.078, 0.1293 ± 0.0806, 4.3440 ± 0.0008, 0.0426 ± 0.0036, 1.6278 ± 0.8242, 0.0263 ± 0.0015), for the JHLP data, and (1.676 ± 1.338, 0.085 ± 0.078, 0.1293 ± 0.0806, 4.340 ± 0.076, 0.190 ± 0.076, 2.509 ± 0.927, 0.886 ± 0.287), for the HIP data. The Gibbs sampler is defined by the following full conditional distributions except for age-specific parameterθ:

\[
\left[ \theta_1, \ldots, \theta_K, \Sigma_p \right] \propto \prod_{i=1}^{K} \left[ \text{Prob}(\theta_i|\theta, \Sigma_p) \right] \times \text{Prior}(\theta) \\
- \text{MVN}(V_p (K \cdot \Sigma_p^{-1} \Sigma + C_p^{-1}) \cdot V_p); \\
\left[ \Sigma_p^{-1} \right] \propto \prod_{i=1}^{K} \left[ \text{Prob}(\theta_i|\theta, \Sigma_p) \right] \times \text{Prior}(\Sigma_p) \\
- W \left( K + \omega, \left( \sum_{i=1}^{K} (\theta_i - 0)(\theta_i - 0) + \omega \cdot R_p \right)^{-1} \right), \\
\end{align}
\]

where

\[
\bar{\theta} = \frac{1}{K} \sum_{i=1}^{K} \theta_i \\ \\
V_p^{-1} = K \cdot \Sigma_p^{-1} + C_p^{-1}.
\]

Because of the nonlinear functions D_i and I_p, the conditional distribution of \( \theta_i \) is non-standard and known up to a constant,

\[
\left[ \theta_i | \{ \theta_j \}_j, 0, \Sigma_p \right] \propto L_i \left( \theta_i | 0, \Sigma_p \right) \\
\propto \left[ \prod_{j \neq i} D_j \right]^{1/2} \left( 1 - D_i - I_i \right)^{1/2} \cdot \exp \left( -\frac{1}{2} (\theta_i - 0)^T \Sigma_p^{-1} (\theta_i - 0) \right),
\]

where \( L_i(\theta_i) \) denote the conditional log-likelihood for the ith age of Equation (2).

Applications

The developed methods are applied to both the Johns Hopkins Lung Project (JHLP) data [5,7] and the Health Insurance Plan of Greater New York (HIP) study [8]. Since no analytical formulas were available for the likelihood function, we used the Markov chain Monte Carlo (MCMC) approach to estimate the posterior distribution for each parameter. In details, let the full conditional posterior distribution of a vector of parameters, \( \theta \), be \( \{ \theta | \cdot \} \), that is, the posterior distribution of \( \theta \) given all other quantities in the model. Since our model is nonlinear, it leads to a form for \( \{ \theta | \cdot \} \) that is non-standard and is known only up to a normalizing constant. For this reason, we updated the parameters via Metropolis-Hastings-within-Gibbs steps and chose random-walk Metropolis for updating the \( \theta_i \), parameters, which is a natural choice of Metropolis-Hastings [9]. For setting of the prior distribution (hyper-parameters), we employed the previous results in Kim and Wu [5] and Wu et al. [2] as stated before.

For comparison, we analyzed the JHLP and HIP data using both the conventional and developed approaches. Here the conventional approach means that all the parameters were estimated based on the overall likelihood, which is Equation (3), without considering the variation in different age groups. For convenience, we call the developed algorithm the mixed-effects disease model (ME-DM) and the conventional algorithm the fixed-effects disease model (FE-DM).

For both ME-DM and FE-DM, we generated one MCMC chain for each of JHLP and HIP data until the MCMC chain reached at least 20,000 iterations. We then obtained the MCMC chain with the size of 1,000 using the last 10,000 iterations for each chain with burn-in of at least 10,000 and a thinning of every 10 steps. Supplementary Information (Figures S1 and S2 in Appendix) are the trace plots of the simulated Markov chains only for population-level parameters. The solid and dotted horizontal lines represent the mean and the median of each parameter, respectively.

The JHLP and HIP data

In the Baltimore metropolitan area from 1973 to 1978, the Johns Hopkins Lung Project (JHLP) trials enrolled 10,386 men aged 45 years and older who smoked at least one pack of cigarettes per day (or who had smoked this much within one year of enrollment) and who had no prior history of respiratory cancer. All participants were then randomized to either chest X-ray only or a dual screen (chest X-ray and sputum cytology) groups, resulting 5,160 men in the chest X-ray only arm and 5,226 in the dual-screen arm. Participants in the chest X-ray arm received chest X-ray screening test annually, for 8 consecutive years. If any of the tests were positive, the screen was considered positive and a definitive work-up exam, such as biopsy, was done. In this study, we used the chest X-ray arm, including the total number of participants in each screening exam, the number of detected and confirmed cancer cases in each screening exam, and the number of interval cases. These data were stratified by age at study entry from 45 to 88 years old.

The Health Insurance Plan of Greater New York (HIP) study began at the end of 1963 and was the first randomized clinical trial for regular screening exams that include mammography as a screening test for breast cancer [8]. The study enrolled asymptomatic women aged 40 to 64 years who had no history of breast cancer. The participants were randomized into study and control arms, with about 31,000 women in each arm. The screening program for the study arm specified up to four annual breast exams with both a mammogram and a clinical breast exam, while the control arm received usual care. Data from the study arm was used for this study, where the data were stratified by age at study entry from 40 to 64 years old.

Results

Table 1 displays the empirical means, standard deviations, and 95% credible intervals (CI) of the posterior distributions of parameters. As for ME-DM, the fixed-effect estimates (i.e., population-level estimates) are considered to compare with the estimates of FE-DM. We can see the large absolute difference in log (α) and log (γ) between two estimation methods. However, all 95% CIs of estimates of FE-DM overlap with these of population-level estimates of ME-DM except for the estimate \( \hat{\mu} \) of JHLP and HIP and the estimate \( \hat{\mu} \) of HIP (Table 1).

Estimates of the variance-covariance matrix \( \Sigma \) of ME-DM are shown in Table 2. Since only log (α), β, log (γ), and μ are considered as random-effects, the size of \( \Sigma \) is four by four. For both JHLP and HIP data, there is greater variation in the parameters log (α) and log (γ)
than these in other parameters, indicating that sensitivity is influenced by age at diagnosis. Forest plots of each individual-level estimate of ME-DM are plotted in Figure 1. In case of the parameters $\beta$ and $\mu$, the empirical means of the individual-level estimates are very close to that of the population-level estimates for both JHLP and HIP data. On the other hand, we can see a larger variation of the individual-level estimates of $\log(\alpha)$ and $\log(\gamma)$. These imply that the parameters $\alpha$ and $\beta$ have a large influence on age, so does sensitivity. The individual-level estimates of each age at diagnosis can be found in Supplementary Information (Tables S1 and S2 in appendix).

The developed sensitivity models depend on age at diagnosis, the time spent in the preclinical state and the sojourn time, resulting in a function of age and the proportion of time spent in the preclinical state to the sojourn time. Note that the average age $E$ in Equation (1) is equal to zero in Equation (1), our model becomes same as their model. Generally, our results are consistent with these of Kim and Wu [5]. However, our estimate of $\gamma$ is smaller than their estimate, 0.01 vs. 0.13, respectively (Table 3 in Appendix), resulting that our sensitivity increases much faster than theirs. This might be due to age-effect in the sensitivity.

When the population-level sensitivity of JHLP data is compared with that of HIP data, we can see a different trend from each other in the sense that the sensitivity increases as men get older in lung cancer, while the sensitivity decreases as women get older. In other words, the probability to detect lung cancer is higher in old than in young, and

| HIP     | log(\alpha)  | \beta  | log(\gamma) | \mu   |
|---------|--------------|--------|-------------|-------|
| JHLP    | 204.28 ± 83.92 (91.46,404.52) | -0.04 ± 0.56 (-1.21,1.05) | 90.80 ± 47.89 (21.52,206.16) | 0.11 ± 0.90 (-1.65,1.98) |
| ME-DM   | 0.01 ± 0.00 (0.00,0.02) | -0.01 ± 0.38 (-0.82,0.73) | 0.00 ± 0.01 (-0.01,0.01) |
| HIP     | 113.40 ± 42.72 (55.80,217.48) | 0.04 ± 0.56 (-1.05,1.18) |
| ME-DM   | 0.03 ± 0.02 (0.01,0.07) |

Table 1: Estimates of fixed-effects and mixed-effects using JHLP and HIP data. The empirical means, standard deviation, and 95% credible intervals of posterior distributions are reported.

The population-level sensitivities of JHLP are an increasing function in age regardless of estimation methods, while these of HIP are a decreasing function in age in ME-DM, based on the subplots between age and $s/T$ in Figure 2. This is because the posterior estimates $\hat{\beta}$ of HIP and HIP are positive and negative, respectively. In general, both JHLP and HIP data show large differences in sensitivity between FE-DM and ME-DM.

The individual-level posterior sensitivities are shown in Supplementary Information (Figures S3 and S4 in appendix). In particular, these predicted sensitivities show significant variations among age groups, which might be resulted from the large variations in parameters $\log(\alpha)$ and $\log(\gamma)$ in Table 2.

Figure 3 shows the posterior transition probability estimated by FE-DM and ME-DM. The estimates $\sigma^2$ of ME-DM for both JHLP and HIP are larger than these of FE-DM, resulting that the modes of FE-DM are a little smaller than these of ME-DM (61 vs. 72 years and 51 vs. 73 years, respectively, for HIP data). The individual-level variation of the transition probability can be seen in Supplementary Information (Figure S5 in appendix). The variation in age is larger in HIP data than in HIP data.

The posterior sojourn time distributions are depicted in Figure 4. As expected by that the 95% CIs of the estimates $\hat{\beta}$ of HIP are not overlapped, the sojourn time distributions of HIP are very different between FE-DM and ME-DM of HIP. The modes of sojourn time in HIP are 1.01 and 15.15 years for FE-DM and ME-DM, respectively, while these of JHLP are 21.21 and 38.38 years for FE-DM and ME-DM, respectively (Figure 4).

Concluding Remarks

We propose a generalized sensitivity model which depends on age at diagnosis, time spent in the preclinical state and sojourn time, and the developed sensitivity model is applied to a novel nonlinear mixed-effects model for a disease progression model in a Bayesian framework.

As for JHLP data, FE-DM along with the developed sensitivity model estimates the parameters using the same data as used in Kim and Wu [5]. The main difference is the sensitivity model, and their sensitivity model is a special case of our model. That is, when the parameter $\beta$ is equal to zero in Equation (1), our model becomes same as their model. Generally, our results are consistent with these of Kim and Wu [5]. However, our estimate of $\gamma$ is smaller than their estimate, 0.01 vs. 0.13, respectively (Table 3 in Appendix), resulting that our sensitivity increases much faster than theirs. This might be due to age-effect in the sensitivity.

When the population-level sensitivity of JHLP data is compared with that of HIP data, we can see a different trend from each other in the sense that the sensitivity increases as men get older in lung cancer, while the sensitivity decreases as women get older. In other words, the probability to detect lung cancer is higher in old than in young, and

| JHLP | log(\alpha)  | \beta  | log(\gamma) | \mu   |
|------|--------------|--------|-------------|-------|
| FE-DM | -1.10 ± 2.21 (-6.50,1.51) | 0.04 ± 0.09 (-15.0,19) | -4.55 ± 5.48 (-17.30,1.04) |
| ME-DM | 0.17 ± 0.14 (-0.12,0.44) | 0.02 ± 0.06 (-0.10,0.14) | 0.54 ± 0.09 (0.37,0.71) |
| HIP  | -0.92 ± 1.06 (-3.28,0.81) | 0.00 ± 0.12 (-0.19,0.18) | -1.58 ± 1.32 (-4.46,0.59) |
| ME-DM | 0.18 ± 0.07 (0.03,0.32) | -0.03 ± 0.05 (-1.12,0.06) | 0.53 ± 0.12 (0.29,0.77) |

Table 2: Estimates of variance-covariance matrices of ME-DM using JHLP and HIP data. The empirical means, standard deviation, and 95% credible intervals of posterior distributions are reported.
Figure 1: The forest plots of individual-level estimates of ME-DM. (a) JHLP and (b) HIP. The red dotted lines indicate the means of the posterior population-level estimates of log(α), β, log(γ), and μ. The solid dots and the solid lines represent empirical means and 95% credible intervals of the posterior distributions of each estimate.
The breast cancer might be detected more in young than in old by a screening exam. This can be explained by the fact that lung cancer does not have a reliable early detection test compared with other cancers [10].

The main advantage of ME-DM over FE-DM is to incorporate variation in age into the disease progression model, resulting in estimates with better precision. By doing so, we can obtain not only population-level estimates but also individual-level estimates. Accurate estimates are critical for policy makers to predict the performance of a screening exam. In this regard, the proposed ME-DM along with a generalized sensitivity model might provide a more accurate assessment of screening for policy makers [11].

Acknowledgements

We appreciate the helpful comments of the anonymous reviewer and the editor for helpful suggestions. This work is partially supported by NSF grant DMS-1312603. The Biostatistics Core is supported, in part, by NIH Center grant P30 CA022453 to the Karmanos Cancer Institute at Wayne State University.

Conflict of Interest

The authors have declared no conflict of interest.

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