STA6171 - FINAL EXAM

Instructor: Dr. Ick Hoon Jin

Due: Dec. 20. 2020

1. (5 pts) Consider the function

$$h(x) = \Big[\cos\big(50x\big) + \sin\big(20x\big)\Big]^2, \quad 0 < x < 1$$

   (a) Try to derive its maximum with a Newton-Raphson method and a fixed point iteration methods. You need to try multiple starting points.

   (b) Apply a simulated annealing algorithm to find the maximum. The algorithm you can use is

   At iteration t the algorithm is at $\big(x^{(t)}, h(x^{(t)})\big)$

   i. Simulate $u \sim \text{Uniform}(a_t, b_t)$ where $a_t = \max\big(x^{(t)} - r, 0\big)$ and $b_t = \min\big(x^{(t)} + r, 1\big)$.

   ii. Accept $x^{(t+1)} = u$ with probability

$$\rho^{(t)} = \min\left\{\exp\left(\frac{h\big(u\big) - h\big(x^{(t)}\big)}{T_t}\right), 1\right\},$$

   take $x^{(t+1)} = x^{(t)}$ otherwise.

   iii. Update T_t and T_{t+1}.

   With $r = .5$ and $T_t = 1/\log(t)$, run simulated annealing algorithm four times with 2500 iterations and draw their trajectories.

2. (5 pts) EM Algorithm for a linear mixed-effect model.

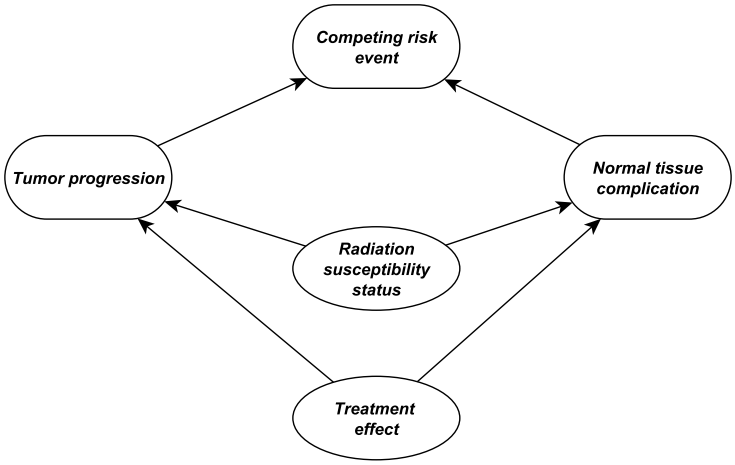
   (a) Derive EM algorithm to estimate parameters of a linear mixed-effect model.

   (b) With `rikz.txt`, estimate parameters of a linear mixed-effect model using the EM algorithm.

   - Response Variable Y: Richness
   - Fixed Effect Variable X: NAP
   - Random Effect Variable Z: Beach

3. (15 pts) We want to propose a Bayesian adaptive phase I/II clinical trial design with competing risk endpoints. The proposed design is motivated by an ongoing lung cancer clinical trial, which treats

Figure 1: Flow chat of the competing risk model



patients at different levels of radiotherapy (RT). Patients are classified into the radiation-resistant (RE) subgroup and radiation-sensitive (SE) subgroup based on a gene signature pathway and the treatment effect is evaluated within each subgroup respectively. The RE patients are randomized to receive either the high-dose RT or standard RT whereas the SE patients are randomized to receive either the low-dose RT or standard RT. The rational of excluding the low-dose RT for the RE patients is that the low-dose RT is not enough for RE patients to control tumor. Along the same line, the high-dose RT is excluded for the SE patients because it can induce severity toxicity for the SE patients. The purpose of the trial is to study whether the RE patients perform better in the high-dose RT arm and whether the SE patients perform better in the low-dose RT arm, both compared with the standard RT. The RT is a "double-edged sword" for patients. On one hand, the RT on tumor cell can prevent the tumor progression; on the other hand, the RT on the normal cell can induce the normal tissue complication. Consequently, patients in the trial can experience different cause-specific events. In particular, for the motivating trial, if a patient experiences either tumor progression or normal tissue complication, he/she is dropped off from the trial and a second-line treatment is assigned. Since we can observe only the first event for each patient, competing risks arise.

As depicted in Figure (1), tumor progression and normal tissue complication constitute the competing risk model and we are interested in both endpoints. Specifically, the cumulative incidence rate for tumor progression is the measure for efficacy endpoint and the counterpart for normal tissue complication is the measure for toxicity endpoint. A RT arm is claimed to be promising if it yields reasonably low value for both rates. The patient's response is jointly determined by the RT dose level such as high-dose, low-dose or standard and radiation susceptibility status (RSS) such as RE or SE. Specifically, the RE patients are expected to yield better performance in the

high-dose RT because the RE status in tumor requires a high-dose RT to kill tumor and the RE status in normal tissue can prevent them from developing normal tissue complication at a high-dose RT. Similarly, the SE patients are generally in favor of a low-dose RT. However, for a early phase I/II clinical trial, there are lot of uncertainty remaining on patients' response. Therefore, it is necessary to evaluate patients' response at different dose levels stratified by the RSS.

We propose a Bayesian adaptive phase I/II clinical trial design to evaluate the patient's performances at different RT dose levels. We use the cause-specific hazard method to model the competing risk endpoints. **An utility function** is constructed to compromise both the efficacy and toxicity endpoints into a real value measuring the patient's overall desirability at each dose level.

We derive the competing risk probability model for the composite tumor progression and normal tissue complication endpoints. For the ith patient in the trial, we define Y_{ki} as the potential failure times for different cause-specific events and let $k = 1, 2$ represent event of tumor progression and event of normal tissue complication. Let $T_i = \min(Y_{1i}, Y_{2i})$ be the potential failure time and C_i be the potential censoring time, which are assumed to be independent with Y_{ki}. We also define $X_i = \min(T_i, C_i)$ as the observation time.

We use the cause-specific hazard approach to characterize the competing risk model. Let W_i be the RSS with $W_i = 0, 1$ representing the RE and SE status. Let A_i be the treatment arm with $A_i = 0, 1, 2$ represent the lower-dose, standard and higher-dose RT arms. We use $\lambda_k(X_i|W_i, A_i)$ to denote the cause specific hazard function for the ith patient experiencing cause k as the first event with RSS W_i and treated in RT dose level A_i. Under the Cox proportional hazard model, we have:

$$\lambda_k(X_i|W_i, A_i) = \eta_k(X_i)\exp(\gamma_{k1}W_i + \gamma_{k2}A_i + \gamma_{k3}W_iA_i), \tag{1}$$

where $\eta_k(X_i)$ is the baseline hazard. Let ν be the total follow-up time for each patient, after equally partitioning ν into m non-overlapping intervals, we use the piecewise exponential distribution to model the baseline hazard as $\eta_k(X_i) = \sum_{j=1}^{m} \eta_{kj}\mathrm{I}\Big(\frac{(j-1)\nu}{m} < X_i \leq \frac{j\nu}{m}\Big)$ with $\mathrm{I}(\cdot)$ denoting an indicate function. We use $\nu = 6$ and $m = 4$.

We denote $\delta_{ki} = 1$ if the ith patient experiences the kth cause specific event as the first event and $\delta_{ki} = 0$ otherwise. Then, after defining $S_k(X_i|W_i, A_i) = \exp\Big\{ - \int_0^{X_i} \lambda_k(x|W_i, A_i)dx\Big\}$, the likelihood function for all the n patients with composite endpoints can be expressed as:

$$L(\mathcal{D}|\Theta) = \prod_{i=1}^{n}\prod_{k=1}^{2} \lambda_k(X_i|W_i, A_i)^{\delta_{ki}} S_k(X_i|W_i, A_i), \tag{2}$$

where $\mathcal{D}$ is the data set and Θ is all the parameters of interest. We propose to estimate Θ under the Bayesian framework. Hence, we need to specify the prior distribution for Θ. With proper prior distribution, the posterior mean of parameters are given in `output.csv`.

The purpose of the proposed design is to evaluate each patient's overall performance at each RT arm stratified by his/her RSS and select the best arm for each RSS subgroup. For this objective, we need a trade-off measurement to compromise the composite tumor progression and normal tissue complication. We propose to use **an utility function** to measure a patient's overall desirability at different RT ams. Specifically, the primary interest of the utility function is the RT response outcomes listed as developing tumor progression, developing normal tissue complication and no treatment-related event happening. Additionally, the utility function should also take into account the time point of happening event because a deferred adverse event is always more preferred. For this purpose, we equally partition the total follow-up time ν into two intervals and study whether the happening event belongs to the first or second intervals. By doing so, we classify the whole response space into five subgroups based on the response type and the time interval. After consulting the clinicians of the trial, we can assign different desirability weight to each subgroup. The desirability weight ranges from 0 to 5 with a large value of weight representing a higher desirability. In Table 1 we provide a example of the desirability weight. Conceptually, we can partition ν into more intervals rather than two and re-define the desirability weight correspondingly. However, when there are more intervals, assigning an appropriate score for each subgroup is not an easy task for clinicians and can be somewhat unpractical.

Table 1: Definition of subgroups of response outcomes and desirability weights

Subgroup	$X_i \leq \nu/2, k=1;$	$X_i \leq \nu/2, k=2;$	$\nu/2 < X_i \leq \nu, k=1;$	$\nu < X_i \leq \nu, k=2$
Weight	0.5	5	10	20

We use E_1 to E_5 to denote the subgroups listed in Table 1 (left to right) and O_1 to O_4 the associated desirability weight. Then, for any patient with the RSS W_i and RT arm A_i, we construct the utility function as

$$U(W_i, A_i) = \sum_{s=1}^{4} \Pr(E_s) O_s.$$

Under the competing risk model (2), we can explicitly write down $U(W_i, A_i)$ as

$$\begin{aligned} U(W_i, A_i) = &\sum_{s=1}^{2} \Big[\int_0^{\nu/2} \Big\{ \prod_{k=1}^{2} S_k(x|W_i, A_i) \Big\} \lambda_s(x|W_i, A_i) dx \Big] O_s \\ &+ \sum_{s=1}^{2} \Big[\int_{\nu/2}^{\nu} \Big\{ \prod_{k=1}^{2} S_k(x|W_i, A_i) \Big\} \lambda_s(x|W_i, A_i) dx \Big] O_{s+2} \end{aligned} \tag{3}$$

Calculate **the utility function**, $U(W_i, A_i)$ with clinical data (`data.csv`) and posterior mean (`output.csv`) using numerical integration (Trapezoidal and Simpson's rule).

4. (15 pts) The spatial autologistic model has been widely used in spatial data analysis. Let $y = \{y_i : i \in \mathcal{D}\}$ denote the observed binary data, where y_i is called a spin and $\mathcal{D}$ is the set of indices of

the spins. Let $|\mathcal{D}|$ denote the total number of spins in $\mathcal{D}$, and let $n(i)$ denote the set of neighbors of spin i. The likelihood function of the model is given by

$$f\Big(\mathbf{y} \mid \alpha, \beta\Big) = \frac{1}{\kappa(\alpha, \eta)} \exp\left\{\alpha \sum_{i \in \mathcal{D}} y_i + \frac{\beta}{2} \sum_{i \in \mathcal{D}} y_i \left(\sum_{j \in n(i)} y_j\right)\right\} \tag{4}$$

where the parameter α determines the overall proportion of $y_i = \pm 1$, the parameter β determines the intensity of interaction between y_i and its neighbors, and $\kappa(\alpha, \beta)$ is the intractable normalizing constant defined by

$$\kappa(\alpha, \beta) = \sum_{\text{for all possible } y} \exp\left\{\alpha \sum_{i \in \mathcal{D}} y_i + \frac{\beta}{2} \sum_{i \in \mathcal{D}} y_i \left(\sum_{j \in n(i)} y_j\right)\right\}$$

An exact evaluation of $\kappa(\alpha, \beta)$is prohibited even for a moderate system. To conduct a Bayesian analysis for the model, a uniform prior on

$$(\alpha, \beta) \in \Theta = [-1, 1] \times [0, 1]$$

is assumed for the parameters, which restricts Θ to be a compact set. Since $\mathcal{D}$ is finite, the sample space $\mathcal{X}$ (of y) is also finite.

U.S. cancer mortality maps have been used for investigating the possible association of cancer with unusual demographic, environmental, and industrial characteristics, or employment patterns. `UScancer.map` shows the mortality map for cancer of the liver and gallbladder (including bile ducts) cancers in white males during the decade 1950–1959, which indicates some apparent geographic clustering. We modeled the data with a spatial autologistic model. The total number of spins is $\mathcal{D} = 2293$. A free boundary condition is assumed for the model, under which the boundary points have fewer neighboring points than the interior points. This assumption is natural to this dataset, as the lattice has an irregular shape. We use four estimation method: maximum pseudo-likelihood estimator (MPLE), a double Metropolis-Hasting sampler (DMH), and an adaptive exchange algorithm (AEX). The results are summarized in a following table.

Method	α	β
MPLE	-0.3205	0.1115
DMH	-0.3020	0.1227
AEX	-0.3017	0.1224

To further assess the accuracy of the AEX, DMH and MCHA estimates, we evaluate the root mean squared error (RMSE) of the estimates of statistics based on the idea of parametric bootstrap. Since the statistics are sufficient for α and β, statisticss can be reversely estimated by the simulated lattices from the distribution $f\Big(\mathbf{y} \mid \hat{\alpha}, \hat{\beta}\Big)$, where $\hat{\alpha}$ and $\hat{\beta}$ denote estimates of α and β. Calculate the RMSE for statistics corresponding to parameter estimates of MPLE, DMH, and AEX. Then, discuss the performance of MPLE, DMH, and AEX.