A Latent Gaussian Process Model with Application to Monitoring Clinical Trials

Yanxun Xu
Division of Statistics and Scientific Computing, The University of Texas at Austin, Austin, TX

Yuan Ji *
Center for Biomedical Informatics, NorthShore University HealthSystem, Evanston, IL

Department of Health Studies, The University of Chicago, Chicago, IL

Abstract

In many clinical trials treatments need to be repeatedly applied as diseases relapse frequently after remission over a long period of time (e.g., 35 weeks). Most research in statistics focuses on the overall trial design, such as sample size and power calculation, or on the data analysis after trials are completed. Little is done to improve the efficiency of trial monitoring, such as early termination of trials due to futility. The challenge faced in such trial monitoring is mostly caused by the need to properly model repeated outcomes from patients. We propose a Bayesian trial monitoring scheme for clinical trials with repeated and potentially cyclic binary outcomes. We construct a latent Gaussian process (LGP) to model discrete longitudinal data in those trials. LGP describes the underlying latent process that gives rise to the observed longitudinal

*Address for correspondence: NorthShore University HealthSystem / The University of Chicago, 1001 University Place, Evanston, Illinois, USA 60091. Email: jiyuan@uchicago.edu
binary outcomes. The posterior consistency property of the proposed model is studied. Posterior inference is conducted with a hybrid Monte Carlo algorithm. Simulation studies are conducted under various clinical scenarios, and a case study is reported based on a real-life trial. Matlab program for implementing the interim monitoring procedure is freely available at [http://www.ma.utexas.edu/users/yxu](http://www.ma.utexas.edu/users/yxu).

**KEY WORDS:** Clinical Trial; Forecast; Hierarchical Model; Hybrid Monte Carlo; Latent Variable; Longitudinal Data.

## 1 Introduction

### 1.1 Background

We consider Bayesian monitoring for clinical trials with longitudinal binary outcomes, such as multiple disease remissions over time. This is an area that has received little attention in the trial design field. Most work has focused on the overall design of the trial (Frison and Pocock, 1992; Raudenbush and Liu, 2001; Galbraith et al., 2002; Hedeker et al., 1999), such as sample size calculation and choice of followup time points, or methods for analyzing data after trials are completed (Liang and Zeger, 1986; Hedeker and Gibbons, 2006). In many trials, the primary outcome data for each subject are recurrent and cyclic based on a longitudinal binary variable. For example, a data vector of interest could be binary values observed on consecutive time points, and the vector values alternate between 1’s and 0’s. This type of data arises from clinical trials in many therapeutic areas, such as auto-immune diseases like multiple sclerosis or Schizophrenia (see Goldman et al., 2010 and references therein). Typically, treatments need to be applied multiple times in hopes to slow down disease progression. When multiple drugs are to be evaluated, it is challenging to quantify and compare the efficacy of the drugs due to the temporal and periodic nature of disease progression and treatment response. For example, when two drugs are compared in a clinical
trial involving one new treatment and a standard treatment, therapeutic effects are usually assessed by comparing the relapse rates of treatments within a time framework. However, that strategy might not be ideal since a treatment with a slightly inflated relapse rate might still be preferred if it allows patients to stay in disease remission for a longer period of time.

In this paper, we consider an important design issue for trials of the same nature. For each patient, multiple responses to treatments and multiple disease relapses are expected. One goal is to demonstrate that one treatment allows patients to stay in disease remission longer than the other, and a second goal is to predict future responses for individual patients based on observed outcomes. A typical patient response vector may look like \((1, 1, 0, 0, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, \ldots)\) with binary outcomes at multiple time points, where “1” represents a response and “0” a nonresponse. In addition, each binary outcome is associated with a time point at which the outcome is recorded. Therefore, the data is summarized as \(\{e(t_k), k = 1, \ldots, K\}\) where \(e(t_k) \in \{0, 1\}\) is binary. In Comi et al. (2012), a response \(e(t_k) = 1\) is defined as a combination of cognitive improvements assessed by psychiatric tests. An important presumption that underpins this type of trial is that the unobserved disease progression is a continuous process over time, although measurements of outcome can only be taken at discrete time points, e.g., once a month. In other words, the observed binary longitudinal outcomes are manifestations of latent continuous processes.

To model a latent process, Zeger et al. (1985) considered an extension of logistic regression to binary longitudinal observations. However, their method was only applied to stationary binary series. Czado and Song (2008) developed a state space mixed model for binary longitudinal observations using the standard linear state-space formulation (Kalman, 1963). But the linear state-space models are limited and may not work well on the aforementioned trials with nonlinear and cyclic responses. Hall et al. (2008) proposed a latent Gaussian process model for sparse generalized longitudinal observations. They estimated the mean function by smoothing the mean of all trajectories and covariance kernel by calcu-
lating functional principle components as the eigenfunctions. While useful, their smoothing technique must be applied to all observations collectively, not allowing random effects that deviate from the population curve. More importantly, available models for longitudinal data cannot accommodate all our needs for trial monitoring, which include 1) to model cyclic binary responses, 2) to forecast future outcomes for each patient based on the cyclic pattern, 3) to compare population patterns between different conditions (treatment v.s. control), 4) to reflect the underlying continuous disease progression mechanism. Also, to our knowledge, there does not exist an adaptive monitoring scheme for trials with binary longitudinal outcomes. For example, there are no existing statistical methods for terminating such trials when the treatment arm is not effective as the control. To this end, we consider a latent stochastic process with cyclic features to describe the relapsing nature of the disease. Specifically, let $a_j(t) = \mu(t) + \tau_j(t)$ be a sum of the mean process $\mu(t)$ describing the treatment effect over time, and a cyclic process $\tau_j(t)$ describing the subject-$j$-specific recurrent disease progression. For example, the treatment effect $\mu(t)$ could be increasing over time due to the continuous usage of the drug but $\tau_j(t)$, to be modeled as the latent Gaussian process, could be cyclic mimicking the recurrent disease progression as a result of the battle between the disease-causing antigens and the disease-fighting immune cells. We model the binary outcome at a time point $t_k$ as an indicator $e_j(t_k) = I\{a_j(t_k) > a_h\}$ with a fixed and arbitrary threshold value $a_h$. This construction can be considered a stochastic-process version of the latent probit model in Albert and Chib (1993). We defer the construction of $a_j(t)$ to Section 2.

1.2 Gaussian Process

Gaussian process (GP) has been frequently applied to research areas in finance, engineering, cognitive research, and others. Examples of such applications include work in machine learning (Rasmussen and Williams 2006), neural networks (Neal 1995), and batched data
Initially introduced in O’Hagan and Kingman (1978), GP priors have also been used in Bayesian inference for regression and classification problems; see a review by Williams (1998). GP models are considered nonparametric in curve fitting as they are not dependent on any functions to describe the shapes of the curves. At the same time, GP models are relatively easy to compute since they are based on multivariate Gaussian distributions.

A Gaussian process is a stochastic process $a(t)$, for which any $n$-finite variates $a_n = \{a(t_1), \ldots, a(t_n)\}'$ has a multivariate Gaussian distribution given by

$$P(a_n | \mu, C) \propto |C|^{-\frac{1}{2}} \exp \left\{ -\frac{1}{2} (a_n - \mu)' C^{-1} (a_n - \mu) \right\}$$

for any $n$ and collection of input $\{t_1, \ldots, t_n\}$. Vector $\mu$ is the mean vector with dimension $n$ and $C$ represents the $n \times n$ covariance matrix, and is often parameterized as a covariance function $C_{uv}(t_u, t_v; \Theta)$, where $\Theta$ is a set of hyperparameters. In other words, a Gaussian process is one which every finite-dimensional joint distribution is multivariate Gaussian. Since we are expressing the correlations between different points in the input space through the covariance function, it is crucial to study the characteristics of the GP, such as its smooth properties and differentiability (Abrahamsen 1997).

### 1.3 Motivating Examples

The key idea of our proposed LGP is to model observed discrete longitudinal outcomes by thresholding the latent variates that follow a GP prior. We consider two motivating examples. The first example is a randomized, double-blind, placebo-controlled clinical trial aiming to evaluate the efficacy and safety of a 200-mcg dose of a new drug (drug name masked for copyright protection) in patients with systemic lupus erythematosus (SLE). We will refer to this trial as the “lupus trial” hereinafter. SLE is a long-term auto-immune disease in which
the body mistakenly attacks healthy organs, such as the skin and brain. There is no cure for the disease, and immuno-therapies only reduce symptoms and must be applied frequently. Patients respond to treatments quickly, typically within weeks, although the disease also relapses quickly. A clinical response is based on the SLE responder index, which is defined by a combination of four different cognitive test scores. In the presence of control, each patient is randomized and followed for 35 weeks, during which time multiple relapses and responses might be observed. The trial objective is to compare the response rates of the new treatment and the control. It is desirable to terminate the trial early since the 35-week follow-up time period is long; for example, whenever there is substantial evidence that the new treatment is no better than the control, the trial should be stopped for both ethical and financial considerations. The total sample size for the lupus trial is 200 patients, who are randomized 1:1 between the two treatments.

A second similar example is a placebo-controlled trial of oral laquinimod for multiple sclerosis (Comi et al., 2012). The efficacy and safety of laquinimod in patients with relapsing-remitting multiple sclerosis were evaluated in a randomized, double-blind, phase III trial with 1,106 patients randomly assigned in a 1:1 ratio to receive placebo or laquinimod. The primary end point was whether or not the disease had relapsed during the study period. An event was counted as a relapse if the patient’s symptoms were accompanied by objective neurologic changes according to predefined criteria.

A common feature in both trials is that multiple responses and relapses are expected for each patient during the follow-up period, and therefore simple monotonic parametric dose-response models such as logistic regression are no longer suitable. The observed data for each patient will be a binary vector \( \mathbf{e} = (e_1, e_2, \ldots, e_K) \) for \( K \) time points. The indicators are temporally correlated.

In Section 2 we present probability models and computational methods based on the posterior distributions. In Section 3 we derive posterior consistency results. In Section 4
we propose inference for predicting future responses and introduce stopping rules as part of the trial design. We examine the performance of LGP through extensive simulation studies in Section 5. In Section 6, we report numerical results based on the lupus trial. Finally, we conclude with a brief discussion in Section 7.

2 Probability Model

2.1 Latent Gaussian Process

In the aforementioned lupus trial, patients are randomized between two arms, with arm 1 being the standard control and arm 2 the new treatment. Multiple interim analyses are proposed to monitor the progress of the trial and to compare the two treatments. At the time of interim analysis, assume that $N_1$ and $N_2$ patients have been assigned to arms 1 and 2, respectively ($N_1 = N_2$ if equal randomization). For each patient $j$ in group $i$, we assume that disease outcomes have been measured at $K_{ij}$ time points, denoted as $t_{ij} = (t_1, t_2, \ldots, t_{K_{ij}})$. Here a time point refers to the duration of follow-up. Let $e_{ijk}(t_k)$ be the binary response at time point $t_k$, simplified as $e_{ijk}$. If the $j$th patient in group $i$ responded at time $t_k$, then $e_{ijk} = 1$; otherwise, $e_{ijk} = 0$. Therefore, the observed data are tuple $e^K = \{e_{ijk}\}, i = 1, 2; j = 1, 2, \ldots, N_i; k = 1, 2, \ldots, K_{ij}$.

Define a stochastic process

$$a_{ij}(t) = \mu_i(t) + \tau_{ij}(t)$$

where $\mu_i(t)$ is the mean process that describes the effects of drug $i$ and $\tau_{ij}(t)$ is a zero-mean GP that induces temporal correlation within a patient.
Denoting the latent variable \( a_{ijk} \equiv a_{ij}(t_k) \), we assume \( e_{ijk} = I(a_{ijk} > a_h) \), i.e.,

\[
e_{ijk} = \begin{cases} 
1 & \text{if } a_{ijk} > a_h \\
0 & \text{otherwise}
\end{cases},
\]

where \( a_h \) is an arbitrary threshold and \( I(\cdot) \) is the indicator function.

In (1), the choice of \( \mu_i(t) \) depends on the underlying disease and drug mechanism. Based on prior knowledge, for example, if we believe that the efficacy of a drug is increasing over time, we could simply use a linear function \( \mu_i(t) = \beta_i^0 + \beta_i t \) with a positive slope; if we believe the efficacy increases first then decreases due to drug resistance, we could use a quadratic function. To accommodate different shapes of response curves, we choose the polynomial regression model to describe the drug mean effects over time, i.e.,

\[
\mu_i(t) = \beta_{i0} + \beta_{i1} t + \cdots + \beta_{i,m_i} t^{m_i},
\]

where \( \beta_i = (\beta_{i0}, \beta_{i1}, \ldots, \beta_{i,m_i})' \) are regression coefficients of time for each of the two treatment arms \((i = 1, 2)\). In practice, the degree \( m_i \) of the polynomial is unknown, and we let \( m_i = \{0, 1, \ldots, M\} \) be a random variable taking integer values between 0 and a large number \( M \). It is important to allow \((m_i, \beta_i)\) to vary for different arms \( i \) so that the drug effects can be easily compared by posterior inference using these parameters. Also, we do not consider nonparametric functions for modeling \( \mu_i(t) \) to avoid potential identifiability issue in the model since \( \tau_{ij}(t) \) is already nonparametric.

Note that \( \beta_i \) describes the global response pattern of each arm \( i \). For the dependence across time within each patient \( j \), we assume that \( \tau_{ij}(t) \) follows a zero-mean GP that induces the cyclic correlation of \( a_{ij}(t) \). Let

\[
\tau_{ij}(t) \mid \Theta \sim \text{GP} \left( \mathbf{0}_{K_{ij}}, C(t_{ij}; \Theta) \right),
\]

where
where $\mathbf{0}_{K_{ij}}$ is a $K_{ij}$-dimension 0-vector, and $\mathbf{C}(\mathbf{t}_{ij}; \Theta)$ is a $K_{ij} \times K_{ij}$ covariance matrix indexed by $\Theta$.

Based on (1), (2) and (3), the proposed latent Gaussian process functional regression model is given by

$$P(\mathbf{a}^K | \beta, m, \Theta) \propto 2^{\frac{K_{ij}}{2}} \prod_{i=1}^{N_i} \prod_{j=1}^{K_{ij}} |\mathbf{C}(\mathbf{t}_{ij})|^{-\frac{1}{2}} \exp \left\{ -\frac{1}{2} (\mathbf{a}_{ij}^K - \mathbf{X}_{ij} \beta_i)' \mathbf{C}(\mathbf{t}_{ij})^{-1} (\mathbf{a}_{ij}^K - \mathbf{X}_{ij} \beta_i) \right\}, \quad (4)$$

where $\mathbf{a}_{ij}^K = (a_{ij1}, \ldots, a_{ijK_{ij}})'$, $\beta = \{\beta_i\}$, $m = \{m_i\}$, $i = 1, 2$ and the design matrix $\mathbf{X}_{ij}$ of the polynomial (2) is

$$\mathbf{X}_{ij} = \begin{pmatrix}
1 & t_1 & \cdots & t_{m_i}^1 \\
1 & t_2 & \cdots & t_{m_i}^2 \\
\vdots & \vdots & \ddots & \vdots \\
1 & t_{K_{ij}} & \cdots & t_{K_{ij}}^m
\end{pmatrix}.$$ 

The covariance matrix $\mathbf{C}(\mathbf{t}_{ij})$ is usually parameterized to induce within-patient dependence over time. The most popular parametrization (Williams, 1998) of the stationary covariance function $\mathbf{C}(\mathbf{t}_{ij}; \Theta)$ is a $K_{ij} \times K_{ij}$ matrix with the $uv$-th element $C_{uv}$ defined by

$$C_{uv}(\Theta) = \theta_1^2 \exp \left\{ -r^2 (t_u - t_v)^2 \right\} + \delta_{uv} J^2, \quad u, v = 1, \ldots, K_{ij}. \quad (5)$$

In (5) $\Theta = (\theta_1, r)'$, $C_{uv}(\Theta)$ is the covariance of the GP for time points $t_u$ and $t_v$, $\delta_{uv} = I(u = v)$, and $J$ is the variance on the diagonal reflecting the amount of jitter (Bernardo et al., 1999), which usually takes on a small value (e.g., $J = 0.1$). This construction of the covariance matrix yields a strong correlation for observations at time points close to each other and has been widely adopted (Williams, 1998).

However, if the system is recurrent, which is the case here for the lupus trial, formulation (5) is not suitable since it is aperiodic. Instead, we should consider other forms of covariance functions with periodicity. For example, a periodic model with known wavelength $\theta_2$ is given
by

\[ C_{uv}(\Theta) = \theta_1^2 \exp \left\{ -r^2 \sin^2 \left( \frac{\pi (t_u - t_v)}{\theta_2} \right) \right\} + \delta_{uv} J^2, \]  

(6)

and \( \Theta = (\theta_1, \theta_2, r)' \). This covariance function provides strong correlations not only for adjacent time points but also for those separated from each other by a distance \( \theta_2 \) or its multiplications. We will use (6) as the model for our trial applications. As an illustration, Figure 1 shows some realizations of \( \tau_{ij}(t) \) with different covariance functions \( C \). The realizations display some periodic patterns although their shapes can be quite different. This implies that the class of GP models with covariance (6) is general and can describe curves with a variety of different shapes.

Define the column vector \( \mathbf{a^K} = \{ a_{ijk}, i = 1, 2; j = 1, 2, \ldots, N_i; k = 1, 2, \ldots, K_{ij} \}' \). The likelihood function is given by

\[
P(e^K | a^K) = \prod_{i=1}^{N_i} \prod_{j=1}^{K_{ij}} \prod_{k=1}^{K_{ij}} P(e_{ijk} | a_{ijk})
\]

\[
= \prod_{i=1}^{N_i} \prod_{j=1}^{K_{ij}} \prod_{k=1}^{K_{ij}} \left\{ I(a_{ijk} > a_h)I(e_{ijk} = 1) + I(a_{ijk} \leq a_h)I(e_{ijk} = 0) \right\}.
\]

(7)

As a summary, the hierarchical model factors as

\[
P(e^K, a^K, m, \beta, \Theta) \propto P(e^K | a^K) P(a^K | \beta, m, \Theta) P(\beta | m) P(m) P(\Theta),
\]

(8)

where \( m = (m_1, m_2)' \) and \( \beta = (\beta'_1, \beta'_2)' \). The first factor is the sampling model (7). The second factor is the latent Gaussian process functional regression model (4). The remaining factors are priors of \( m, \beta \) and \( (\theta_1, \theta_2, r) \). We assume a uniform prior on \( P(m_i) \). For example,
Figure 1: Three random samples drawn from the Gaussian process $\tau_{ij}$ with four different covariance matrices. The corresponding covariance is given below each plot. The decrease in length scale from (a) to (b) produces more rapidly fluctuating functions. The periodic properties of the covariance function in (c) and (d) can clearly be seen.

given a large integer $M$, $P(m_i) = 1/(M+1)$ for $m_i = 0, 1, \ldots, M$. We assume

$$\beta_i \sim \text{Gaussian}(\mu_0^{m_i+1}, \sigma_0^2 I_{m_i+1})$$

$$\theta_1 \sim \text{Gaussian}(\mu_1, \sigma_1^2), \ r \sim \text{Gaussian}(\mu_2, \sigma_2^2), \ \theta_2 \sim \text{Gaussian}(\mu_3, \sigma_3^2),$$

where $\mu_0^{m_i+1}$ is $(m_i+1)$-dimension mean vector, and $I_{m_i+1}$ is an $(m_i+1) \times (m_i+1)$ dimension identity matrix. We assume vague priors for $\beta_i, \theta_1, r, \theta_2$ by imposing large values of variances $(\sigma_0^2, \sigma_1^2, \sigma_2^2, \sigma_3^2)$. 

11
We will show that the LGP model in (8) possesses desirable theoretical and numerical properties, such as consistency, the ability to forecast for individual patients and to stop trials early.

2.2 MCMC Simulations

The most significant computational cost of implementing a GP model when dealing with a vast number of time points is the inversion of the covariance matrix $C$. Such an inversion is required to make any predictions and, most significantly, in Bayesian inference to evaluate the gradient of the log posterior distribution over $\Theta$ in every Markov chain Monte Carlo (MCMC) iteration.

We carry out posterior inference based on MCMC simulation. The proposed Gibbs sampler proceeds by iterating over the following transition probabilities

$$P(a^K | e^K, \beta, m, \Theta), P(m | a^K, \Theta), P(\beta | a^K, m, \Theta), P(\Theta | a^K, \beta, m).$$

We start by generating $a^K$ from their full conditional posterior distributions – truncated Gaussian. Efficient ways to sample from truncated Gaussian can be found in Geweke (1991); Liechty and Lu (2010); Pakman and Paninski (2013). Through a cycle of Gibbs steps we also generate random draws of $m, \beta$ and $\Theta$. When updating $m$, we sample from the full conditional posterior distributions, marginalized with respect to $\beta$ (See Appendix A). Given $m$, sampling of $\beta$ is straightforward because of the fixed dimensionality and Gaussianity. This avoids the need for trans-dimensional MCMC. The challenging step is to sample $\Theta$, the full conditional of which is analytically intractable. However, we can obtain the approximations using the most probable values such as Evidence maximization (MacKay, 1992) or other non-Gibbs MCMC samplers. The most commonly used and straightforward method is the random-walk Metropolis sampling, but [Bernardo et al., 1999]
argued that simple Metropolis algorithms were not efficient and therefore advocated for the use of hybrid Monte Carlo (Duane et al. 1987). This idea was implemented by Barber and Williams (1997) who analyzed classification problems and achieved better results using hybrid Monte Carlo compared to Metropolis algorithms. With the same motivation, we propose a hybrid MCMC algorithm to sample the hyperparameters \( \Theta \) in the covariance function \( C(\Theta) \). The idea behind hybrid MCMC is to augment the parameter space and draw Metropolis proposals with improved samplers. Suppose we want to draw Monte Carlo samples from a proposed density \( P(\Theta) \propto \exp\{-E(\Theta)\} \), where \( \Theta = (\theta_1, \ldots, \theta_n) \). In physics terminology, \( \Theta \) can be regarded as a position vector and \( E(\Theta) \) the potential energy function. As a data augmentation step, we then introduce another set of variables called “momentum variables”, \( w = \{w_1, w_2, \ldots, w_n\} \), one \( w_i \) for each \( \theta_i \), with a kinetic energy function, \( P(w) = \frac{1}{Z_K} \exp(-K(w)) = (2\pi)^{-n/2} \exp(-\frac{1}{2} \sum_i w_i^2) \). The momentum variables are introduced to make random walks continue in a consistent direction until a region of low probability is encountered. The total energy function, known as Hamiltonian, is \( H(\Theta, w) = E(\Theta) + K(w) = E(\Theta) + \frac{1}{2} \sum_i w_i^2 \). The canonical distribution defined by this energy function is \( P(\Theta, w) = \frac{1}{Z_H} \exp\{-H(\Theta, w)\} = P(\Theta)P(w) \). Random samples of \( (\Theta, w) \) are jointly proposed by appropriate probabilities (see Appendix A for details). Samples from the marginal distribution for \( \Theta \) can be obtained by ignoring the values \( w \). Specifically, we use a discretized approximation called the leapfrog algorithm (Neal 1997), details of which are again described in Appendix A.

To summarize, the proposed MCMC algorithm includes a Gibbs sampler for \( a^K, m, \beta \) and a hybrid Monte Carlo algorithm for sampling \( \Theta \). The algorithm converges well with an initial burn-in of 2,000 iterations and a total of 10,000 iterations with a lag of 10 in our simulation studies. We conduct convergence diagnostics using R package coda and find no evidence for convergence problems. Traceplots and empirical autocorrelation plots (not shown) for the imputed parameters indicate a well mixing Markov chain.
3 Posterior Consistency

We discuss theoretical properties of the LGP model and show that it is consistent as the number of treated patients goes to infinity. For simplicity in the following discussion, we only consider one treatment arm by dropping index $i$ and use $n$ to denote the number of patients and $K_j$ to denote the number of time points observed for patient $j$. The proposed LGP model can be summarized as follows:

$$e_{jk} = e_j(t_k) \mid p(t_k) \sim \text{Bernoulli}(p(t_k)), \quad k = 1, \ldots, K_j, \quad j = 1, \ldots, n$$

$$p(t) = H(a(t)) \equiv \text{Pr}(a(t) > a_h), t \in [0, T_E]$$

$$a(\cdot) \sim \text{GP}(\mu(\cdot), C(\cdot, \cdot)),$$  \hspace{1cm} \text{(9)}

where observation times $t_k$'s are irregularly spaced points for each patient and fixed in advance on the compact set $\mathcal{T} = [0, T_E] \subset \mathcal{R}$ in which $T_E$ is the length of the trial, and $H$ is a known, strictly increasing, Lipschitz continuous cumulative function. Note that $a(\cdot)$ is a Gaussian process parameterized by its mean function $\mu: \mathcal{T} \rightarrow \mathcal{R}$ and its covariance function $C: \mathcal{T}^2 \rightarrow \mathcal{R}$, denoted by $\text{GP}(\mu, C)$. Additionally, we assume that the underlying true probability function is $p_0(t) = H(a_0(t))$, and $a_0(t)$, the true GP, has a continuously differentiable sample path on $\mathcal{T}$. Without loss of generality, we assume a linear mean function $\mu(t) = \beta_0 + \beta_1 t$. The proof for the case of $m$-polynomial is easily extended. In addition, we assume that the true covariance function has the form $C_0(t_u, t_v; \Theta) = C_0(|t_u - t_v|)$, where $C_0$ is a positive multiple of a nowhere-zero density function of one real variable. In our model, we consider a simple form of covariance function [6] without the jitter part. Then $C_0(t) = \theta_1^2 \exp \left\{ -r^2 \sin^2 \left( \frac{\pi}{\theta_2} t \right) \right\}$. We rewrite $C_0(t) \equiv C_0(t; \theta_1, r, \theta_2)$ to prepare for the coming discussion.

Posterior consistency using GP priors has been extensively studied, see Choudhuri et al. [14].
Choi and Schervish (2004, 2007), Ghosal and Roy (2006), and Tokdar and Ghosh (2007), among others. However, little is known about the type of LGP models proposed in this paper. We first present posterior consistency results based on a general modeling framework under a wide class of GP priors $a(\cdot)$ and link functions $H$, which can be any strictly increasing, Lipschitz continuous function. Our proposed LGP model in (9) is simply a special case of the general results. The proofs of all lemmas and theorems stated in this section are given in Appendix B.

To start, let $\mathcal{F}$ be the set of Borel measurable functions defined on $\mathcal{R}$, the real line. For now, assume that we have a topology on $\mathcal{F}$ that measures the distance between any two functions in $\mathcal{F}$. We also follow Ghosal et al. (1999), to define a probability measure on the functional space. That is, we operate under the probability space $(\mathcal{F}, \sigma_\mathcal{F}, P_\mathcal{F})$, where $\sigma_\mathcal{F}$ is the $\sigma$-field of $\mathcal{F}$ and $P_\mathcal{F}$ is the probability measure for functions. Suppose $p(t) \in \mathcal{F}$, and let $P_p$ stand for the probability measure corresponding to $p(t)$ on the probability space for the real line, $(\mathcal{R}, \mathcal{B}, P)$, where $\mathcal{B}$ and $P$ are the Borel set and the probability measure on the real line, respectively. To clarify, we use $(\mathcal{F}, \sigma_\mathcal{F}, P_\mathcal{F})$ and $(\mathcal{R}, \mathcal{B}, P)$ to denote the probability spaces for random functions and random variables, respectively. Denote $K = \sum_{j=1}^{n} K_j$. Dropping index $j$ we let $(e_{t_1}, \ldots, e_{t_K})$ be the collection of $K$ observed binary outcomes across $n$ patients, sorted over time. Under (9) each $e_{t_k} \mid p(t_k) \sim \text{Bern}(p(t_k))$. We assign prior distribution $\Pi$ for $p(t)$ and the posterior distribution given $e_{t_1}, \ldots, e_{t_K}$, denoted by $\Pi(\cdot \mid e_{t_1}, \ldots, e_{t_K})$. We will show consistency of the posterior distribution of $p$ under some regularity conditions, if $e_{t_k}$'s are generated conditional on the true function $p_0(t)$, i.e., $e_{t_k} \mid p_0(t_k) \sim \text{Bern}(p_0(t_k))$.

Below we introduce the metric on $\mathcal{F}$, three lemmas, and the main theorem.

**Definition 1.** Let $\mathcal{F}$ be the set of Borel measurable functions defined on $\mathcal{R}$. For any $f_0 \in \mathcal{F}$, denote the Kullback-Leibler neighborhood $KL_\epsilon(f_0) = \{ f : \int f_0 \log(f_0/f) < \epsilon \}$. Let $\Pi$ be a prior on $\mathcal{F}$, we say $f_0$ is in the K-L support of $\Pi$ if $\Pi(KL_\epsilon(f_0)) > 0$ for all $\epsilon > 0$.
Lemma 1. Let \((0, T_E], \mathcal{B}, P)\) be a probability space on the real line, and let \(\mathcal{F}\) be the set of all real-valued Borel measurable functions \(f: [0, T_E] \to [0, 1]\). Let \(P(t) = l(t)/T_E\) be a probability measure, where \(l(t)\) is the Lebesgue measure on \([0, T_E]\). Define

\[
d(f, g) = \inf\{\epsilon : P(\{t : |f(t) - g(t)| > \epsilon\}) < \epsilon\}.\]

Then \(d(\cdot, \cdot)\) induces a metric, and \(f_K\) converges to \(f\) in probability if and only if \(\lim_{K \to \infty} d(f_K, f) = 0\).

Lemma 2. Let \(0 < \epsilon_0 < \frac{1}{2}\) and \(\epsilon_0 < a, b < 1 - \epsilon_0\). Then there exists a constant \(L\) depending on \(\epsilon_0\) such that

\[
a \log \frac{a}{b} + (1 - a) \log \frac{1 - a}{1 - b} \leq L(a - b)^2.\]

Lemma 3. Assume the compact supports of \(\theta_1, r, \theta_2\) are \(B_1, B_2\) and \(B_3\) respectively. Let \(B = B_1 \times B_2 \times B_3\), a compact support of \((\theta_1, r, \theta_2)\). Define two functions \(\rho_1(\theta_1, r, \theta_2) = C_0(0; \theta_1, r, \theta_2)\) and \(\rho_2(\theta_1, r, \theta_2) = -C''_0(0; \theta_1, r, \theta_2)\), where \(C''_0\) is the second derivative of \(C_0\). Let \(a(\cdot)\) be the GP on \(T\) in (9), where \(T\) is a bounded subset of \(\mathcal{R}\). Then \(a(\cdot)\) has differentiable sample paths and the derivative process \(a'(\cdot)\) is also a GP. Further, there exist constants \(A\) and \(d_1, d_2\) such that

\[
\sup_{(\theta_1, r, \theta_2) \in B} \Pr\{\sup_{t \in [0, T_E]} |a(t)| > M_n \mid \theta_1, r, \theta_2\} \leq Ae^{-d_1n}
\]

\[
\sup_{(\theta_1, r, \theta_2) \in B} \Pr\{\sup_{t \in [0, T_E]} |a'(t)| > M_n \mid \theta_1, r, \theta_2\} \leq Ae^{-d_2n},
\]

where \(M_n = O(n^{1/2})\).

Next we present the main results in Theorem 1. Choi and Schervish (2007) proposed a Consistency Theorem (see the Appendix C) as an extension of Schwartz’s theorem.
to independent but non-identically distributed cases. We make use of such an extension to achieve the posterior consistency for our proposed LGP by verifying the two conditions in [Choi and Schervish (2007)].

**Theorem 1.** Suppose that $K/n = O(1)$, i.e., when the number of patients $n$ goes to infinity, the total number of distinct observational time points $K = \sum_{j=1}^{n} K_j$ in $[0, T_E]$ also goes to infinity. Assume that the mean function $\mu(\cdot)$ and $C(\cdot, \cdot)$ in the Gaussian process prior $\theta$ satisfy the following conditions:

1. $C(\cdot, \cdot)$ is nonsingular,
2. $C(t_u, t_v)$ has the form $C_0(|t_u - t_v|)$, where $C_0(t)$ is a positive multiple of a nowhere zero density function on $\mathbb{R}$ and four times continuously differentiable on $\mathbb{R}$,
3. the mean function $\mu(t)$ is continuously differentiable in $[0, T_E]$, and
4. there exist $0 < \delta < \frac{1}{2}$ and $b_1, b_2 > 0$ such that

$$Pr(\theta_1^2 > n^\delta) < b_1 \exp(-b_2 n), \quad Pr(r^2 > n^\delta) < b_1 \exp(-b_2 n),$$

$$Pr(\theta_2^2 < n^{-\delta}) < b_1 \exp(-b_2 n).$$

Let $P^K_0$ denote the joint distribution of $\{e_{tk}\}_{k=1}^{K}$ assuming that $p_0(t) = H(a_0(t))$ is the true probability function, where $a_0(t)$ is the true GP that has a continuously differentiable sample path on $\mathcal{T}$. Then for every $\epsilon > 0$, letting $S^1_\epsilon(p_0) = \{p \in \mathcal{F} : d(p, p_0) > \epsilon\}$, as $n \to \infty$

$$\Pi\{S^1_\epsilon(p_0) \mid e_{t_1}, \ldots, e_{t_K}\} \to 0 \quad [P^K_0]$$

(10)
In addition, for every $\epsilon > 0$, letting $S^2_\epsilon(p_0) = \{ p \in F : \int |p(t) - p_0(t)| dt > \epsilon \}$, as $n \to \infty$

$$\Pi\{S^2_\epsilon \mid e_{t_1}, \ldots, e_{t_K} \} \to 0 \ [P_0^\infty] \quad (11)$$

In general, if more hyperparameters are introduced in the covariance function, we can verify posterior consistency by assuming compact supports of hyperparameters and proper continuity conditions as in Theorem [3]

4 Posterior Inference

4.1 Forecast

An important and useful feature of the LGP model is the ability to forecast, i.e., making predictions on $e_{ij}(t_{K_{ij}+s})$ for future time points $t_{K_{ij}+s}$, $s = 1, 2, \ldots, S_{ij}$. The forecast uses the posterior predictive distribution $p\{e_{ij}(t_{K_{ij}+s}) \mid \mathbf{e}^K\}$, where $\mathbf{e}^K$ are observed data at $K_{ij}$ past time points. In particular, define the posterior predictive probability of response as

$$q_{ijs} \equiv Pr\{e_{ij}(t_{K_{ij}+s}) = 1 \mid \mathbf{e}^K\} = Pr\{a_{ij}(t_{K_{ij}+s}) > a_h \mid \mathbf{e}^K\} = \int I\{a_{ij}(t_{K_{ij}+s}) > a_h\} p\{a_{ij}(t_{K_{ij}+s}) \mid \mathbf{a}^K_{ij}, m_i, \beta_i, \Theta\} \times p\{\mathbf{a}^K_{ij}, m_i, \beta_i, \Theta \mid \mathbf{e}^K\} \ da_{ij}(t_{K_{ij}+s}) \ da^K_{ij} \ dm_i \ d\beta_i \ d\Theta. \quad (12)$$

The key component in $q_{ijs}$ is the conditional distribution $p\{a_{ij}(t_{K_{ij}+s}) \mid \mathbf{a}^K_{ij}, m_i, \beta_i, \Theta\}$, for all future points $t_{K_{ij}+s}$, $s = 1, 2, \ldots, S_{ij}$. Therefore, we consider the vector $\mathbf{a}^{(S-K)}_{ij} = (a_{ij}(t_{K_{ij}+1}), a_{ij}(t_{K_{ij}+2}), \ldots, a_{ij}(t_{K_{ij}+S_{ij}}))^\prime$, the latent Gaussian variables for future time points. By definition of the GP model, the joint distribution of $p\{\mathbf{a}^K_{ij}, \mathbf{a}^{(S-K)}_{ij} \mid m_i, \beta_i, \Theta\}$ is a multivariate Gaussian, and so is the conditional $p\{a_{ij}(t_{K_{ij}+s}) \mid \mathbf{a}^K_{ij}, m_i, \beta_i, \Theta\}$. Denote its con-
ditional CDF by \( \Phi_{S-K|K} (\cdot \mid a_{ij}^K, m_i, \beta_i, \Theta) \). Then the Monte Carlo estimate of \( q_{ij} \) is given by

\[
\hat{q}_{ij} = \sum_{b=1}^{B} \frac{1 - \Phi_{S-K|K} (a_h \mid a_{ij}^{K(b)}, m_i^{(b)}, \beta_i^{(b)}, \Theta^{(b)})}{B},
\]

(13)

where superscript \(^{(b)}\) denotes the MCMC sample of the \( b \)-th iteration and \( B \) is the total number of MCMC samples kept for posterior inference.

Note that the forecast is subject-\( j \)-specific. That is, based on the observed outcomes for patient \( j \), the forecast could be different due to the subject-specific \( \tau_{ij} \) in our original LGP model (1). This is useful in practice allowing individual patients and their physicians to prepare for future disease relapses.

### 4.2 Trial Monitoring Rules

In Section 2.1 we assume that the treatment mean effect for arm \( i \) is \( \mu_i(t) = \beta_{i0} + \beta_{i1} t + \cdots + \beta_{i,m_i} t^{m_i} \) with a random degree \( m_i \). For example, when \( m_i = 1 \) and slope \( \beta_{i1} \) is positive, the mean effect \( \mu_i(t) \) is a simple linear function increasing with time; if \( m_i = 2 \) with \( \beta_{i2} < 0 \), the mean effect \( \mu_i(t) \) first increases and then decreases, potentially due to drug resistance. Estimating \( \beta_i \) for two arms allows for the comparison of the overall drug effects and hence trial monitoring. For example, if the experimental arm is considered to perform no better than the control arm in terms of increasing disease remission time, the trial should be stopped early due to ethical and logistic reasons.

Denote the duration of the disease remission (DDR) as

\[
T_i(\beta_i, m_i) = \{ t : \mu_i(t) > a_h \},
\]

(14)

where \( \{ \} \) is the Lebesgue measure on the real line. That is, \( T_i \) is the length of time intervals
in which \( \mu_i(t) \) is above \( a_h \) for arm \( i \), i.e., patients stay in remission. The arm with longer DDR is more desirable.

The proposed monitoring criterion uses the posterior probability

\[
\eta = \Pr(T_2 > T_1 + \delta \mid e^K) = \int I\{T_2(\beta_2, m_2) > T_1(\beta_1, m_1) + \delta\} \, p(\beta, m \mid e^K) \, d\beta \, dm, \tag{15}
\]

where \( \delta \geq 0 \) is a threshold that defines the desirable increment of the efficacy outcome for the experimental arm over the control. The value of \( \delta \) is fixed by investigators, and should reflect the minimum clinically meaningful improvement. A larger \( \eta \) value indicates a larger chance that treatment 2 is better at keeping patients in remission than treatment 1.

The Monte Carlo estimate of \( \eta \) is given by

\[
\hat{\eta} = \frac{1}{B} \sum_{b=1}^{B} I\{T_2^{(b)}(\beta_2^{(b)}, m_2^{(b)}) > T_1^{(b)}(\beta_1^{(b)}, m_1^{(b)}) + \delta\}, \tag{16}
\]

Let \( \xi_U \) be an upper probability boundary above which the trial will be terminated early and the experimental treatment declared superior if \( \Pr(T_2 > T_1 + \delta \mid e^K) \geq \xi_U \). Similarly, let \( \xi_L \) be a lower boundary below which the trial will be terminated early due to futility if \( \Pr(T_2 > T_1 + \delta \mid e^K) \leq \xi_L \).

Our proposed trial-monitoring rules are given as

\[
\text{Decision} = \begin{cases} 
\text{stop and declare arm 2 superior} & \text{if } \hat{\eta} \geq \xi_U, \\
\text{continue enrolling patients} & \text{if } \xi_L < \hat{\eta} < \xi_U, \\
\text{stop and declare arm 2 not superior} & \text{if } \hat{\eta} \leq \xi_L. 
\end{cases}
\]

Cutoffs \( \xi_U \) and \( \xi_L \) can be calibrated based on simulations. The values \( \xi_U = 0.95 \) and \( \xi_L = 0.05 \) provided desirable performance in the simulation for the lupus trial.
5 Model Assessment via Sensitivity Analysis

When making forecasts on \( e_{ij}(t_{K_{ij}+s}) \) for future time points, three factors can affect the forecasting accuracy: 1) the choice of the mean functions \( \mu_i(t) \) and covariance functions \( \tau_{ij}(t) \), 2) the number of observed time points \( K_{ij} \) at the time of forecast, and 3) the choice of the threshold \( a_h \). To evaluate the impact of these model components, we perform a sensitivity analysis based on simulation. To simplify the simulation setup, we only consider data from one arm and focus on the accuracy of posterior estimation and forecast instead of trial characteristics. Therefore the index \( i \) is dropped in the discussion within this section.

We assumed that the sample size was 100 patients for a single arm. We first generated values \( a^K \) given \( \mu(t) \) and \( \tau_j(t) \) at a total of 35 time points \( t_1, t_2, \ldots, t_{35} \), out of which the first \( K_j \leq 32 \) time points were used to predict the responses of patient \( j \) at the last three time points. After generating \( a^K \), we generated \( e^K \) given the threshold \( a_h \) of our choice. Without loss of generality, we assumed that all the patients had the same \( K_j = K \) for \( j = 1, \ldots, 100 \).

We specified various choices of \( K = 20, 23, 26, 29, 32 \) to study their effects on forecasting in each scenario. To show the robustness to the threshold \( a_h \), we assumed \( a_h = 0 \) when we generated the simulation data and set \( a_h = 0 \) or \( a_h = 0.5 \) when we fitted models to the simulated data.

We considered five scenarios. In scenarios 1-3, we generated data by using different polynomial mean functions \( \mu(t) \) and the covariance function (6) with \( \theta_1 = 1, \theta_2 = 3.5 \) and \( r = 2 \). For ease of exposition, we display (6) again: \( C_{uv}(\Theta) = \theta_1^2 \exp \left\{ -r^2 \sin^2 \left( \frac{\pi(t_u-t_v)}{\theta_2} \right) \right\} + \delta_{uv} J^2 \). In scenario 1, the true mean \( \mu(t) = \beta_0 \), where \( \beta_0 = -0.8 \). In scenario 2, the true \( \mu(t) = \beta_0 + \beta_1 t \), where \( \beta_0 = -0.8, \beta_1 = 0.4 \). In scenario 3, the true \( \mu(t) = \beta_0 + \beta_1 t + \beta_2 t^2 \), where \( \beta_0 = -1, \beta_1 = 3.5, \beta_2 = -1 \). In words, scenarios 1-3 represent constant mean, linear mean, and quadratic mean respectively. We fitted the LGP model (8) to the simulated data and assumed vague priors \( \beta \sim \text{Gaussian}(0, 10^2 I), \theta_1, \theta_2, r \sim \text{Gaussian}(0, 10^2) \).
In scenario 4, we generated data from the trigonometric mean function \( \mu(t) = \alpha + \sin(\beta_0 \pi t) \) with \( \alpha = -0.8, \beta_0 = 1.5 \), and the covariance function \( \tau_j(t) \) with \( \theta_1 = 1 \) and \( r = 3 \). We then fitted the model using the same trigonometric mean function but with unknown parameters, and the covariance function \( \tau_j(t) \) to the simulated data and estimated unknown parameters \( \alpha, \beta_0, \theta_1 \) and \( r \), for which we also assumed vague priors \( \alpha, \beta_0, \theta_1, r \sim \text{Normal}(0, 10^2) \).

In scenarios 1-4, we took periodicity into consideration by placing the trigonometric function in the fitted model. Scenarios 1-3 had a trigonometric function in the covariance function, while scenario 4 assumed a trigonometric mean function. To show the differences between these two configurations, in Figure 2 we plotted simulated \( a \) for 20 randomly selected replications under scenarios 1-4. We can see that the overall mean in the top right panel increases with time and each patient curve has a different periodic behavior in scenario 2. In contrast, in the bottom right panel for scenario 4, the overall mean has an obvious periodic pattern and each individual curve has its own variability around the mean.

As discussed above, putting a trigonometric function in the mean function \( \mu(t) \) or covariance function \( \tau_j(t) \) leads to different group and individual behaviors. Since both models are periodic, we designed scenario 5 to investigate whether one model can predict for the other. For this purpose, we generated data from the true model with mean \( \mu(t) = \sin(\beta_0 \pi t) \), where \( \beta_0 = 1 \) and \( \tau_j(t) \) from a GP with zero mean and covariance function \( C \) in \( \tau_j(t) \) with \( \theta_1 = 1 \) and \( r = 3 \), which does not have a trigonometric component. Then we fitted model \( \tau_j(t) \) with a polynomial mean function and the covariance function having trigonometric components.

For each of the five scenarios described above, we specified five different values for \( K = 20, 23, 26, 29, 32 \), and two threshold values \( a_h = 0 \) or \( 0.5 \). Therefore, we obtained a total of \( 5 \times 2 \times 5 = 50 \) cases. For each case, we implemented the proposed LGP model with 10,000 MCMC iterations with a burn-in of 2,000 iterations, finished in 30 minutes. The convergence of the MCMC algorithm was diagnosed by standard methods in R package \textit{coda}. All the chains converged quickly and mixed well.
Figure 2: Sample curves of latent variable values for 20 randomly selected patients in scenarios 1-4. The red curve in each plot represents the mean function $\mu(t)$ of the GP. The horizontal blue line represents the threshold $a_h$.

Figure 3 shows the proportion of posterior estimates of the degree of polynomial $m$ in scenarios 1-3. Recall that $m$ follows a discrete uniform prior taking values in the set \{0, 1, 2, \ldots, M\}; here we set $M = 5$. We can see that the degree of the polynomial from the true model dominates the posterior estimates. In scenarios 4-5 there are no true $m$ values since the true $\mu(t)$ is not a polynomial function.
Figure 3: The proportion of posterior estimates of $m$ in all cases for scenarios 1-3 in the simulation.

For each case, we computed the average posterior predictive probability of response at a future time point $t_s$ over 100 patients, defined as

$$q_s = \frac{1}{100} \sum_{j=1}^{100} Pr\{e_j(t_s) = 1 \mid e^K\},$$

where $Pr\{e_j(t_s) = 1 \mid e^K\}$ was calculated according to (12) and (13). We used $t_s = 33, 34$ and 35, since the lupus trial protocol plans to make
forecasts at these three future time points. Also, we computed the posterior mean DDR

\[ \hat{T} = \frac{1}{B} \sum_{b=1}^{B} l \{ t : \mu(t; \beta^{(b)}, m^{(b)}) > a_h \} . \]

Table 1 summarizes the results.

After obtaining the posterior imputation of the latent variables \( \mathbf{a}^K \) and posterior predictive values of \( \mathbf{a}^{(35-K)} \) for the new time points, we plotted 20 realizations of the latent variables for one randomly selected patient in case \((K = 32, a_h = 0)\) for scenario 2 and case \((K = 29, a_h = 0)\) for scenario 4 as shown in Figures 4 and 5, respectively. The left panel presents the latent variable values given the first 32 observed time points and the right panel presents those with the first 29 time points observed. It can be seen that our model fits the simulated data well in both panels.

**Figure 4:** A set of 20 realizations of latent variables for two cases in scenario 2. The left panel presents the latent variable values for one patient with the first 32 time points observed. The right panel presents one patient with the first 29 time points observed. The red solid line represents the truth. Black solid lines represent 20 realizations at observed time points, and blue dashed lines represent predicted values at future time points.

In scenario 5, we generated simulated data using the model with a trigonometric mean function and covariance function (5) without trigonometricity, but fitted the model with the
Table 1: True probability, empirical probability and average posterior predictive estimate (PPE) of response probability at future time point $t_{33}$, $t_{34}$ and $t_{35}$. The posterior mean DDR, $\hat{T}$, is also presented.

| Scenario | Truth     | $q_{33}$ | $q_{34}$ | $q_{35}$ | $\hat{T}$ |
|----------|-----------|----------|----------|----------|-----------|
| 1        | 0.2130    | 0.2130   | 0.2130   | 0        |           |
| K = 32, $a_h = 0$ | PPE 0.2212 | 0.2398   | 0.2491   | 0        |           |
| K = 32, $a_h = 0.5$ | PPE 0.2205 | 0.2389   | 0.2488   | 0        |           |
| K = 29, $a_h = 0$ | PPE 0.2683 | 0.2637   | 0.2613   | 0        |           |
| K = 29, $a_h = 0.5$ | PPE 0.2712 | 0.2667   | 0.2640   | 0        |           |
| K = 26, $a_h = 0$ | PPE 0.2734 | 0.2691   | 0.2663   | 0        |           |
| K = 26, $a_h = 0.5$ | PPE 0.2726 | 0.2687   | 0.2665   | 0        |           |
| K = 23, $a_h = 0$ | PPE 0.2683 | 0.2637   | 0.2613   | 0        |           |
| K = 23, $a_h = 0.5$ | PPE 0.2712 | 0.2667   | 0.2640   | 0        |           |
| K = 20, $a_h = 0$ | PPE 0.2399 | 0.2399   | 0.2399   | 0        |           |
| K = 20, $a_h = 0.5$ | PPE 0.2399 | 0.2399   | 0.2399   | 0        |           |

| Scenario | Truth     | $q_{33}$ | $q_{34}$ | $q_{35}$ | $\hat{T}$ |
|----------|-----------|----------|----------|----------|-----------|
| 2        | 0.6976    | 0.7113   | 0.7248   | 15       |           |
| K = 32, $a_h = 0$ | PPE 0.7459 | 0.7568   | 0.7717   | 18.06    |           |
| K = 32, $a_h = 0.5$ | PPE 0.7482 | 0.7604   | 0.7755   | 18.701   |           |
| K = 29, $a_h = 0$ | PPE 0.7778 | 0.7920   | 0.8053   | 19.008   |           |
| K = 29, $a_h = 0.5$ | PPE 0.7800 | 0.7944   | 0.8075   | 19.142   |           |
| K = 26, $a_h = 0$ | PPE 0.7684 | 0.7826   | 0.7960   | 18.762   |           |
| K = 26, $a_h = 0.5$ | PPE 0.7747 | 0.7878   | 0.8010   | 18.896   |           |
| K = 23, $a_h = 0$ | PPE 0.7906 | 0.8034   | 0.8156   | 18.892   |           |
| K = 23, $a_h = 0.5$ | PPE 0.7979 | 0.8106   | 0.8227   | 19.353   |           |
| K = 20, $a_h = 0$ | PPE 0.7732 | 0.7852   | 0.7967   | 17.985   |           |
| K = 20, $a_h = 0.5$ | PPE 0.7718 | 0.7840   | 0.7957   | 18.269   |           |

| Scenario | Truth     | $q_{33}$ | $q_{34}$ | $q_{35}$ | $\hat{T}$ |
|----------|-----------|----------|----------|----------|-----------|
| 3        | 0.3676    | 0.2557   | 0.1599   | 28.723   |           |
| K = 32, $a_h = 0$ | PPE 0.4179 | 0.3140   | 0.2244   | 29.457   |           |
| K = 32, $a_h = 0.5$ | PPE 0.4212 | 0.3201   | 0.2317   | 29.506   |           |
| K = 29, $a_h = 0$ | PPE 0.4763 | 0.3723   | 0.2731   | 29.893   |           |
| K = 29, $a_h = 0.5$ | PPE 0.4594 | 0.3538   | 0.2546   | 29.728   |           |
| K = 26, $a_h = 0$ | PPE 0.6648 | 0.5795   | 0.4873   | 31.261   |           |
| K = 26, $a_h = 0.5$ | PPE 0.6465 | 0.5625   | 0.4742   | 30.962   |           |
| K = 23, $a_h = 0$ | PPE 0.4690 | 0.3814   | 0.2999   | 29.547   |           |
| K = 23, $a_h = 0.5$ | PPE 0.3744 | 0.2866   | 0.2105   | 28.762   |           |
| K = 20, $a_h = 0$ | PPE 0.7575 | 0.7160   | 0.6731   | 30.931   |           |
| K = 20, $a_h = 0.5$ | PPE 0.7483 | 0.7068   | 0.6646   | 30.869   |           |
| Scenario | Truth | \( q_{33} \) | \( q_{34} \) | \( q_{35} \) | \( \hat{T} \) |
|----------|-------|----------------|----------------|----------------|-------|
| 4        |       | 0.2610         | 0.1349         | 0.0669         | 8.194 |
|          | Empirical | 0.3100         | 0.1800         | 0.1200         | 10.980 |
| \( K = 32, a_h = 0 \) | PPE | 0.3118         | 0.1660         | 0.0823         | 9.985 |
| \( K = 32, a_h = 0.5 \) | PPE | 0.3123         | 0.1664         | 0.0825         | 9.988 |
| \( K = 29, a_h = 0 \) | PPE | 0.2458         | 0.1228         | 0.0614         | 9.687 |
| \( K = 29, a_h = 0.5 \) | PPE | 0.2458         | 0.1228         | 0.0614         | 9.687 |
| \( K = 26, a_h = 0 \) | PPE | 0.2640         | 0.1366         | 0.0683         | 9.095 |
| \( K = 26, a_h = 0.5 \) | PPE | 0.2687         | 0.1400         | 0.0699         | 9.093 |
| \( K = 23, a_h = 0 \) | PPE | 0.2528         | 0.1314         | 0.0677         | 9.143 |
| \( K = 23, a_h = 0.5 \) | PPE | 0.2522         | 0.1310         | 0.0675         | 9.143 |
| \( K = 20, a_h = 0 \) | PPE | 0.2641         | 0.1387         | 0.0710         | 9.230 |
| \( K = 20, a_h = 0.5 \) | PPE | 0.2632         | 0.1378         | 0.0705         | 9.231 |
| 5        |       | 0.2104         | 0.1720         | 0.1599         | 20.00 |
|          | Empirical | 0.2300         | 0.2200         | 0.1900         | 19.54 |
| \( K = 32, a_h = 0 \) | PPE | 0.1544         | 0.0679         | 0.0181         | 23.62 |
| \( K = 32, a_h = 0.5 \) | PPE | 0.1447         | 0.0711         | 0.0287         | 23.06 |
| \( K = 29, a_h = 0 \) | PPE | 0.0068         | 0.0002         | 0.0000         | 19.52 |
| \( K = 29, a_h = 0.5 \) | PPE | 0.0103         | 0.0003         | 0.0000         | 19.66 |
| \( K = 26, a_h = 0 \) | PPE | 0.0035         | 0.0028         | 0.0024         | 16.66 |
| \( K = 26, a_h = 0.5 \) | PPE | 0.0017         | 0.0012         | 0.0011         | 16.87 |
| \( K = 23, a_h = 0 \) | PPE | 1.0000         | 1.0000         | 1.0000         | 25.79 |
| \( K = 23, a_h = 0.5 \) | PPE | 0.9960         | 0.9950         | 0.9950         | 25.73 |
Figure 5: A set of 20 realizations of latent variables for two cases in scenario 4. The left panel presents the latent variable values for one patient with the first 32 time points observed. The right panel presents one patient with the first 29 time points observed. The red solid line represents the truth. Black solid lines represent 20 realizations at observed time points, and blue dashed lines represent predicted values at future time points.

polynomial mean function and the trigonometric covariance function (6) to the simulated data. As seen in Table 1, the predictions are poor. This implies that the model choice is important in terms of the placement of the trigonometric functions, in the mean or covariance of the GP.

Next we checked the robustness of the choice of $a_h$. As shown in Table 1, the estimations remained consistently well when we varied the values of $a_h$ ($a_h = 0$ and $a_h = 0.5$). Thus, the model is robust to choice of $a_h$.

Finally we examined the impact of different $K$’s on the forecast. From Table 1 and Figure 3 we can see that the fewer the observed time points, i.e. the smaller the value of $K$, the worse the prediction. For example, in scenario 3, when $K = 32$ and $a_h = 0$, the degree of polynomial of the true model is successfully recovered 99% of times; but when $K = 20$ and $a_h = 0$, this percentage drops to 85%. Also, the true $q_{33} = 0.3676$, while the posterior estimate of $q_{33}$ is 0.4179 when ($K = 32$, $a_h = 0$) and 0.7575 when ($K = 20$, $a_h = 0$). This
also echoes the consistency results in Section 3 to be shown next; that is, the larger the number of time points observed, the better the estimation.

Next in the lupus trial example, one concern is how to choose the proper time point to start the forecast, which also depends on the drug effects. Based on previous clinical experiments and prior knowledge, we can make assumptions about the mean of the drug effects and the start time point can be determined by simulation and calibration. Examining the simulation results observed so far, we decided to use $K = 23$ as the starting time for forecast.

\section{Trial Example}

Using the lupus trial as an example, we simulated a large number of clinical trials on computer and applied the proposed monitoring rules to examine the operating characteristics of our method. According to the original trial setup, we set the duration of the simulated trials at 35 weeks and the maximum number of patients to be 200, equally randomized between the standard arm and experimental arm. We assumed that patients were recruited over time and the number of patients enrolled weekly for each arm was a random number following a discrete uniform in $\{2, 3, 4\}$. Patients were observed and followed each week, when their responses $e$’s were recorded. The experimental treatment (arm 2) is considered more effective than the control (arm 1) if the DDR in (14) for the treatment arm $T_2$ is at least 2 weeks longer than that of the control arm $T_1$, i.e., the minimum difference between the two arms must be $\delta = 2$.

We considered six scenarios and simulated 100 trials for each scenario. The binary response outcomes were generated over time using the following scheme. We first specified true mean functions (see Table 2 for different $\mu_i(t)$) and the true covariance function (6) with $\theta_1 = 1$, $\theta_2 = 3.5$ and $r = 2$. We then generated the LGP $a(t_k)$ and $e(t_k)$ at 35 weeks of
Table 2: True Values of $m_i$, $\beta_i$ and $T_i$, $i = 1, 2$ for all six scenarios in the simulation.

| Group     | $m_i$  | $\beta_i$       | $T_i$ |
|-----------|--------|-----------------|-------|
| Scenario 1| Standard 2 | (-2, 3.5, -1) | 20.6  |
|           | Experimental 3 | (-1.4, 7.5, -5.3, 1) | 27.6  |
| Scenario 2| Standard 3 | (-1.5, 7.5, -5.3, 1) | 25.9  |
|           | Experimental 2 | (-1, 3.5, -1) | 28.7  |
| Scenario 3| Standard 3 | (-2.4, 7.5, -5.3, 1) | 15.4  |
|           | Experimental 2 | (-2.4, 3.5, -1) | 16.3  |
| Scenario 4| Standard 3 | (-2, 7.5, -5.3, 1) | 19.7  |
|           | Experimental 2 | (-1, 3.5, -1) | 28.7  |
| Scenario 5| Standard 3 | (-1.28, 3.5, -1) | 26.7  |
|           | Experimental 3 | (-1.2, 3.6, -1) | 28.6  |
| Scenario 6| Standard 2 | (-0.39, 0.3) | 22.0  |
|           | Experimental 2 | (-1.1, 1) | 24.0  |

follow up, $k = 1, 2, \ldots, 35$.

For all six scenarios, the true DDR $T_i$ according to the true $\mu_i(t)$ were calculated, and the configurations including $m_i$, $\beta_i$ and $T_i$, $i = 1, 2$ are displayed in Table 2. Figure 6 shows the true mean functions of the standard and experimental arms in all six scenarios, in which we also mark the true $T_i$ values. The arm with a larger $T_i$ value is more effective since it leads to a longer DDR. For example, in scenario 1, $T_1 = 20.616$ and $T_2 = 27.616$, so arm 2, the experimental treatment, is better.

We fitted the proposed model (8) to the simulated data and assumed vague priors $\beta \sim \text{Normal}(0, 10^2I)$, $\theta_1, \theta_2, r \sim \text{Normal}(0, 10^2)$. The trial monitoring started at week $K = 23$ and was based on the proposed monitoring rules with $\delta = 2$. Table 3 summarizes the operating characteristics of the LGP method for all six scenarios, including the average duration of trials, the maximum duration of trials, the average number of patients studied and stopping probabilities.

In scenario 1, $m_1 = 2$ and $m_2 = 3$, and from Figure 6, patients in the experimental arm relapse more often than patients in the control arm. However, the experimental arm is still preferred since it has longer DDR as $T_2 = 27.616 > (20.616 + 2) = (T_1 + \delta)$. Thus, scenario
Figure 6: The true DDR $T_i$ and the true mean functions $\mu_i(t)$ in the control and experimental arms in all six scenarios for the lupus trial simulation. The red line represents the true mean in the control arm, while the blue line represents the true mean in the experimental arm. The black horizontal line represents the threshold $a_h = 0$.

I explored the ability of the proposed LGP method to stop if the experimental arm has a longer DDR but more frequent relapses. The average trial duration was 24.9 weeks and the maximum trial duration was 29 weeks, which indicated that the trial stopped quickly after it was monitored at week 23. The average number of patients was 76.1 per group and the maximum was 100 patients. Among 100 simulated trials, 97 were stopped early due to superiority.

In scenario 2, $m_1 = 3$, $m_2 = 2$ and $T_1 = 25.939$, $T_2 = 28.723$. Here $T_2 - T_1 \approx 2.8$ which is close to $\delta = 2$. Among the 100 trials simulated, 52 stopped early due to superiority. In this
Table 3: Results for the simulations based on the lupus trial. AD: average trial duration (weeks); MD: maximum duration (weeks); AP: average number of patients in each group.

| Scenario | Group       | T_i  | AD   | MD   | AP   | Stopping probabilities          |
|----------|-------------|------|------|------|------|---------------------------------|
| 1        | Standard    | 20.6 | 24.9 | 29   | 76.1 | 97%(superiority)               |
|          | Experimental| 27.6 |      |      |      |                                 |
| 2        | Standard    | 25.9 | 29.72| 35   | 87.43| 52%(superiority)               |
|          | Experimental| 28.7 |      |      |      |                                 |
| 3        | Standard    | 15.4 | 29.06| 35   | 87.68| 60%(futility)                  |
|          | Experimental| 16.3 |      |      |      |                                 |
| 4        | Standard    | 19.7 | 23.31| 26   | 70.65| 100%(superiority)              |
|          | Experimental| 28.7 |      |      |      |                                 |
| 5        | Standard    | 26.7 | 29.11| 35   | 86.91| 25%(superiority) and 30%(futility) |
|          | Experimental| 28.6 |      |      |      |                                 |
| 6        | Standard    | 22.0 | 30.90| 35   | 91.59| 16%(superiority) and 19%(futility) |
|          | Experimental| 24.0 |      |      |      |                                 |

In scenario 1, the average trial duration was 29.72 weeks and the maximum trial duration was 35 weeks. The average number of patients was 87.43 per group.

In scenario 3, \( m_1 = 3, m_2 = 2 \) and \( T_1 = 15.414, T_2 = 16.279 \). Among the 100 simulated trials, 60 stopped early due to futility as expected. In this scenario, the average trial duration was 29.06 weeks. The average number of patients was 87.68 per group. In scenario 4, \( m_1 = 3, m_2 = 2 \) and \( T_1 = 19.736, T_2 = 28.723 \), implying that arm 2 was much better than arm 1. All 100 trials stopped early due to superiority of arm 2. The average trial duration was 23.31 weeks and the maximum trial duration was 26 weeks. The average number of patients was 70.65 per group.

In the last two scenarios, different arms had the same \( m_i \) value. In scenario 5, \( m_1 = m_2 = 2 \). The average trial duration was 29.11 weeks, and the average number of patients was 86.91 per group. Among the 100 trials simulated, 25 stopped due to superiority, 30 stopped due to futility, and 45 did not stop early. In scenario 6, \( m_1 = m_2 = 1 \) and \( T_1 = 22, T_2 = 24 \). The DDR in arm 2 was exactly 2 weeks longer than in arm 1, making it difficult to stop early. Among 100 simulated trials, 65 didn’t stop early, 16 stopped early due to superiority, and 19
stopped early due to futility. The average trial duration was 30.9 weeks and the maximum trial duration was 35 weeks. The average number of patients was 91.59 per group.

In summary, the proposed LGP model and trial monitoring rules exhibited desirable operating characteristics in all six scenarios.

7 Discussion

We have proposed a Bayesian LGP model for monitoring clinical trials with binary repeated outcomes. Through the posterior estimates, we can predict the probability of efficacy response for each patient at future time points. The proposed trial monitoring rules allow for early termination of a trial if one arm is considered more effective than the other. The Bayesian paradigm works very well and yields desirable results in our simulation studies.

Although our current models are set up for binary outcomes, they can be easily extended to other applications with ordinal or categorical outcomes. Furthermore, the LGP provides a framework for the inclusion of patient- or group-specific covariates such as patients’ weights, ages, etc., which can be easily implemented by expanding the columns of the design matrix $X_{ij}$ in (4). This will be a future direction of our research.

Acknowledgements

Yuan Ji’s research is partly supported by NIH grant R01 CA132897.
APPENDIX A: MCMC Details

Joint Distributions

\[
P(e^K, a^K, m, \beta, \Theta) = P(e^K \mid a^K)P(a^K \mid \beta, m, \Theta)P(\beta \mid m)P(m)P(\Theta)
\]
\[
= \prod_{i=1}^{2} \left[ \prod_{j=1}^{N_i} \prod_{k=1}^{K_{ij}} \left\{ P(e_{ijk} \mid a_{ijk}) = I(a_{ijk} > a_h)I(e_{ijk} = 1)
\right. \\
+ I(a_{ijk} = a_h)I(e_{ijk} = 0) \right\} \right] \\
\times (2\pi)^{-\frac{K_{ij}}{2}} |C(t_{ij})|^{-\frac{1}{2}} \\
\times \exp \left\{ -\frac{1}{2}(a^K_{ij} - X_{ij}\beta_i)'C(t_{ij})^{-1}(a^K_{ij} - X_{ij}\beta_i) \right\} \\
\times (2\pi)^{-\frac{m_i+1}{2}} |\sigma_0^2 I_{m_i+1}|^{-\frac{1}{2}} \\
\times \exp \left\{ -\frac{1}{2}(\beta_i - \mu_{0, m_i})'(\sigma_0^2 I_{m_i+1})^{-1}(\beta_i - \mu_{0, m_i}) \right\} \\
\times P(m)P(\Theta)
\]

where \( a^K_{ij} = (a_{ij1}, \ldots, a_{ijK_{ij}})' \), \( \beta_i = (\beta_{i0}, \beta_{i1}, \ldots, \beta_{i,m_i})' \), \( I_{m_i+1} \) is an \((m_i + 1) \times (m_i + 1)\) dimension identity matrix, and

\[
X_{ij} = \begin{pmatrix}
1 & t_1 & \cdots & t_{m_i} \\
1 & t_2 & \cdots & t_{m_i} \\
\vdots & \vdots & \ddots & \vdots \\
1 & t_{K_{ij}} & \cdots & t_{K_{ij}}
\end{pmatrix}.
\]
Full Conditional

Algorithm for simulating $a_{ij}^K$

\[
P(a_{ij}^K \mid e^K, \beta, m, \Theta) \propto \left\{ \prod_{k=1}^{K_{ij}} P(e_{ijk} \mid a_{ijk}) = I(a_{ijk} > a_h)I(e_{ijk} = 1) + I(a_{ijk} \leq a_h)I(e_{ijk} = 0) \right\} \\
\times (2\pi)^{-\frac{K_{ij}}{2}} |C(t_{ij})|^{-\frac{1}{2}} \\
\times \exp \left\{ -\frac{1}{2} (a_{ij}^K - X_{ij} \beta_i)'C(t_{ij})^{-1}(a_{ij}^K - X_{ij} \beta_i) \right\}
\]

To sample this truncated multivariate normal distribution, we use the method of Geweke (1991) to compose a cycle of Gibbs steps through the components of $a_{ij}$.

To draw the samples from multivariate normal distribution subject to linear inequality restrictions:

\[x \sim N(\mu, \Sigma), \quad a < Dx < b,\]

where $x$ is $n-$dimensional vector, $a$ and $b$ are $m-$dimensional vectors, and $D$ is $m \times n$ matrix imposing linear inequality restrictions.

This is equivalent to:

\[z \sim N(0, T), \quad \alpha < z < \beta. \quad (17)\]

where

\[T = D\Sigma D', \quad \alpha = a - D\mu, \quad \beta = b - D\mu, \]

and we then take $x = \mu + D^{-1}z$.

Suppose that in the non-truncated distribution $N(0, T)$,
\[ E[z_i \mid z_1, \ldots, z_{i-1}, z_{i+1}, \ldots, z_n] = \sum_{j \neq i} c_{ij} z_j. \]

Then in the truncated normal distribution of (17), the distribution of \( z_i \) conditional on \( \{z_1, \ldots, z_{i-1}, z_{i+1}, \ldots, z_n\} \) has the construction

\[ z_i = \sum_{j \neq i} c_{ij} z_j + h_i \epsilon_i, \, \epsilon_i \sim TN[(\alpha_i - \sum_{j \neq i} c_{ij} z_j)/h_i, (\beta_i - \sum_{j \neq i} c_{ij} z_j)/h_i]. \]

Denote the vectors of coefficients \( c^i = (c_{i1}, \ldots, c_{i,i-1}, c_{i,i+1}, \ldots, c_{in})', i = 1, \ldots, n \). From the conventional theory of the conditional multivariate normal distribution, \( c^i = -(Tii)^{-1} T_{i,<i} \) and \( h_i^2 = (Tii)^{-1} \), where \( Tii \) is the element in row \( i \) and column \( i \) of \( T^{-1} \), and \( T_{i,<i} \) is row \( i \) of \( T^{-1} \) with \( T_{ii} \) deleted.

Therefore, to sample \( a_{ij} \) from the posterior conditional probabilities, we compose a cycle of \( K_{ij} \) Gibbs steps through the components of \( a_{ij} \). In the \( k \)th step of this cycle, \( a_{ijk} \) is simulated from \( a_{ijk} \mid e^K, a_{ijq}(q \neq k), \beta, m, \Theta \), which is a univariate normal distribution truncated to one region.

Sample the degree of polynomial \( m_i \)

\[
P(m_i \mid a^K, \Theta) \propto P(a^K \mid m, \Theta)P(m_i) = P(m_i) \int P(a^K \mid \beta, m, \Theta)P(\beta \mid m) \, d\beta
\]

\[
\propto P(m_i) \frac{|A_{m_i}|^{\frac{1}{2}}}{|\sigma_0^2 I_{m_i+1}|^{\frac{1}{2}}}
\times \exp \left\{ \frac{1}{2} b'_m A_{m_i}' b_m - \frac{1}{2} \mu_{m_i+1}' (\sigma_0^2 I_{m_i+1})^{-1} \mu_{m_i+1} \right\},
\]

36
where

\[ A_{m_i} = \left\{ \sum_{j=1}^{N_j} X'_{ij} C(t_{ij})^{-1} X_{ij} + (\sigma_0^2 I_{m_i+1})^{-1} \right\}^{-1}, \]

\[ b_{m_i} = \left\{ \sum_{j=1}^{N_j} X'_{ij} C(t_{ij})^{-1} X_{ij} + (\sigma_0^2 I_{m_i+1})^{-1} \mu_{m_i+1}^0 \right\}. \]

We only consider \((M + 1)\) possible models, so we compute \(r_h = P(h \mid a^K, \Theta), h = 0, 1, \ldots, M\). Let \(w_j = r_j / \sum_{h=0}^M r_h\), then we sample \(m_i \sim \text{Multinomial}(w_0, \ldots, w_M)\).

**Posterior conditional distribution of \(\beta_i\)**

The posterior conditional distribution of \(\beta_i\) is a multivariate normal distribution.

\[
P(\beta_i \mid a^K, m_i, \Theta) \sim MVN(\mu_i^\beta, \left\{ \sum_{j=1}^{N_j} X'_{ij} C(t_{ij})^{-1} X_{ij} + (\sigma_0^2 I_{m_i+1})^{-1} \right\}^{-1}),
\]

where

\[
\mu_i^\beta = \left\{ \sum_{j=1}^{N_j} X'_{ij} C(t_{ij})^{-1} X_{ij} + (\sigma_0^2 I_{m_i+1})^{-1} \right\}^{-1} \times \left\{ \sum_{j=1}^{N_j} X'_{ij} C(t_{ij})^{-1} a^K_{ij} + (\sigma_0^2 I_{m_i+1})^{-1} \mu_{m_i+1}^0 \right\}.
\]

**Hybrid Monte Carlo algorithm to sample \(\Theta\)**

We apply Hybrid Monte Carlo method to sample \(\Theta\). Suppose we want to sample from the canonical distribution for a set of variables, \(\Theta = \{\theta_1, \theta_2, \ldots, \theta_n\}\), with respect to the potential energy function \(E(\Theta)\). Assuming that \(E(\Theta)\) is differentiable with respect to \(\theta_i\),
this canonical distribution is

\[ P(\Theta) = \frac{1}{Z_E} \exp\{-E(\Theta)\}. \]

We then introduce another set of variables, \( \mathbf{w} = \{w_1, w_2, \ldots, w_n\} \), one \( w_i \) for each \( \theta_i \), with a kinetic energy function, \( P(\mathbf{w}) = \frac{1}{Z_K} \exp\{-K(\mathbf{w})\} = (2\pi)^{-n/2} \exp\left(-\frac{1}{2} \sum_i w_i^2\right) \). The total energy function, known as Hamiltonian, is \( H(\Theta, \mathbf{w}) = E(\Theta) + K(\mathbf{w}) = E(\Theta) + \frac{1}{2} \sum_i w_i^2 \). The canonical distribution defined by this energy function is \( P(\Theta, \mathbf{w}) = \frac{1}{Z_H} \exp\{-H(\Theta, \mathbf{w})\} = P(\Theta)P(\mathbf{w}) \).

The unknown parameters \( (\theta_1, \theta_2, \ldots, \theta_n) \) can be sampled from the marginal distribution for \( \Theta \) by ignoring the values we obtained for \( \mathbf{w} \). In practice, the differentiation equations that describe the Hamiltonian equilibrium through time need to be discretized. In our case, to obtain the posterior samples of our unknown parameters, we use leapfrog discretization. In order to perform a leapfrog discretization, the derivative of the log of the posterior probability with respect to hyper-parameters is needed.

A single leapfrog iteration calculates approximations \( \hat{\theta} \) and \( \hat{\mathbf{w}} \) at time \( \tau + \epsilon \) from \( \hat{\theta} \) and \( \hat{\mathbf{w}} \) at time \( \tau \) as follows:

\[
\hat{w}_i(\tau + \frac{\epsilon}{2}) = \hat{w}_i(\tau) - \frac{\epsilon}{2} \frac{\partial E}{\partial \theta_i}\{\hat{\theta}_i(\tau)\}
\]

\[
\hat{\theta}_i(\tau + \epsilon) = \hat{\theta}_i(\tau) + \epsilon \hat{w}_i(\tau + \frac{\epsilon}{2})
\]

\[
\hat{w}_i(\tau + \epsilon) = \hat{w}_i(\tau + \frac{\epsilon}{2}) - \frac{\epsilon}{2} \frac{\partial E}{\partial \theta_i}\{\hat{\theta}_i(\tau + \epsilon)\}.
\]
The hybrid Monte Carlo algorithm

Given values for the magnitude of the leapfrog stepsize, $\epsilon_0$, and the number of leapfrog steps, $L$, the dynamical transitions of the hybrid Monte Carlo algorithm operate as follows:

- Randomly choose a direction, $\lambda$, for the trajectory with the two values $\lambda = +1$ representing a forward trajectory, and $\lambda = -1$ representing a backward trajectory, both being equally likely.

- Starting from the current state, $(\theta, w) = (\hat{\theta}(0), \hat{w}(0))$, perform $L$ leapfrog steps with a stepsize of $\epsilon = \lambda \epsilon_0$, resulting in the state $(\hat{\theta}(\epsilon L), \hat{w}(\epsilon L)) = (\theta^*, w^*)$.

- Regard $(\theta^*, w^*)$ as a candidate for the next state, as in the Metropolis algorithm: accepting it with probability $A\{(\theta, w), (\theta^*, w^*)\} = \min\left\{1, \exp\{-H(\theta^*, w^*) - H(\theta, w)\}\right\}$, otherwise letting the new state be the same as the old one.

For our problem,

$$E(\Theta) = \frac{1}{2} \sum_{i=1}^{N_i} \sum_{j=1}^{2} \left\{ (a_{ij}^K - X_{ij} \beta_i)'C(t_{ij})^{-1}(a_{ij}^K - X_{ij} \beta_i) + \log(|C(t_{ij})|) \right\}$$

$$- \log P(\Theta),$$

$$\frac{\partial E(\Theta)}{\partial \Theta} = -\frac{1}{2} \sum_{i=1}^{N_i} \sum_{j=1}^{2} (a_{ij}^K - X_{ij} \beta_i)'C(t_{ij})^{-1}\frac{\partial C(t_{ij})}{\partial \Theta}C(t_{ij})^{-1}(a_{ij}^K - X_{ij} \beta_i)$$

$$+ \frac{1}{2} \sum_{i=1}^{N_i} \sum_{j=1}^{2} \text{tr}\left\{ C(t_{ij})^{-1}\frac{\partial C(t_{ij})}{\partial \Theta} \right\} - \frac{\partial \log P(\Theta)}{\partial \Theta}. $$
Since $C_{uv} = C(t_u,t_v) = \theta_1^2 \exp \left\{-r^2 \sin^2 \left(\frac{\pi(t_u-t_v)}{\theta_2}\right)\right\} + \delta_{uv} J^2$, and we have the formula

$$\frac{\partial C^{-1}}{\partial \theta} = -C^{-1} \frac{\partial C}{\partial \theta} C^{-1},$$

therefore,

$$C_{\theta_1}'(t_i,t_j) = \frac{\partial C}{\partial \theta_1} = 2 \theta_1 \exp \left\{-r^2 \sin^2 \left(\frac{\pi(t_u-t_v)}{\theta_2}\right)\right\};$$

$$C_r'(t_i,t_j) = \frac{\partial C}{\partial r} = \theta_2^2 \exp \left\{-r^2 \sin^2 \left(\frac{\pi(t_u-t_v)}{\theta_2}\right)\right\} (-2r) \sin \left(\frac{\pi(t_u-t_v)}{\theta_2}\right),$$

$$C_r'(t_i,t_j) = \frac{\partial C}{\partial \theta_2} = 2r^2 \theta_1^2 \exp \left\{-r^2 \sin^2 \left(\frac{\pi(t_u-t_v)}{\theta_2}\right)\right\} \sin \left(\frac{\pi(t_u-t_v)}{\theta_2}\right) \cos \left(\frac{\pi(t_u-t_v)}{\theta_2}\right) \left(\frac{\pi(t_u-t_v)}{\theta_2^2}\right).$$
Appendix B: Proofs of Lemmas and Main Theorem

B.1: Proof of Lemma 1

Proof. Clearly \( d(f, g) \geq 0 \) and \( d(f, g) = d(g, f) \). Also, we can easily show \( d(f, g) = 0 \) if and only if \( f = g \) a.s.. To prove \( d(\cdot, \cdot) \) induces a metric, the last condition we need to verify is triangle inequality \( d(f, h) \leq d(f, g) + d(g, h) \) for each \( f, g, h \in \mathcal{F} \).

Define \( Q_{fg} = \{ \epsilon : P(\{ t : |f(t) - g(t)| > \epsilon \}) < \epsilon \} \), then \( d(f, g) = \inf Q_{fg} \). So we need to show

\[
\inf Q_{fh} \leq \inf Q_{fg} + \inf Q_{gh}. \tag{18}
\]

Assuming \( \epsilon_1 \in Q_{fg} \) and \( \epsilon_2 \in Q_{gh} \), then

\[
P(\{ t : |f(t) - h(t)| > \epsilon_1 + \epsilon_2 \}) \leq P(\{ t : |f(t) - g(t)| > \epsilon_1 \}) + P(\{ t : |g(t) - h(t)| > \epsilon_2 \}) \leq \epsilon_1 + \epsilon_2
\]

So if \( \epsilon_1 \in Q_{fg} \) and \( \epsilon_2 \in Q_{gh} \), then \( \epsilon_1 + \epsilon_2 \in Q_{fh} \), which implies \( \tag{18} \).

Lastly we show \( f_n \) converges to \( f \) in probability if and only if \( \lim_{n \to \infty} d(f_n, f) = 0 \). First, assume that \( \lim_{n \to \infty} d(f_n, f) = 0 \). Then for every \( \epsilon > 0 \) there exists \( N \) such that for all \( n \geq N \), \( d(f_n, f) \leq \epsilon \), which is equivalent to \( P(\{ t : |f_n - f| > \epsilon \}) < \epsilon \). Hence, \( f_n \) converges to \( f \) in probability. Finally, assume that \( f_n \) converges to \( f \) in probability. Then for every \( \epsilon > 0 \), \( \lim_{n \to \infty} P(\{ t : |f_n - f| > \epsilon \}) = 0 \). So, for every \( \epsilon > 0 \), there exists \( N \) such that for all \( n \geq N \), \( d(f_n, f) \leq \epsilon \), which completes the proof. \( \square \)

B.2: Proof of Lemma 2

Proof. It follows easily from applying Taylor’s expansion to \( \log(\frac{a}{b}) \) and \( \log(\frac{1-a}{1-b}) \). \( \square \)
B.3: Proof of Lemma 3

Proof. Our mean function \( \mu(t) = \beta_0 + \beta_1 t \) is continuously differentiable in \([0, T_E]\). For sufficiently large \( M \),

\[
Pr(\sup_t |a(t)| > M) \leq Pr(\sup_t |a(t) - \mu(t)| > M - \sup_t |\mu(t)|) \leq Pr(\sup_t |a(t) - \mu(t)| > M/2)
\]

Thus, without generality, we assume that the mean function is identically zero.

From the result of Theorem 5 in Ghosal and Roy (2006), there exist constants \( A_w, c_w, d_w(\theta_1, r, \theta_2) \) such that

\[
Pr\left\{ \sup_{t \in [0, T_E]} |D^w a(t)| > M_n \mid \theta_1, r, \theta_2 \right\} \leq A_w e^{-c_w d^w n},
\]

where \( w = 0, 1 \) and \( c_w > 0 \). Through calculations (details not shown), \( d^0 = 1/C_0(0; \theta_1, r, \theta_2) = \frac{1}{\theta_1} \), \( d^1 = -1/C_1^w(0; \theta_1, r, \theta_2) = -\frac{1}{2\pi \theta_1 r^2 \theta_2^2} \). Furthermore, since we assume \( \rho_1(\theta_1, r, \theta_2) \) and \( \rho_2(\theta_1, r, \theta_2) \) are continuous on the compact set \( B \), they are uniformly bounded. Thus, there exist universal constant \( S_1, S_2, S_3 \) and \( S_4 \) such that

\[
0 < S_1 \leq \sup_{(\theta_1, r, \theta_2) \in B} |\rho_1| \leq S_2 \n
0 < S_3 \leq \sup_{(\theta_1, r, \theta_2) \in B} |\rho_2| \leq S_4
\]

Consequently,

\[
\sup_{(\theta_1, r, \theta_2) \in B} Pr\left\{ \sup_{t \in [0, T_E]} |a(t)| > M_n \mid \theta_1, r, \theta_2 \right\} \leq Ae^{-d_1 n}
\]

\[
\sup_{(\theta_1, r, \theta_2) \in B} Pr\left\{ \sup_{t \in [0, T_E]} |a(t)'| > M_n \mid \theta_1, r, \theta_2 \right\} \leq Ae^{-d_2 n}
\]

where \( d_1 = c_0/S_2, d_1 = c_1/S_4 \) and \( A = \max(A_0, A_1) \).
**B.4: Proof of Theorem 1**

*Proof.* In trials as the lupus trial, disease relapses frequently. Whenever that happens, an binary outcome is observed and time recorded. Assuming the relapse time is random, it is reasonable to assume that $K \to \infty$ when $n \to \infty$. On the other hand, the theorem will not be valid if the observational time points are regularly spaced and all patients are observed at the same time. For example, the theorem will not hold if $K_1 = \cdots = K_n = K_0$ and we observe each $e_{jk}$ only at the points $T_E/k$, where $k = 1, \ldots, K_0$.

The first condition of the Consistency Theorem in [Choi and Schervish (2007)] we need to verify is prior positivity of neighborhoods. If the prior satisfies this condition, the probability of every Kullback-Leibler (KL) neighborhood of true density function is positive. The density of $e_{tk}$ with respect to the counting measure on $\{0, 1\}$, say $Q$, is given by $f(e_{tk}) = p(t_k)^{e_{tk}}(1 - p(t_k))^{1-e_{tk}}$. For simplicity, the index $t_k$ is dropped here. So we have $f(e) = p^e(1 - p)^{1-e}$. The corresponding true density function is $f_0(e) = p_0^e(1 - p_0)^{1-e}$ and $\int f_0 \log(f_0/f) \, dQ = p_0 \log(p_0/p) + (1 - p_0) \log((1 - p_0)/(1 - p))$.

To show that the probability of every KL neighborhood of true density function is positive, we first show that $\Pi\{f : \int f_0 \log(f_0/f) \, dQ < \epsilon\} > 0$ for all $\epsilon > 0$, where $\Pi$ is the prior for $f$, or equivalently, $\Pi\{p : p_0 \log(p_0/p) + (1 - p_0) \log((1 - p_0)/(1 - p)) < \epsilon\} > 0$ for all $\epsilon > 0$. Let $\Upsilon = \{p : ||p - p_0||_{\infty} < \frac{1}{2} \epsilon_1\}$, where $\epsilon_1 = \inf\{\min(p_0, 1 - p_0) : 0 \leq t \leq T_E\} > 0$ and $||p - p_0||_{\infty} = \sup_{0 \leq t \leq T_E}(|p(t) - p_0(t)|)$. If $p \in \Upsilon$, following Lemma 2, there exists a constant $L$ depending only on $\epsilon_1$ such that $p_0 \log(p_0/p) + (1 - p_0) \log((1 - p_0)/(1 - p)) \leq L||p - p_0||_{\infty}^2$. Therefore, it suffices to show that $\Pi(p : ||p - p_0||_{\infty} < \epsilon) > 0$ for every $\epsilon > 0$. Since our link function $H$ is assumed to be bounded and Lipschitz continuous, it suffices to show that $\Pi(a : ||a - a_0||_{\infty} < \epsilon) > 0$ for every $\epsilon > 0$.

The prior distribution of $a$ is $a \sim GP(\mu, C)$, where $||\mu||_{\infty} < A_2$ and $||\mu'||_{\infty} < A_3$ for some constants $A_2$ and $A_3$ under our assumptions. Without loss of generality we assume $\mu \equiv 0$. [Choi and Schervish (2004)] examined the general result on the uniform support for
a Gaussian process prior with zero mean. It is easily extended to support \([0, T_E]\) and our mean assumption. Therefore the positivity of neighborhoods holds.

The second condition is the existence of tests. We construct a similar sieve as in [Choi and Schervish (2004)] and then construct a test for each element of the sieve.

\[
SI_K = \{ p(\cdot): p(t) = H(a(t)), ||D^{\omega}a||_\infty < M_K \}.
\]

Let \( p_1 \) be a continuous function on \([0, T_E]\). Let \( h_k = 1 \) if \( p_1(t_k) \geq p_0(t_k) \) and \(-1\) otherwise. Let \( r > 0, m_K = K^{1/2} \) and \( I_K \) be the indicators of set \( U_1 = \{ \sum_{k=1}^{K} h_k(e_0(t_k) - p_0(t_k)) > 2m_K\sqrt{K} \} \), where \( e_0(t_k) \sim \text{Bernoulli}(p_0(t_k)) \). For all \( p_1 \) that satisfy

\[
\sum_{k=1}^{K} |p_1(t_k) - p_0(t_k)| > rK, \tag{19}
\]

by Bernstein’s inequality, we have

\[
\text{E}_{P_0}(I_K) = P_0 \left\{ \sum_{k=1}^{K} h_k(e_0(t_k) - p_0(t_k)) > 2m_K\sqrt{K} \right\} \\
= 2 \exp\left(-\frac{1}{2} \frac{4m_K^2K}{K + 2m_K\sqrt{K}} \right) \leq 2 \exp(-2m_K^2). \tag{20}
\]

Also, let us assume \( e(t_k) \sim \text{Bernoulli}(p(t_k)) \). For all sufficiently large \( K \) such that
\[ m_K/\sqrt{K} < 4/r \text{ and all } p \text{ satisfying } ||p - p_1||_{\infty} < r/4, \] we have

\[
E_P(1 - I_K) = \Pr \left\{ \sum_{k=1}^{K} h_k(e(t_k) - p_0(t_k)) \leq 2m_K\sqrt{K} \right\}
\[
= \Pr \left\{ \frac{1}{\sqrt{K}} \sum_{k=1}^{K} h_k(e(t_k) - p(t_k)) + \frac{1}{\sqrt{K}} \sum_{k=1}^{K} h_k(p(t_k) - p_1(t_k)) \right. 
+ \left. \frac{1}{\sqrt{K}} \sum_{k=1}^{K} h_k(p_1(t_k) - p_0(t_k)) \leq 2m_K \right\}
\[
\leq \Pr \left\{ \frac{1}{\sqrt{K}} \sum_{k=1}^{K} h_k(e(t_k) - p(t_k)) \leq \frac{r\sqrt{K}}{4} - r\sqrt{K} + 2m_K \right\}
\[
\leq 2 \exp\left( -\frac{1}{2} \frac{r^2}{1 + r} \right), \tag{21}
\]

where the second to last inequality is by Bernstein’s inequality.

We showed how to construct consistent test functions when the inequality (19) holds. 
Choi (2007) examined inequality (19) held with metric \(d\) introduced in Lemma 1. By (20), (21) and Lemma 3, the second condition of Consistency Theorem in Choi (2007) is verified.

So far the two conditions of Consistency Theorem in Choi and Schervish (2007) have been verified. We have showed that the posterior probability

\[
\sup_{(\theta_1, r, \theta_2) \in B} \Pi \{ S^2_\epsilon | e, \theta_1, r, \theta_2 \} \to 0 \quad [P_0^{\infty}], \tag{22}
\]

where \(S^2_\epsilon = \{ p : \int |p(t) - p_0(t)|dt > \epsilon \} \) and \(e = (e_{t_1}, \ldots, e_{t_K})'\).

Finally, let us consider the goal of our theorem. By Fubini’s Theorem,

\[
\Pi \{ S^2_\epsilon | e \} = \int_B \Pi \{ S^2_\epsilon | e, \theta_1, r, \theta_2 \} d\Pi \{ (\theta_1, r, \theta_2) | e \}
= \int_{B_1} \int_{B_2} \int_{B_1} \Pi \{ S^2_\epsilon | e, \theta_1, r, \theta_2 \} d\Pi(\theta_1 | e) d\Pi(r | e) d\Pi(\theta_2 | e).
\]

Since the supermum of the conditional probability in (22) converges to 0 in \(P_0^K\) probabil-
ity, the marginal posterior probability converges to 0 in $P_0^K$ probability regardless of the asymptotic distribution of $\Pi(\theta_1 \mid e)$, $\Pi(r \mid e)$ and $\Pi(\theta_2 \mid e)$. This is formalized as follows:

$$
\Pi\{S^2_\varepsilon \mid e\} = \int_{B_3} \int_{B_2} \int_{B_1} \Pi\{S^2_\varepsilon \mid e, \theta_1, r, \theta_2\} \, d\Pi(\theta_1 \mid e) \, d\Pi(r \mid e) \, d\Pi(\theta_2 \mid e)
$$

$$
\leq \sup_{(\theta_1, r, \theta_2) \in B} \Pi\{S^2_\varepsilon \mid e, \theta_1, r, \theta_2\} \int_{\theta_1 \in B_1} d\Pi(\theta_1 \mid e)
$$

$$
\times \int_{r \in B_2} d\Pi(r \mid e) \int_{\theta_2 \in B_3} d\Pi(\theta_2 \mid e) \rightarrow 0 \quad [P_0^\infty]
$$

So, (11) is proved. From Lemma 1, (10) is also proved. \qed
Appendix C

Theorem (Choi and Schervish, 2007) Let \( \{Z_i\}_{i=1}^{\infty} \) be independently distributed with densities \( \{f_i(\cdot; \theta)\}_{i=1}^{\infty} \), with respect to a common \( \sigma \)-finite measure, where the parameter \( \theta \) belongs to an abstract measurable space \( \Theta \). The densities \( f_i(\cdot; \theta) \) are assumed to be jointly measurable. Let \( \theta_0 \in \Theta \) and let \( P_{\theta_0} \) stand for the joint distribution of \( \{Z_i\}_{i=1}^{\infty} \) when \( \theta_0 \) is the true value of \( \theta \). Let \( \{U_n\}_{i=1}^{\infty} \) be a sequence of subsets of \( \Theta \). Let \( \theta \) have prior \( \Pi \) on \( \Theta \). Define

\[
\Lambda_i(\theta_0, \theta) = \log \frac{f_i(Z_i; \theta_0)}{f_i(Z_i; \theta)},
\]

\[
K_i(\theta_0, \theta) = E_{\theta_0}(\Lambda_i(\theta_0, \theta)),
\]

\[
V_i(\theta_0, \theta) = \text{Var}_{\theta_0}(\Lambda_i(\theta_0, \theta)).
\]

(A1) Prior positivity of neighborhoods.
Suppose that there exists a set \( B \) with \( \Pi(B) > 0 \) such that

1. \( \sum_{i=1}^{\infty} \frac{V_i(\theta_0, \theta)}{i^2} < \infty, \forall \theta \in B, \)

2. For all \( \epsilon > 0 \), \( \Pi(B \cap \{\theta : K_i(\theta_0, \theta) < \epsilon \text{ for all } i\}) > 0. \)

(A2) Existence of tests
Suppose that there exist test functions \( \{\Phi_n\}_{i=1}^{\infty} \), sets \( \{\Theta_n\}_{i=1}^{\infty} \) and constants \( C_1, C_2, c_1, c_2 > 0 \) such that

1. \( \sum_{i=1}^{\infty} E_{\theta_0} \Phi_n < \infty, \)

2. \( \sup_{\theta \in U_n^C \cap \Theta_n} E_\theta (1 - \Phi_n) \leq C_1 e^{-c_1 n}, \)

3. \( \Pi(\Theta_n^C) \leq C_2 e^{-c_2 n}. \)

Then

\[
\Pi(\theta \in U_n^C | Z_1, \ldots, Z_n) \to 0 \quad \text{a.s.} \quad [P_{\theta_0}].
\]
References

Abrahamsen, P. (1997). A review of Gaussian random fields and correlation functions. Norsk Regnesentral/Norwegian Computing Center.

Albert, J. H. and Chib, S. (1993). Bayesian analysis of binary and polychotomous response data. *Journal of the American Statistical Association*, 88(422):669–679.

Barber, D. and Williams, C. K. I. (1997). Gaussian Processes for Bayesian Classification via Hybrid Monte Carlo. In *Advances in Neural Information Processing Systems 9*, pages 340–346. MIT Press.

Bernardo, J., Berger, J., and Smith, A. D. F. (1999). Regression and classification using Gaussian process priors. In *Bayesian Statistics 6: Proceedings of the Sixth Valencia International Meeting, June 6-10, 1998*, volume 6, page 475. Oxford University Press.

Choi, T. (2007). Alternative posterior consistency results in nonparametric binary regression using Gaussian process priors. *Journal of statistical planning and inference*, 137(9):2975–2983.

Choi, T. and Schervish, M. J. (2004). Posterior consistency in nonparametric regression problems under Gaussian process priors. *Technical Report, Carnegie Mellon University*.

Choi, T. and Schervish, M. J. (2007). On posterior consistency in nonparametric regression problems. *Journal of Multivariate Analysis*, 98(10):1969–1987.

Choudhuri, N., Ghosal, S., and Roy, A. (2004). Bayesian estimation of the spectral density of a time series. *Journal of the American Statistical Association*, 99(468):1050–1059.

Comi, G., Jeffery, D., Kappos, L., Montalban, X., Boyko, A., Rocca, M., and Filippi, M. (2012). Placebo-controlled trial of oral laquinimod for multiple sclerosis. *New England Journal of Medicine*, 366(11):1000–1009.
Czado, C. and Song, P. X.-K. (2008). State space mixed models for longitudinal observations with binary and binomial responses. *Statistical Papers*, 49(4):691–714.

Duane, S., Kennedy, A., Pendleton, B., and Roweth, D. (1987). Hybrid monte carlo. *Physics letters B*, 195(2):216–222.

Frison, L. and Pocock, S. J. (1992). Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design. *Statistics in medicine*, 11(13):1685–1704.

Galbraith, S., Stat, M., and Marschner, I. C. (2002). Guidelines for the design of clinical trials with longitudinal outcomes. *Controlled clinical trials*, 23(3):257–273.

Geweke, J. (1991). Efficient simulation from the multivariate normal and student-t distributions subject to linear constraints and the evaluation of constraint probabilities. In *Computing science and statistics: proceedings of the 23rd symposium on the interface*, pages 571–578. Citeseer.

Ghosal, S., Ghosh, J. K., and Ramamoorthi, R. (1999). Posterior consistency of Dirichlet mixtures in density estimation. *Annals of Statistics*, 27(1):143–158.

Ghosal, S. and Roy, A. (2006). Posterior consistency of Gaussian process prior for nonparametric binary regression. *The Annals of Statistics*, 34(5):2413–2429.

Goldman, M. D., Motl, R. W., and Rudick, R. A. (2010). Possible clinical outcome measures for clinical trials in patients with multiple sclerosis. *Therapeutic advances in neurological disorders*, 3(4):229–239.

Hall, P., Müller, H.-G., and Yao, F. (2008). Modelling sparse generalized longitudinal observations with latent gaussian processes. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 70(4):703–723.
Hedeker, D. and Gibbons, R. D. (2006). *Longitudinal data analysis*, volume 451. John Wiley & Sons.

Hedeker, D., Gibbons, R. D., and Waternaux, C. (1999). Sample size estimation for longitudinal designs with attrition: comparing time-related contrasts between two groups. *Journal of Educational and Behavioral Statistics*, 24(1):70–93.

Kalman, R. E. (1963). Mathematical description of linear dynamical systems. *Journal of the Society for Industrial & Applied Mathematics, Series A: Control*, 1(2):152–192.

Liang, K.-Y. and Zeger, S. L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika*, 73(1):13–22.

Liechty, M. W. and Lu, J. (2010). Multivariate normal slice sampling. *Journal of Computational and Graphical Statistics*, 19(2).

MacKay, D. (1992). A practical bayesian framework for backpropagation networks. *Neural computation*, 4(3):448–472.

Neal, R. (1995). *Bayesian Learning for Neural Networks*. PhD thesis, Graduate Department of Computer Science, University of Toronto.

Neal, R. (1997). Monte Carlo Implementation of Gaussian process Models for Bayesian Regression and Classification. Technical Report GRG-TR-97-2, Dept. of Computer Science, University of Toronto.

O’Hagan, A. and Kingman, J. (1978). Curve fitting and optimal design for prediction. *Journal of the Royal Statistical Society. Series B (Methodological)*, 40(1):1–42.

Pakman, A. and Paninski, L. (2013). Exact Hamiltonian Monte Carlo for truncated multivariate Gaussians. *Journal of Computational and Graphical Statistics*, (accepted).
Rasmussen, C. and Williams, C. (2006). *Gaussian Processes for Machine Learning*. ISBN 0-262-18253-X. MIT Press.

Raudenbush, S. W. and Liu, X.-F. (2001). Effects of study duration, frequency of observation, and sample size on power in studies of group differences in polynomial change. *Psychological methods, 6*(4):387.

Schwartz, L. (1965). On bayes procedures. *Zeitschrift für Wahrscheinlichkeitstheorie und verwandte Gebiete, 4*(1):10–26.

Shi, J. Q., Wang, B., Murray-Smith, R., and Titterington, D. M. (2007). Gaussian Process Functional Regression Modeling for Batch Data. *Biometrics, 63*(3):714–723.

Tokdar, S. T. and Ghosh, J. K. (2007). Posterior consistency of logistic gaussian process priors in density estimation. *Journal of Statistical Planning and Inference, 137*(1):34–42.

Williams, C. (1998). Prediction with gaussian processes: From linear regression to linear prediction and beyond. *NATO ASI SERIES D BEHAVIOURAL AND SOCIAL SCIENCES, 89*:599–621.

Zeger, S. L., Liang, K.-Y., and Self, S. G. (1985). The analysis of binary longitudinal data with time independent covariates. *Biometrika, 72*(1):31–38.