Bayesian Design Using Historical Data that Inform the Treatment Effect with Applications to Cure Rate Models

Joseph G. Ibrahim

Department of Biostatistics, University of North Carolina, Chapel Hill, NC 27599, USA
E-Mail: ibrahim@bios.unc.edu

Joint work with Matthew A. Psioda

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We propose a trial design methodology (Bayesian sample size determination) for the cure rate model based on Bayesian versions of type I error rate and power.

Cure rate models have become popular tools for analyzing data from oncology clinical trials.

We use historical data as prior information to design the trial.

We borrow information from both the experimental and control arms of the historical data, and thus we use the historical data to inform the treatment effect.

Our results demonstrate that when one permits control of a Bayesian type I error rate, a significant fraction of the prior information can be incorporated into the design and analysis of the new trial.
Introduction

- However, borrowing the prior information is not free. When the historical data posterior distribution is highly informative, the size of the future trial must be large to justify borrowing a significant amount of the available information.

- So our Bayesian design methodology is not simply a mechanism for reducing sample size in the new trial, but rather a procedure for utilizing the information from the historical trial to inform all aspects of the new trial’s design and analysis while assuring reasonable Bayesian type I error control.

- Furthermore, when one designs a trial to have high Bayesian power, the sample size required will generally be larger than the sample size required for a similarly designed trial that is powered to detect the most likely treatment effect suggested by the historical data.
Promotion Time Cure Rate Model

- We consider a flexible promotion time cure rate model where the promotion time distribution is allowed to vary over levels of a stratification variable.
- The model is typically motivated through a latent competing risks framework. We let $N_i$ denote the number of metastasis-competent tumor cells for subject $i$ that remain after initial treatment.
- We assume that $N_i$ follows a Poisson distribution with mean
  \[ \theta_i = \exp \left( \gamma z_i + x_i^T \beta \right), \]
  where $z_i$ is a binary treatment indicator,
  \[ x_i = (x_{i1}, \ldots, x_{ip}) \]
  is a $p \times 1$ vector of baseline covariates that includes an intercept, $\gamma$ is the treatment effect, and
  \[ \beta = (\beta_1, \ldots, \beta_p) \]
  is a $p \times 1$ vector of regression coefficients corresponding to the covariates.
Further let $Z_{ij}$ denote the random time for the $j^{th}$ metastasis-competent tumor cell to produce detectable disease in subject $i$. Hence, one can view $Z_{ij}$ as the “promotion time” for the $j^{th}$ metastasis-competent tumor cell.

Conditional on $N_i$, the $Z_{ij}$ are assumed to be independent and identically distributed according to the cumulative distribution function

$$F(z | \psi_{s_i}) = 1 - S(z | \psi_{s_i}),$$

where $s_i$ is the stratum to which subject $i$ belongs and $\psi_s$ represents the promotion time model parameters for stratum $s$.

The time to detectable cancer relapse for subject $i$ is given by

$$Y_i = \min \{Z_{ij}, 0 \leq j \leq N_i\},$$

where $Z_{i0} = \infty$. 
Suppressing the notation for covariates, the marginal probability of survival past time $y$ for subject $i$ is given as follows:

$$S_p(y \mid \theta_i, \psi_{si}) = P(N_i = 0 \mid \theta_i) + P(Y_i > y \mid N_i \geq 1, \theta_i, \psi_{si})$$

$$= \exp(-\theta_i) + \sum_{k=1}^{\infty} S(y \mid \psi_{si})^k \exp(-\theta_i) \frac{\theta_i^k}{k!}$$

$$= \exp(-\theta_i F(y \mid \psi_{si})) . \quad (1.1)$$
The subdensity corresponding to (1.1) is given by

\[ f_p(y \mid \theta_i, \psi_{s_i}) = \theta_i f(y \mid \psi_{s_i}) \exp(-\theta_i F(y \mid \psi_{s_i})) \]

with corresponding subhazard given by

\[ h_p(y \mid \theta_i, \psi_{s_i}) = \theta_i f(y \mid \psi_{s_i}). \]  \hfill (1.2)

From (1.2), it is apparent that the promotion time formulation of the cure rate model leads to a proportional hazards structure for the subhazard.

To complete the specification of the survival model in (1.1), we must specify a distribution for the promotion times. Common choices are the Weibull distribution (fully parametric) and piecewise exponential distribution (semi-parametric).
Promotion Time Cure Rate Model

- For the design example we will illustrate, we utilize a separate Weibull model for each level of the stratification variable. The model selection results suggest that this approach can lead to better fit compared to the more standard modeling framework.

- The complete data likelihood based on a Weibull model for the promotion times can be written as follows

\[
\mathcal{L}(\xi, N | D) = \prod_{i=1}^{n} S(y_i | \psi_{s_i})^{N_i-v_i} (N_i f(y_i | \psi_{s_i}))^v_i \frac{e^{-\theta_i \theta_i^{N_i}}}{N_i!},
\]

where \( \xi = \{\gamma, \beta, \psi_s : s = 1, ..., S\} \) is the set of all parameters in the model, \( \psi_s = \{\lambda_s, \alpha_s\} \) is the set of Weibull promotion time model parameters for stratum \( s \), and \( D = \{(y_i, v_i, z_i, x_i, s_i) : i = 1, ..., n\} \) is the observed data with \( v_i \) representing whether an event occurred for subject \( i \).
We represent the collection of all promotion time model parameters by $\psi$ to simplify exposition.

One can analytically sum out the latent $N_i$ variables to obtain the observed data likelihood

$$
\mathcal{L} (\xi \mid D) = \prod_{i=1}^{n} \left[ \theta_i f (y_i \mid \psi_{s_i}) \right]^{v_i} \exp \left\{ -\theta_i F (y_i \mid \psi_{s_i}) \right\}. \tag{1.3}
$$
The form of the power prior of Ibrahim and Chen (2000) using the observed data likelihood formulation in (1.3) is as follows:

\[
\pi_0 (\xi | D_0, a_0) \propto [L(\xi | D_0)]^{a_0} \pi_0(\xi)
\] (1.4)

where \(0 \leq a_0 \leq 1\) is a fixed scalar parameter,

\[D_0 = \{(y_j, v_j, z_j, x_j, s_j) : j = 1, ..., n_0\}\]

is the historical data, \(L(\xi | D_0)\) is the likelihood for the historical data, and \(\pi_0(\xi)\) is an initial non-informative prior.

- When \(a_0 = 0\) the historical data is essentially discarded and the power prior reduces to the initial prior.
- In contrast, when \(a_0 = 1\), the power prior corresponds to the posterior distribution from an analysis of the historical data using the initial prior.
We take $a_0$ to be fixed.

$a_0$ will control the Bayesian type 1 error rate.

An appealing property of the power prior with fixed $a_0$ is that analysis using it with a non-informative initial prior is closely related to weighted maximum likelihood analysis where historical trial subjects are given a weight of $a_0$ and new trial subjects are given a weight of one.
The Power Prior

To see this connection, note that the logarithm of the posterior (ignoring the normalizing constant) is given by

\[
\log \pi (\xi \mid D, D_0, a_0) = \log \mathcal{L}(\xi \mid D) + a_0 \log [\mathcal{L}(\xi \mid D_0)] + \log \pi_0(\xi)
\]

\[
= \sum_{i=1}^{n} w_i \left[ v_i \{ \log \theta_i + \log f (y_i \mid \lambda_{s_i}, \alpha_{s_i}) \} - \theta_i F (y_i \mid \lambda_{s_i}, \alpha_{s_i}) \right]
\]

\[
+ \sum_{j=1}^{n_0} w_{0,j} \left[ v_j \{ \log \theta_j + \log f (y_j \mid \lambda_{s_j}, \alpha_{s_j}) \} - \theta_j F (y_j \mid \lambda_{s_j}, \alpha_{s_j}) \right]
\]

\[
+ \log \pi_0(\xi),
\]

which is \textit{approximately} equal to the weighted log-likelihood based on the combined trials with \( w_i = 1 \) for new trial subject \( i \) and \( w_{0,j} = a_0 \) for historical trial subject \( j \).
When the sample sizes for the new and historical trials are reasonably large, the Bayesian central limit theorem assures us that

\[ \pi (\gamma | D, D_0, a_0) \propto \text{Normal} (\gamma | \hat{\gamma}, \sigma^2_{\hat{\gamma}}). \]  

(1.5)

- \( \hat{\gamma} \) is the weighted maximum likelihood estimator (MLE) from a joint analysis of both trials with weights described above.
- \( \sigma^2_{\hat{\gamma}} \) is the relevant diagonal element of the inverse of the observed information matrix for the weighted log-likelihood evaluated at the weighted MLE.
The Power Prior

- The null and alternative hypotheses of a superiority trial are

\[ H_0 : \gamma \geq 0 \text{ vs. } H_1 : \gamma < 0. \]

- One can approximate the posterior probability

\[
P(\gamma < 0 \mid D, D_0, a_0) \approx P \left( Z_1 \leq -\frac{\hat{\gamma}}{\sigma_{\hat{\gamma}}} \bigg| D, D_0, a_0 \right) \\
\approx P \left( Z_2 \geq \frac{\hat{\gamma}}{\sigma_{\hat{\gamma}}} \bigg| D, D_0, a_0 \right) \\
\approx 1 - \Phi \left( \frac{\hat{\gamma}}{\sigma_{\hat{\gamma}}} \right). \tag{1.6}
\]

- \( Z_1 \) and \( Z_2 \) are standard normal variables.

- When \( \hat{\gamma} \) and \( \sigma_{\hat{\gamma}}^2 \) are weighted MLEs, the right hand side of (1.6) is one minus the one-sided p-value from a weighted maximum likelihood analysis of the combined trials.
We will accept $H_1$ if $P(\gamma < 0 \mid D, D_0, a_0)$ is at least as large as some threshold value $\phi$.

During design, we examine various possible values for the number of subjects to be enrolled in the new trial ($n$), the duration of the new trial ($T$), $a_0$, and $\phi$ in search of a set of values that provide sufficient Bayesian power while controlling the Bayesian type I error rate at no more than $\alpha^{(s)}$.

We refer to the set of values $\{n, T, a_0, \phi\}$ as the key controllable trial characteristics.

In general, $T$ should be at least as large as the duration of time it is expected to take for the survival curves to plateau.
We further restrict the search space for the key controllable trial characteristics by fixing $\phi = 1 - \alpha^{(s)}$, where $\alpha^{(s)}$ is the Bayesian type I error rate (to be defined).

This choice of $\phi$ is justified by the fact that the posterior probability

$$P(\gamma < 0 \mid D, D_0, a_0 = 0)$$

(based on an analysis of the new trial data without incorporating historical data) will be asymptotically uniformly distributed when $\gamma = 0$ and the model is correct.
Accordingly, rejecting the null hypothesis when

\[ P(\gamma < 0 \mid D, D_0, a_0 = 0) \geq \phi = 1 - \alpha^{(s)} \]

will provide frequentist type I error control at level \( \alpha^{(s)} \) (asymptotically).

One can view our design procedure as starting out with a size \( \alpha^{(s)} \) frequentist hypothesis test (based on taking \( a_0 = 0 \)) and then modifying the test by borrowing increasing amounts of information from the historical trial until it functions as a size \( \alpha^{(s)} \) hypothesis test with respect to the Bayesian type I error rate.
Formal Definition of the Bayesian Type I Error Rate and Power

- Let $\pi_0^s(\xi)$ and $\pi_1^s(\xi)$ be the null and alternative sampling priors and let $\pi^f(\xi)$ be the fitting prior (Wang and Gelfand, 2000, Chen, Ibrahim, et al. 2011).

- A sampling prior specifies a probability distribution for the model parameters conditional on a particular hypothesis being true.

- In the context of the cure rate model, the null sampling prior will give zero weight to values of $\xi$ having a negative $\gamma$ component and the alternative sampling prior will give zero weight to values of $\xi$ having a non-negative $\gamma$ component.
Formal Definition of the Bayesian Type I Error Rate and Power

- The sampling priors are referred to as such because they are used to sample parameter values in the simulation-based estimation procedure for the Bayesian type I error rate and power.
- The fitting prior \( \pi^{(f)} (\xi) \) is simply the prior used to analyze the data. In our case \( \pi^{(f)} (\xi) \) is the power prior given in (1.4).
Formal Definition of the Bayesian Type I Error Rate and Power

- For a fixed value of $\xi$, define the null hypothesis rejection rate as

$$r (\xi \mid D_0, a_0) = E \left[ 1 \{ P (\gamma < 0 \mid D, D_0, a_0) \geq \phi \} \mid \xi, D_0, a_0 \right] ,$$

where $1 \{ P (\gamma < 0 \mid D, D_0, a_0) \geq \phi \}$ is an indicator that we accept $H_1$ based on the posterior probability $P (\gamma < 0 \mid D, D_0, a_0)$ determined by the observed data $D$.

- For null values of $\xi$, the quantity $r (\xi \mid D_0, a_0)$ is the type I error rate and for alternative values of $\xi$ it is the power.
For chosen null and alternative sampling priors, the Bayesian type I error rate $\alpha^{(s)}$ and Bayesian power $1 - \beta^{(s)}$ are defined as

$$\alpha^{(s)} = \mathbb{E}_{\pi_0^{(s)}(\xi)} \left[ r(\xi | D_0, a_0) \right]$$ (1.7)

and

$$1 - \beta^{(s)} = \mathbb{E}_{\pi_1^{(s)}(\xi)} \left[ r(\xi | D_0, a_0) \right].$$ (1.8)
Formal Definition of the Bayesian Type I Error Rate and Power

- The expectation in (1.7) is with respect to the null sampling prior distribution for $\xi$ and the expectation in (1.8) is with respect to the alternative sampling prior distribution for $\xi$.

- We note that Chen, Ibrahim et al. (2011) define the Bayesian type I error rate and power in terms of the null and alternative prior predictive distribution of the data,

$$\int p(D | \xi) \pi_0^{(s)}(\xi) \, d\xi \quad \text{and} \quad \int p(D | \xi) \pi_1^{(s)}(\xi) \, d\xi,$$

respectively.

- Our presentation here simply changes the order of integration to highlight the fact that the Bayesian type I error rate and Bayesian power are weighted averages of the quantities based on fixed values of $\xi$. 
Sampling Prior Elicitation

- We develop default sampling priors that are constructed through conditioning the historical trial posterior distribution on either the null or alternative hypothesis.
- Extensions to the default priors that remove implausible effects by truncating the tails of the default prior distributions are called truncated sampling priors.
- We consider sampling priors where the treatment effect distribution is elicited independently of the historical data, called partially-elicited sampling priors.
Flow Diagram for Null Sampling Prior Selection

Inferiority Plausible?

Yes

Condition on $H_0$

Tails Plausible?

Yes

Default Prior

No

Partially -Elicited Prior

Condition on $γ = 0$

Limiting-Case Truncated Prior

No

Truncated Prior

Yes

Condition on $H_0$

Tails Plausible?

No

Truncated Prior
The default sampling priors arise naturally when the entirety of one’s knowledge about $\xi$ comes by way of the historical data. After collecting that data, one’s belief about the parameters is determined by

$$\pi (\xi \mid D_0) = \pi_0 (\xi \mid D_0, a_0 = 1)$$

(i.e., the power prior with no discounting).

Reasonable choices for the null and alternative sampling priors are

$$\pi_0^{(s)} (\xi) = \pi (\xi \mid D_0, \gamma \geq 0)$$

(the historical posterior given that $H_0$ is true) and

$$\pi_1^{(s)} (\xi) = \pi (\xi \mid D_0, \gamma < 0)$$

(the historical posterior given that $H_1$ is true).
\( \pi (\gamma | D_0) \) and corresponding default marginal sampling priors for Melanoma Data
$$\pi_1^{(s)} (\gamma, \beta_1)$$

$$\pi_0^{(s)} (\gamma, \beta_1)$$
Null and Alternative Sampling Priors

- If one assumes there is a null effect (i.e., \( \gamma \geq 0 \)), that implies larger negative values for \( \beta_1 \) (i.e., a higher cured fraction in the control arm).
- Researchers may deem it impossible for the investigational therapy to decrease the cured fraction by more than a certain amount relative to the control.
- In addition, researchers may want to compute power over a restricted alternative space that rules out implausibly large or clinically insignificant effect sizes.
- The truncated null sampling prior is defined as
  \[
  \pi_0^{(s)} (\xi) = \pi (\xi | D_0, 0 \leq \gamma \leq \gamma_{0, u}).
  \]
  As \( \gamma_{0, u} \to 0 \), less and less information can be borrowed from the historical data if the Bayesian type I error rate is to be controlled at level \( \alpha^{(s)} \).
When $\gamma_{0,u} = 0$ (i.e., the limiting-case), Bayesian type I error control is similar to frequentist type I error control in that no information can be borrowed if the Bayesian type I error rate is to be controlled at level $\alpha^{(s)}$.

The fundamental difference between frequentist and Bayesian type I error control is that the latter implicitly assumes the nuisance parameters in the cure rate model for the new trial are consistent with the posterior distribution from the historical trial after conditioning on the appropriate null event (i.e., $0 \leq \gamma \leq \gamma_{0,u}$).

Bayesian type I error control is defined based on a specific null sampling prior distribution for the nuisance parameters whereas frequentist type I error control is based on a constraint that must be satisfied for any value of the nuisance parameters.
The truncated alternative sampling prior is defined as

\[ \pi_1^{(s)} (\xi) = \pi (\xi \mid D_0, \gamma_{1,l} \leq \gamma < \gamma_{1,u}) . \]

If *any* positive treatment effect would be clinically meaningful and resources permit, we recommend leaving \( \gamma_{1,u} = 0 \) for power analysis.

Otherwise, \( \gamma_{1,u} \) can be set to the smallest clinically meaningful treatment effect.
Elicited Sampling Priors

- The truncated null sampling prior does not provide a mechanism by which one can adjust the relative weighting of plausible treatment effects.

- One straightforward approach of elicitation of the sampling prior is to specify a worst-case treatment effect $\gamma_{0,u}$ and choose a parametric distribution $\pi_0^{(s)}(\gamma)$ with support restricted to $[0, \gamma_{0,u}]$ with rate of decay in the tail such that $\pi_0^{(s)}(\gamma_{0,u}) \approx 0$. 
Default, truncated, and elicited null sampling priors for the treatment effect $\gamma$

**Figure 1**: Default, truncated, and elicited null sampling priors for the treatment effect $\gamma$. 
Simulation-based Estimation of the Bayesian Type I Error and Power

Let $B$ be the number of simulation studies to be performed. To estimate the Bayesian type I error rate, we proceed as follows:

1. Sample $\xi^{(b)}$ from the null sampling prior $\pi_0^{(s)}(\xi)$.
2. Given $\xi^{(b)}$, simulate the new trial data $D^{(b)}$. This can be done using the following steps (for each subject):
   i. Simulate $x_i$, $z_i$, and $s_i$ based on the chosen distribution for the covariates, randomization fraction, and distribution for the stratification variable.
   ii. Calculate $\theta_i = \exp(\gamma z_i + x_i^T \beta)$ and simulate $N_i \sim \text{Poisson}(\theta_i)$.
   iii. Simulate $Z_{ij} \sim F(z \mid \psi_{s_i})$ independently for $j = 1, \ldots, N_i$ and calculate $z_i = \min(Z_{ij} : j = 0, \ldots, N_i)$ with $Z_{i0} = T$.
   iv. Simulate the time-to-censorship, denoted as $c_i$, according to the chosen distribution. If only administrative censoring is entertained, then set $c_i = T$.
   iv. If $z_i < c_i$ then set $y_i = z_i$ and $v_i = 1$, otherwise set $y_i = c_i$ and $v_i = 0$. 
Simulation-based Estimation of the Bayesian Type I Error and Power

3. Update the fitting prior $\pi^{(f)}(\xi)$ based on the likelihood for the simulated data $L(\xi | D^{(b)})$ to obtain the posterior distribution

$$\pi(\xi | D^{(b)}, D_0, a_0)$$

and calculate the posterior probability of the alternative hypothesis

$$P(\gamma < 0 | D^{(b)}, D_0, a_0).$$

4. Compute the null hypothesis rejection indicator for simulated trial $b$:

$$r^{(b)} = 1 \left\{ P \left( \gamma < 0 | D^{(b)}, D_0, a_0 \right) \geq \phi \right\}.$$

5. Approximate the Bayesian type I error rate with the empirical null hypothesis rejection rate:

$$\alpha^{(s)} \approx \frac{1}{B} \sum_{b=1}^{B} r^{(b)}.$$
Simulation-based Estimation of the Bayesian Type I Error and Power

- Steps 1-4 are first repeated for $b = 1, ..., B$ to obtain the outcome for each simulated trial and then step 5 combines the results to estimate the Bayesian type I error rate.

- The process for estimating Bayesian power is identical. One simply needs to use the alternative sampling prior in place of the null sampling prior in the algorithm above.
Bayesian Design of a Superiority Trial in High-Risk Melanoma

- E1690 was a prospective, randomized, three-arm clinical trial designed to evaluate the efficacy of high-dose IFN for one year and low-dose IFN for two years relative to observation (OBS) in high-risk melanoma patients using relapse-free survival (RFS) and overall survival endpoints.
- We restrict our attention to the high-dose IFN regimen and consider the design of a subsequent trial to further evaluate the efficacy of IFN using an RFS endpoint.
- Patients enrolled in the E1690 trial had histologically proven American Joint Committee on Cancer (AJCC) stage IIB or stage III primary or recurrent regional nodal involvement from cutaneous melanoma without evidence of systemic metastatic disease (disease stages 1: T4cN0, 2: T1-4pN1cN0, 3: T1-4cN1, and 4: T1-4N1 recurrent).
The randomization and primary analysis were stratified by disease stage and the number of positive nodes at lymphadenectomy.

The primary analysis was based on a stratified log-rank test and the two-sided p-value was 0.054.

There were 215 subjects and 114 relapses observed in the high-dose IFN group and 211 subjects and 126 relapses observed in the OBS group.

Among the set of subjects who did not experience relapse, the median observation time was over four years. Figure 2 presents the Kaplan-Meier estimator for the survival curves for the high-dose IFN and OBS groups.
Figure 2: Kaplan-Meier curves for the E1690 high-dose IFN and OBS groups.
Table 1: DIC for six best candidate design models

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<th>Covariates</th>
<th>Weibull DIC</th>
<th>Exponential DIC</th>
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Table 2: Summaries for historical trial posterior and default sampling priors

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<th>Default Null</th>
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<td>Mean (SD)</td>
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Table 3: Bayesian power estimates for select sample sizes

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NB = No Borrowing  
EN = Elicited Null  
DN = Default Null  
DA = Default Alternative  
TA = Truncated Alternative  
PM = Point Mass
Figure 3: Estimated Bayesian type I error rate curves and point estimates for sample sizes $n = 580$ and $n = 800$. Each point estimate was based on 100,000 simulated trials. Curves were estimated separately for each null sampling prior using least-squares regression based on cubic polynomials in both $a_0$ and $n$ with interactions ($R^2 > 0.999$).
Figure 4: Worst-case performance of designs with $a_0$ determined using the DN and EN sampling priors compared to a design with no borrowing (i.e., $a_0 = 0$). For scatter plot points corresponding to $n = 560$ and $n = 860$ the identified values of $a_0$ (above) and the estimated supremum Bayesian type I error rate (below) are annotated for reference.
A GitHub repository (https://github.com/psioda/bayes-design-hist-cure-rate) contains the SAS and R programs and other resources needed to reproduce the analyses presented in this paper.

All files (SAS data sets, programs, logs, shell scripts, etc.) used in that example are provided at https://figshare.com.
