Abstract

Modern data sets in various domains often include units that were sampled non-randomly from the population and have a latent correlation structure. Here we investigate a common form of this setting, where every unit is associated with a latent variable, all latent variables are correlated, and the probability of sampling a unit depends on its response. Such settings often arise in case-control studies, where the sampled units are correlated due to spatial proximity, family relations, or other sources of relatedness. Maximum likelihood estimation in such settings is challenging from both a computational and statistical perspective, necessitating approximations that take the sampling scheme into account. We propose a family of approximate likelihood approaches which combine composite likelihood and expectation propagation. We demonstrate the efficacy of our solutions via extensive simulations. We utilize them to investigate the genetic architecture of several complex disorders collected in case-control genetic association studies, where hundreds of thousands of genetic variants are measured for every individual, and the underlying disease liabilities of individuals are correlated due to genetic similarity. Our work is the first to provide a tractable likelihood-based solution for case-control data with complex dependency structures.

Keywords: Gaussian Processes, Expectation Propagation, Composite Likelihood, Selection Bias, Linear Mixed Models
1. Introduction

In the collection and analysis of scientific data, a phenomenon often encountered is the existence of complex dependency structures between analyzed units. This is encountered in diverse fields such as epidemiology, econometrics, ecology, geostatistics, psychometrics and genetics, and can arise due to spatial correlations, temporal correlations, family relations, or other sources of heterogeneity (Pfeiffer, 2008; Rabe-Hesketh et al., 2005; Bolker et al., 2009; Rabe-Hesketh et al., 2004; Yang et al., 2014; Burton et al., 1999; Diggle et al., 1998). This idea is often captured through the use of random or mixed-effects models (McCulloch et al., 2008), or equivalently, through Gaussian process (GPs; Rasmussen and Williams 2006) or latent Gaussian models (Fahrmeir and Tutz, 2001). Such models associate every sampled unit with a latent variable, and express the dependency structures as covariance matrices of latent variables.

A second important concept is that of ascertainment, or the non-random sampling of units. Ascertainment is especially common in case-control studies, when a binary response variable of interest has a highly unbalanced distribution, such as a rare disease wherein cases are much rarer than healthy controls (Breslow, 1996).

In this paper we consider situations that contain both elements—a complex covariance structure and case-control sampling—and the statistical modeling solutions available for these situations. Our interest lies in an extreme form of this combination, where the covariance matrix is dense and full rank (i.e., there is a large number of random effects), and the case-control ascertainment is performed at the individual unit level (i.e., every unit is chosen into the study with a probability that depends only on its response and not on the covariance structure). As we discuss below, special cases of this combination have been addressed in the literature (Glidden and Liang, 2002; Epstein et al., 2002; Neuhaus et al., 2006, 2014), but to our knowledge, there is a limited set of available solutions for the general setting, which is indeed very challenging.

A major motivating application for our study is genome-wide association studies of diseases with a case-control sampling design (GWAS-CC) (Price et al., 2015). In GWAS-CC, the genomes of individuals affected with a disease and of unaffected controls are collected in an effort to uncover the genetic mechanisms driving disease risk (Visscher et al., 2017). Studies in this field have diverse goals, reflected in the diversity of the statistical inference tasks they seek to solve (Price et al., 2015): testing disease associations with genetic variants (Yang et al., 2014; Bush and Moore, 2012), estimating disease heritability (Yang et al., 2010; Golan et al., 2014; Loh et al., 2015), risk prediction (Zhou et al., 2013; Golan and Rosset, 2014; Moser et al., 2015; Weissbrod et al., 2016), and more.

GWAS-CC studies typically employ case-control designs, where patients are recruited in hospitals or clinics whereas healthy controls are recruited independently, owing to the small prevalence of complex genetic diseases—even common diseases like type 1 diabetes or schizophrenia typically have a population prevalence <2%. Furthermore, statistical models for such studies typically treat genetic variant-disease effects as random effects sampled from a distribution. This is because such studies include hundreds of thousands of variants, and the effects are typically very small (Yang et al., 2010; Golan et al., 2014; Zhou et al., 2013; Golan and Rosset, 2014; Moser et al., 2015). Hence, GWAS-CC studies give rise to settings with case-control sampling and a dense covariance structure, because every individual has
a latent genetic effect (given by the inner product of her genotype and the random effects), and the genetic effects are correlated due to genetic similarity.

Despite the extensive interest that GWAS-CC studies have attracted in recent years (Wellcome Trust Case Control Consortium et al., 2007; Ehret et al., 2011; Sawcer et al., 2011; Timmann et al., 2012; Ripke et al., 2014; Okada et al., 2014), the statistical modeling problems this setting generates have been discussed in a limited manner, with application of heuristic methods that do not formally take the probabilistic structure of the problem into account (Lee et al., 2011; Hayeck et al., 2015; Weissbrod et al., 2015; Chen et al., 2016; Jiang et al., 2015).

Similar settings arise in other scientific domains, where case-control sampling, high dimensional random effects and a dense covariance matrix simultaneously occur. Prominent examples include disease mapping studies with a smoothing kernel (Diggle et al., 1998; Kelsall and Diggle, 1998; Held et al., 2005) and GP-based classification of data collected in case-control studies (Chu et al., 2010; Ziegler et al., 2014; Young et al., 2013). The analyses employed in these examples often ignore the effects of case-control sampling, a practice we would like to avoid and whose fundamental flaws we discuss and illustrate below.

The problem we consider poses substantial statistical and computational challenges, various aspects of which have been addressed in the statistics and machine learning literature. The main approaches for maximum likelihood estimation under ascertainment include the profile maximum likelihood and its close variant, the ascertained maximum likelihood (AML), which offer “almost maximum likelihood” solutions (Scott and Wild, 2001; Wild, 1991; Scott and Wild, 1997). The main approach for statistical inference with random effects is generalized linear mixed models (GLMMs; McCulloch et al. 2008), also known in different scientific communities as Gaussian process (Rasmussen and Williams, 2006) or latent Gaussian models (Fahrmeir and Tutz, 2001). GLMMs provide a likelihood-based solution, but do not deal naturally with unit-level ascertainment and can pose significant computational difficulties. Modern approaches for alleviating computational difficulties include pairwise likelihood (PL; Renard et al. 2004) and expectation propagation (EP; Minka 2001).

Here we propose two approaches for approximate likelihood computation in our setting of interest:

1. GLMM + PL + AML, which proposes a tractable likelihood approximation but is very sensitive to model misspecification.

2. GLMM + modified EP + AML. This solution is more computationally intensive, but is more robust and is closer to traditional maximum likelihood estimation.

We evaluate the merits of our approaches on both synthetic and real data sets of genetic studies involving thousands of individuals and hundreds of thousands of explanatory variables treated as having random effects.
2. Detailed Problem Description

We are interested in settings with (i) unit-level ascertainment; (ii) a full-rank covariance matrix; and (iii) a dense covariance matrix. These concepts are explained below.

Unit-level ascertainment indicates that the decision whether to sample a unit is performed for every unit separately (Figure 1 a). This stands in contrast to several common study designs, such as family studies (Neuhaus et al., 2002), ascertainment longitudinal studies (Liang and Zeger, 1986) or clustered case-control studies (Neuhaus and Jewell, 1990), where each correlated cluster is either entirely selected or entirely omitted from the study, and so there is no interaction between the ascertainment and the dependence structure.

A full-rank covariance matrix indicates that there are more random effects than samples, because the matrix rank measures the number of random effects (Figure 1 b). Modern data sets often include a very large number of random effects, either because they are very high dimensional, or because of the use of basis expansions or kernels, which implicitly project a small number of variables into a large (possibly infinite-dimensional) space (Diggle et al., 1998; Rasmussen and Williams, 2006; Held et al., 2005). Likelihood inference in the presence of such high dimensional dependencies is computationally challenging because it requires evaluating an integral whose dimensionality is equal to the matrix rank.
Finally, a covariance matrix is dense when all of its entries are different from zero, indicating that all units are correlated (Figure 1 c). This exacerbates both the computational challenge, because the density does not factorize into multiplicative terms, and the statistical challenge, because classic statistical theory requires a large number of independent samples.

3. Existing Approaches for Likelihood-based Analysis of Correlated Data

We now briefly overview the GLMM and GP approach for analysis of correlated data, and then describe approaches for approximate inference in such settings. Throughout this section we assume that the data is not ascertained. We address analysis of ascertained data in Section 4.

3.1 Generalized Linear Mixed Models / Gaussian Processes

Consider a sample of \( n \) units, each having \( d \) covariates associated with fixed (non-random) effects \( X_i \in \mathbb{R}^{d \times 1} \), \( m \) covariates associated with random effects \( Z_i \in \mathbb{R}^{m \times 1} \) and an outcome variable \( y_i \). GLMMs assume the existence of a latent random effect \( b \in \mathbb{R}^{m \times 1} \) such that

\[
P(y_i | X_i, Z_i, b; \beta) = h(X_i^T \beta + Z_i^T b),
\]

where \( h(\cdot) \) is a likelihood function (which is closely related to an inverse link function in GLM terminology) and \( \beta \in \mathbb{R}^{d \times 1} \) are (non-random) fixed effects. In this work we assume that the random effects \( b \) are normally distributed with a zero mean and a covariance matrix \( D(\theta) \) parameterized by \( \theta \), \( b \sim \mathcal{N}(0, D(\theta)) \). In most random effects formulations in statistical genetics and other areas, it is usually assumed that \( b \sim \mathcal{N}(0, \theta I) \) for some scalar \( \theta \), typically called a variance component.

GLMMs naturally encode a latent variable for every individual, \( g_i = Z_i^T b \), which aggregates the effects of all random variables. The covariance matrix relating the latent variables (which is dense and full rank in our setting) is therefore given by \( ZD(\theta)Z^T \), where \( Z \in \mathbb{R}^{n \times m} = [Z_1, \ldots, Z_n]^T \). This view enables \( Z \) to be implicitly infinite dimensional as long as the matrix \( ZD(\theta)Z^T \) can be defined, and thus unifies the GLMM and GP formulations. A schematic graphical model for GLMMs is shown in Figure 2.

Given a vector of observed outcomes \( y \in \mathbb{R}^{n \times 1} \) and the matrix \( X = [X_1, \ldots, X_n]^T \), the GLMM likelihood is given by:

\[
L(\beta, \theta) = P(y | X, Z ; \theta, \beta) = \int P(g | Z; \theta) \prod_i P(y_i | X_i, g_i; \beta) dg.
\]

Exact likelihood evaluation is computationally infeasible even in the presence of a modest number of random effects \( m \), but efficient approximations have been developed (Kuss and Rasmussen, 2005; Nickisch and Rasmussen, 2008; Varin et al., 2011), two of which are described next.

3.2 Pairwise Likelihood

PL belongs to the family of composite likelihood approximations, which approximate the joint density of a large number of random variables via a product of joint densities of subsets.
of the data (Varin et al., 2011). PL is defined as follows:

\[ P(y \mid X, Z; \theta, \beta) \propto \prod_{i,j} P(y_i, y_j \mid X_i, X_j, Z_i, Z_j; \theta, \beta), \]

where \( \propto \) indicates approximate proportionality with respect to the model parameters \( \theta, \beta \). Hence, the maximum pairwise likelihood estimate is also approximately the maximum likelihood estimate. PL estimation has the favorable properties of being computationally efficient owing to its quadratic dependency on the sample size, and of being consistent under suitable regularity conditions (Varin et al., 2011).

3.3 Expectation Propagation

EP is a popular approach for approximating complex distributions by iteratively replacing every multiplicative term in the joint distribution of the observed and latent variables, with a simpler term from an exponential family distribution (Minka, 2001; Rasmussen and Williams, 2006). The joint distribution of GLMMs is given by \( P(g \mid Z; \theta) \prod_{i} P(y_i \mid X_i, g_i; \beta) \). EP replaces every term in the product above by an unnormalized Gaussian, \( P(y_i \mid X_i, g_i) \approx t_i(g_i) \triangleq r_i N(g_i; \tilde{\alpha}_i, \tilde{\gamma}_i) \), where we omitted the parameters \( \beta \) and \( \theta \) for brevity, and the site parameters \( r_i, \tilde{\alpha}_i, \tilde{\gamma}_i \) implicitly depend on \( X_i, y_i \) and \( \beta \). EP iteratively updates the terms \( t_i(g_i) \), such that each term minimizes the generalized Kullback Leibler divergence (GKL)
between the functions \( q_{-i}(g_i) t_i(g_i) \) and \( q_{-i}(g_i) P(y_i|X_i, g_i) \) (i.e., the KL divergence between these functions after standardizing them to integrate to unity), where the cavity distribution \( q_{-i}(g_i) \propto \int P(g_i|Z) \prod_{j \neq i} t_j(g_j) dg_{j \neq i} \) represents the current approximation of \( P(g_i|Z, y_{j \neq i}) \).

Given an EP approximation, the GLMM likelihood can be approximated as:

\[
P(y | X, Z) \approx \int P(g|Z) \prod_i t_i(g_i) dg.
\]

This expression can be evaluated analytically because it is an integral of a product of (unnormalized) Gaussian densities. EP has proven to consistently outperform alternative approximation methods for binary data (Nickisch and Rasmussen, 2008), and recent theoretical analysis has demonstrated its consistency under certain modeling assumptions (Dehaene and Barthelmé, 2016, 2018).

4. Existing Approaches for Likelihood-based Analysis of Ascertained Data

Analysis of ascertained data is typically carried out by defining a sampling indicator for every unit \( s_i \in \{0, 1\} \) which depends only on \( y_i \), where \( s_i = 1 \) for every unit in the study (Figure 2), and then incorporating these indicators into the analysis. The two main approaches for likelihood-based estimation in the presence of such indicators are maximum profile likelihood and AML, which are described next.

4.1 Maximum profile likelihood

Maximum profile likelihood consists of maximizing the profile likelihood \( L_{\text{profile}}(\theta_{y|X}) = P(y | X, s = 1 ; \theta_{y|X}, \pi) \) (Scott and Wild, 2001). Here, \( \theta_{y|X} \) parameterizes the distribution \( P(y|X) \), \( s = 1 \) is a shorthand notation for \( s_1 = 1, \ldots, s_n = 1 \), and the parameters vector \( \pi \) defines the sampling probability \( P(s_i = 1|y_i) \) for every possible value of \( y_i \). The resulting estimator is equivalent to maximum likelihood estimation, in the sense that it attains the Cramer-Rao lower bound.

4.2 Ascertained Maximum Likelihood

AML is similar to maximum profile likelihood, with the main difference being that the sampling probabilities \( P(s_i = 1|y_i) \) are defined beforehand by exploiting knowledge of the distribution of \( y \) in the population (Scott and Wild, 1997). For a binary outcome with a population prevalence \( K \) and an in-sample prevalence \( P \), every pair of sampling probabilities obeying the constraint \( \frac{P(s_i = 1|y_i = 0)}{P(s_i = 1|y_i = 1)} = \frac{K(1-P)}{(1-K)P} \) guarantees consistent estimates, because it yields the observed case-control ratio in expectation. This approach is often termed pseudo likelihood or conditional likelihood (Manski and McFadden, 1981; Hsieh et al., 1985), but as both terms have alternative meanings in GLMM literature, we use the term ascertained likelihood instead.

AML estimates are less statistically efficient than maximum profile likelihood estimates, but the loss of efficiency has been shown to be negligible in practice (Wild, 1991; Scott and Wild, 1997). The AML approach has previously been used for family-based studies...
(Glidden and Liang, 2002; Epstein et al., 2002), but to our knowledge it has not been used under the combination of a dependency structure and unit-level sampling.

### 4.3 The Challenge in Combining GLMMs with AML

To combine GLMMs with the AML framework, we define the ascertained GLMM likelihood and apply Bayes’ law as follows:

\[
L^* (\beta, \theta) = P(\mathbf{y} | \mathbf{X}, \mathbf{Z}, s = 1 ; \theta, \beta) = \frac{P(\mathbf{y} | \mathbf{X}, \mathbf{Z} ; \theta, \beta)}{P(s = 1 | \mathbf{X}, \mathbf{Z} ; \theta, \beta)} \prod_i P(s_i = 1 | y_i). \tag{1}
\]

The last term in the rhs of Equation 1 is considered known under the AML framework and requires no special treatment. The numerator is equal to the standard GLMM likelihood under no ascertainment, whereas the denominator is equal to the likelihood of a GLMM in which the outcome is \(s_i\) instead of \(y_i\). A naive approach is to approximate the numerator and denominator separately. However, obtaining an accurate estimate of the ratio is extremely challenging, because both the numerator and denominator are challenging to approximate, and any inaccuracy is compounded by the division. In our experience, this approach does not lead to reasonable estimators.

### 4.4 The Implications of Ignoring Ascertainment in GLMMs

GLMMs are often employed in the analysis of case-control data without explicitly accounting for the ascertainment scheme (Chen et al., 2016; Jiang et al. 2015). We demonstrate here that ignoring ascertainment leads to unrealistic conclusions which stand in contrast to some fundamental motivations for GLMM use, like the central limit theorem.

We focus on binary GLMMs, which can be formulated according to the liability threshold model (Dempster and Lerner, 1950). Under this model, every unit has a latent liability value \(l_i = g_i + \epsilon_i\), where \(\epsilon_i\) is a latent residual variable whose distribution depends on the likelihood function (e.g. normally distributed for probit, or logit distributed for logit), and cases are units with \(l_i > t\) for some cutoff \(t\). The cutoff \(t\) is the \(1 - K\) percentile of the liabilities distribution in the population, where \(K\) is the prevalence of cases.

It is common to use likelihood functions associated with a smooth and symmetrically distributed \(\epsilon_i\), such as logit or probit, which leads to a smooth and symmetric distribution of liabilities in the population. However, the liabilities and the latent variables \(g_i\) in an ascertained sample follow a non-symmetric and possibly non-continuous distribution (Figure 3 a), and thus cannot be analyzed with standard likelihood functions. This problem motivates the statistical solutions presented in this work for analysis of case-control studies.

Many studies in practice opt to ignore the complexities above, and instead use common likelihood functions such as a logit or a probit to analyze case-control studies (Chen et al., 2016; Jiang et al., 2015; Hobbs et al., 2016; Kramer et al., 2017; Qi et al., 2017; Sanders et al., 2017). However, this solution implies a non-symmetric and possibly non-smooth distribution of liabilities and latent variables in the population from which units are sampled, in contrast to the central limit theorem assumptions (Figure 3 b). Thus, ignoring the ascertainment scheme in GLMMs may lead to nonsensical probabilistic settings, under common assumptions.
Figure 3: The implications of assuming normality of random effects in the population from which units are sampled (panel a) or in a case-control study (panel b), for a GLMM with a probit likelihood function. The liability is given by \( l_i = g_i + \epsilon_i \), and we assume \( g_i, \epsilon_i \sim \mathcal{N}(0, 0.5) \). Units with liabilities greater than their (1-prevalence) percentile in the population are considered cases. (a) When assuming normality in the underlying population, the distribution of the latent variables and of the liabilities in a case-control study (i.e., conditional on \( s_i = 1 \)) is non-normal, unless the cases prevalence is 50%, in which case the study is a random population sample. (b) When assuming normality in a case-control study, the latent variables and the liabilities are not normally distributed in the underlying population, in contrast to the underlying assumptions of the liability threshold model.

5. Adapting the Statistical Approaches to Ascertained Settings

Here we describe how the GLMM approximations, PL and EP, can be adapted to ascertained settings.
5.1 Adapting Pairwise Likelihood to Ascertained Settings

PL can naturally be adapted to ascertained settings via the approximation:

\[ P(y | X, Z, s = 1) \propto \prod_{i,j} P(y_i, y_j | X_i, X_j, Z_i, Z_j, s_i = 1, s_j = 1) \]

\[ = \prod_{i,j} \frac{P(y_i, y_j | X_i, X_j, Z_i, Z_j)}{P(s_i = s_j = 1 | X_i, X_j, Z_i, Z_j)} P(s_i = s_j = 1 | y_i, y_j), \]

where \( P(s_i = s_j = 1 | y_i, y_j) = P(s_i = 1 | y_i) P(s_j = 1 | y_j) \) are known constants which can be ignored, and we omitted the parameters \( \beta, \theta \) for brevity. The terms in the numerator and the denominator can be separately evaluated as in standard PL, where we treat the denominator as a GLMM with a suitable likelihood function. Unlike before, the evaluation of the ratio is accurate since both the numerator and denominator can be computed exactly. In certain settings, the PL evaluation can be substantially accelerated via a Taylor approximation around \( Z^T_i Z_j = 0 \), which enables factoring each bivariate distribution into a product of marginal distributions (Appendix A).

5.2 Adapting Expectation Propagation to Ascertained Settings

Our novel derivation of ascertained EP (AEP) replaces the standard EP step with a modified step that equates the functions \( \int q_{-i}(g_i) t_i(g_i) dg_i \) and \( \int \frac{q_{-i}(g_i) P(y_i, s_i | g_i, X_i)}{P(s_i | g_i, X_i)} dg_i \). Specifically, at each step we find the unnormalized Gaussian \( t_i(g_i) \) which makes these functions and their first two partial derivatives with respect to \( \mu_{-i} \) (the mean of the Gaussian \( q_{-i}(g_i) \)) have the same value when evaluated at \( \mu_{-i} \). We show in Section 5.3.3 that this step objective coincides with the standard EP objective in the absence of ascertainment (i.e. when \( P(s_i | y_i) \) is a constant regardless of \( y_i \)). Hence, our proposed algorithm generalizes standard EP to handle ascertainment.

The sampling distribution of the AEP maximum likelihood estimator can be approximated efficiently via jackknife sampling, by reusing the functions \( t_i(g_i) \) (Opper and Winther, 2000; Qi et al., 2004; Vehtari et al., 2016). The evaluation of each jackknife sample requires inverting a matrix that is a submatrix of a matrix that was inverted in the original computation, with one row and one column removed. Such an inversion can be computed rapidly while retaining numerical stability, by combining a Cholesky decomposition with a series of Givens rotations (Seeger, 2004).

5.3 Analysis of Ascertained EP

Here we provide an analysis of AEP and its derivation. As the theoretical properties of EP are not well understood (except under relatively strong conditions, e.g. Dehaene and Barthelmé 2018), we do not provide a formal analysis of AEP. Instead, we state several assumptions and then provide an informal analysis under these assumptions. Specifically, we demonstrate the consistency of AEP in Section 5.3.1, provide a justification for the specific form of the AEP step in Section 5.3.2, and demonstrate that EP and AEP coincide in the absence of ascertainment in Section 5.3.3.
Throughout this section, the notation \( s \) is a shorthand notation for \( s_1 = \ldots = s_n = 1 \), \( u_{-i} \) indicates the vector \( u \) with the \( i \)th component removed, and we omit the dependence on \( \beta, \theta \) for brevity.

5.3.1 Consistency of Ascertained EP

Our informal proof of AEP consistency is based on two assumptions:

**Assumption 1** The composite likelihood approximation:

\[
P(s|X, Z) \approx \frac{1}{C(X, Z)} \prod_i P(s_i|X, Z, s_{-i}), \quad \text{for some proportionality factor } C(X, Z).
\]

**Assumption 2** At the fixed point of AEP we have:

\[
\int P(g|Z) \prod_i t_i(g_i) dg \approx \int P(g|Z) \prod_i P(y_i, s_i|g_i, X_i) P(s_i|X, Z, s_{-i}) dg.
\]

Note that if these assumptions hold, this implies that they also hold when replacing \( s \) with \( s_{-j} \) and omitting \( j \) from the product in Assumption 1, and when integrating over \( g_{-j} \) and omitting \( j \) from the products in Assumption 2. These properties will be used in the proofs.

Assumption 1 is motivated by the theory of composite likelihood estimators (Varin et al., 2011). Specifically, the composite maximum likelihood estimator is asymptotically normally distributed around the true parameter value under suitable regularity conditions (Cox and Reid, 2004), indicating consistency. Since both the full and the composite maximum likelihood estimators are asymptotically normal with the same mean, the composite likelihood is approximately proportional to the full likelihood around this mean, with the approximation accuracy depending on the ratio between their variances. This ratio depends on the ratio between the diagonal entries of the Fisher and the Godambe information matrices (Varin et al., 2011).

Assumption 2 arises because the AEP algorithm explicitly strives to improve its underlying approximation until reaching the fixed point, as shown in Section 5.3.2. This is the analogue of the standard EP objective \( t_i(g_i) \approx P(y_i|X_i, g_i) \), with the difference that here \( t_i(g_i) \approx \frac{P(y_i, s_i|g_i, X_i)}{P(s_i|X, Z, s_{-i})} \).

We now provide an informal proof of AEP consistency using Assumptions 1-2.

**Lemma 1** At the fixed point of the AEP algorithm, we have:

\[
\int P(g|Z) \prod_i t_i(g_i) dg \approx C(X, Z) \cdot P(y|X, Z, s).
\]
The last two equalities use the fact that \( y \) and \( s \) are conditionally independent of \( Z \) given \( g \).

Lemma 1 implies consistency because it indicates that the AEP likelihood approximation is approximately proportional to the true likelihood. Hence, the parameters \( \beta, \theta \) which maximize the AEP likelihood are approximately the maximum likelihood estimates.

### 5.3.2 Derivation of the Ascertained EP Step

Here we provide an informal justification for the specific form of the AEP step described in Section 5.2. Our derivation makes use of several propositions, whose proofs are provided in Appendix B. These proofs make use of Assumptions 1-2 and an additional assumption:

**Assumption 3** Weak dependence between \( y_{-i} \) and \( s_i \) conditional on \( X \) and on \( Z \):

\[
P(y_{-i} | X, Z, s) \approx P(y_{-i} | X, Z, s_{-i}).
\]

Recall from Section 5.2 that the AEP step equates the functions \( \int q_{-i}(g_i) t_i(g_i) dg_i \) and \( \int q_{-i}(g_i) P(y_{-i} | s_i, g_i, X_i, Z_i) P(s_i | g_i, X_i, Z_i) dg_i \), where \( q_{-i}(g_i) \propto \int \frac{P(g_i | X, Z, s)}{P(s_i | X, Z)} P(y | s, g, X) dg \). We now write down the derivation leading to this objective function, based on Assumptions 1-3.

We first write down the natural analogue of the standard EP step objective for AEP. Following Assumption 2, this objective finds the unnormalized Gaussian \( t_i(g_i) \) that optimizes the approximation:

\[
\int q_{-i}(g_i) t_i(g_i) dg_i \approx \int q_{-i}(g_i) \frac{P(y_{-i}, s_i | g_i, X_i)}{P(s_i | X, Z, s_{-i})} dg_i.
\]

The above objective is motivated by observing that the lhs of Equation 2 is proportional to the lhs of Lemma 1, and hence is approximately proportional to the likelihood we wish to evaluate. However, we cannot follow the EP approach of minimizing the GKL divergence between the functions in the integrals in Equation 2, because this will lead to the same solution as standard EP, up to a scaling factor that is absorbed in the zeroth moment of \( t_i(g_i) \). To see this, note that the function in the integral on the rhs of Equation 2 can be written as \( q_{-i}(g_i) P(y_i | g_i, X_i) W \), where \( W = \frac{P(s_i | y_i)}{P(s_i | X, Z, s_{-i})} \) is constant with respect to \( g_i \).
This is the same function used in standard EP, up to the scaling factor \( W \). This is a result of Dawid’s selection paradox (Dawid, 1994; Senn, 2008).

Instead of minimizing the GKL divergence, we first use Assumptions 1-3 to approximate the rhs of Equation 2 as follows:

\[
\int q_{-i}(g_i) \frac{P(y_i, s_i | g_i, X_i)}{P(s_i | X, Z, s_{-i})} dg_i \approx \int q_{-i}(g_i) P(y_i, s_i | g_i, X_i) dg_i.
\]

Next, we equate the lhs of Equation 2 with the rhs of Equation 3 by imposing the constraint that the zeroth, first and second derivatives of both functions with respect to \( \mu_{-i} \) (the mean of the Gaussian \( q_{-i}(g_i) \)) have the same value when evaluated at \( \mu_{-i} \). These constraints render AEP equivalent to standard EP in the absence of ascertainment, as shown in Section 5.3.3. The derivation is conceptually simple, because \( \mu_{-i} \) is simply the parameter encoding the mean of the Gaussian \( q_{-i}(g_i) \).

It remains to derive Equation 3. Our main tool is the following approximation:

**Proposition 1** At the fixed point we have: \( q_{-i}(g_i) \approx P(g_i, X, Z, y_{-i}) \).

Our derivation uses Proposition 1 twice. First, we use it to obtain the following approximation to the rhs of Equation 2:

**Proposition 2**

\[
\int q_{-i}(g_i) \frac{P(y_i, s_i | g_i, X_i)}{P(s_i | X, Z, s_{-i})} dg_i \approx P(y_i | X, Z, y_{-i}, s_i).
\]

Afterwards, we use Proposition 1 again, along with the graphical model structure (Figure 2) to approximate the rhs of Equation 4 via \( q_{-i}(g_i) \) as follows:

\[
P(y_i | X, Z, y_{-i}, s_i) = \frac{P(y_i, s_i | X, Z, y_{-i})}{P(s_i | X, Z, y_{-i})} = \frac{\int P(g_i | X, Z, y_{-i}) P(y_i, s_i | X_i, g_i) dg_i}{\int P(g_i | X, Z, y_{-i}) P(s_i | X_i, g_i) dg_i} \approx \frac{\int q_{-i}(g_i) P(y_i, s_i | X_i, g_i) dg_i}{\int q_{-i}(g_i) P(s_i | X_i, g_i) dg_i}.
\]

This completes the derivation.

**5.3.3 Equivalence of AEP and Standard EP Under no Ascertainment**

In standard (non-ascertained) EP we minimize the Generalized Kullback-Leibler (GKL) divergence between \( \hat{m}(g_i) \triangleq q_{-i}(g_i) P(y_i | g_i, X_i) \) and \( \hat{m}(g_i) \triangleq q_{-i}(g_i) \cdot t_i(g_i) \). Since \( \hat{m}(g_i) \) is an unnormalized Gaussian, we can minimize the GKL divergence by equating its zeroth, first and second moments with those of \( \hat{m}(g_i) \) (Rasmussen and Williams, 2006). Hence, standard EP requires computing the mean \( \hat{\mu}_i \) and variance \( \hat{\sigma}_i^2 \) of \( \hat{m}(g_i) \). A straightforward but lengthy derivation shows that we can compute these quantities as follows:

\[
\hat{\mu}_i = \frac{\partial}{\partial \mu_{-i}} \left[ \log \int \hat{m}(g_i) dg_i \right] \sigma_{-i}^2 + \mu_{-i}
\]

\[
\hat{\sigma}_i^2 = \frac{\partial^2}{\partial (\mu_{-i})^2} \left[ \log \int \hat{m}(g_i) dg_i \right] \left( \sigma_{-i}^2 \right)^2 + \sigma_{-i}^2,
\]
where $\mu_{-i}$, $\sigma^2_{-i}$ are the mean and variance of the Gaussian $q_{-i}(g_i)$, and the derivatives are evaluated at the actual value of $\mu_{-i}$. Hence, there is a one-to-one correspondence between the first two moments of $\hat{m}(g_i)$ and its first two partial derivatives with respect to $\mu_{-i}$ (when evaluated at $\mu_{-i}$). Consequently, each step of standard EP can alternatively be described as imposing the constraint that the zeroth, first and second derivatives of the integrals of $\tilde{m}(g_i)$ and $\hat{m}(g_i)$ with respect to $\mu_{-i}$ (when evaluated at $\mu_{-i}$). Hence, EP and AEP coincide in the absence of ascertainment, where $P(s_i = 1|y_i)$ is constant regardless of the value of $y_i$.

6. Results

We evaluated the performance of our methods using extensive simulations and real data analysis. We first describe our simulation studies, and then demonstrate the results obtained on real data.

6.1 Simulations Overview

To evaluate the performance of the methods, we simulated data that closely mimic real GWAS-CC studies, and evaluated the accuracy of genetic heritability estimation (i.e., variance component estimation) under each method. We simulated data according to the liability threshold model, where each subject has liability $l_i = X_i^T \beta + Z_i^T b + \epsilon_i$, and the variance of the liability in the population is 1. The heritability is the fraction of liability variance explained by genetics, which is given by the variance $\sigma^2_g$ of the latent variable $g_i = Z_i^T b$ in the population (assuming $\text{var}(l_i) = 1$).

We simulated genetic data based on single nucleotide polymorphisms (SNPs), which can be encoded as 0/1/2, according to the number of minor alleles carried by an individual at a specific position in the genome. We first generated a minor allele frequency (MAF) $f_j \sim U(0.05, 0.5)$ for every SNP $j$, and then sampled a matrix $Z$ of SNP, such that $Z_{ij} \sim \text{Bin}(2, f_j)$. Finally, we standardized each column in the matrix $Z$ by subtracting the mean and dividing by the standard deviation corresponding to its allele frequency.

To simulate unit-level ascertainment, we (1) generated a population of 1,000,000 individuals, where for every individual $i$ we generated a vector of standardized genotypes $Z_i \in \mathbb{R}^m$ as described above, and a vector $X_i \sim \mathcal{N}(0, I) \in \mathbb{R}^c$ representing additional standardized risk factors such as sex or age; (2) generated a random vector $b \sim \mathcal{N}(0, \sigma^2_c / c I)$ of random effects, and $\beta \sim \mathcal{N}(0, \sigma^2_{\beta} / c I)$ of fixed effects; (3) assigned a latent variable $g_i = Z_i^T b$ and a liability $l_i = g_i + X_i^T \beta + \epsilon_i$ for every individual $i$, where $\epsilon_i \sim \mathcal{N}(0, 1 - \sigma^2_c - \sigma^2_g)$ i.i.d; (4) defined all individuals with $l_i$ greater than the $1 - K$ percentile of the liability distribution as cases, where $K$ is the desired prevalence; and (5) selected a subset of $\frac{n}{2}$ cases and $\frac{n}{2}$ controls for the case-control study, where $n$ is the desired study size. Unless otherwise stated, we used $m = 500$, $n = 500$, $K = 1\%$, $\sigma^2_g = 0.25$, $\sigma^2_c = 0.25$, and $c = 1$.

In all settings, we first estimated the fixed effects via a novel ascertainment-aware generalized estimation equations (AGEE) approach that we developed, and then adjusted the affection cutoffs accordingly (Appendix C).
Figure 4: Evaluating the performance of variance component estimation methods. Shown are box-plots depicting the estimates of each method across 100 different simulations, under data sets with an equal number of cases and controls, and a model with a single variance component, denoted as $\sigma^2$. The dashed horizontal lines represent the true underlying values of $\sigma^2$ used to generate the data. (a) AEP, APL and PCGC provide accurate estimates of $\sigma^2$ when the true trait prevalence (the prevalence of cases in the population) is 1%, for various values of $\sigma^2$, whereas plain EP is severely biased. (b) All methods except for plain EP accurately estimate $\sigma^2$ regardless of the underlying trait prevalence. Plain EP is accurate only when the prevalence is 50%, in which case there is no ascertainment.

### 6.2 Simulation Studies: Estimating Variance Components

Our first experiment evaluated the ability to estimate the variance component $\theta$ (i.e. the parameter governing the distribution of the latent variables $g \sim \mathcal{N}(0, \theta ZZ^T)$). In addition to the methods proposed here we also evaluated a method called phenotype correlation genotype correlation (PCGC), which is the state of the art approach for heritability estimation in genetic studies (Golan et al., 2014). PCGC is similar in spirit to the PL solution proposed in this work, but uses a moment rather than a likelihood-based estimator.

In addition to PCGC, we examined AEP, ascertained pairwise likelihood (APL), and plain EP, which is the standard variant of EP that does not account for ascertainment. The results indicate that all methods except plain EP yield empirically unbiased estimates, whereas plain EP is severely biased (Figure 4 a). To further investigate the behavior of the methods, we generated case-control studies under different prevalence values $K$, and verified that all methods except plain EP remain accurate regardless of $K$, whereas plain EP is only accurate when $K = 0.5$, in which case there is no ascertainment (Figure 4 b).
Figure 5: Investigating how estimation performance is affected by sample size, data dimensionality and modeling violations. (a) All the methods gain accuracy as the sample size increases. The estimator variance of PCGC is consistently larger, because it uses a moment-based rather than a likelihood-based estimator. (b) All the methods gain accuracy as the number of random effects increases. AEP is substantially more accurate than the other methods in the presence of a small number of covariates, because the other two methods use a Taylor expansion around $\mathbf{Z}\mathbf{Z}^T = \mathbf{I}$, which is inaccurate in the presence of a small number of covariates. APL estimates for numbers $<50$ are equal to 1.0, and are omitted for clarity. (c) AEP is robust to covariate standardization misspecification (see main text), whereas PCGC is moderately sensitive and APL is highly sensitive.

In the next experiment, we examined the sensitivity of variance component estimation methods to sample size and data dimensionality (corresponding to the number of rows and columns in the matrix $\mathbf{Z}$, respectively). We first verified that all methods become increasingly accurate with increasing sample size, but PCGC has a consistently larger estimator variance, because it uses a moment-based rather than a likelihood-based estimator (Figure 5 a). We also observed that all methods become increasingly accurate as the number of covariates with random effects increases, but AEP is substantially more accurate in the presence of $<50$ covariates (Figure 5 b). This is because the other two methods use a Taylor expansion around $\mathbf{Z}\mathbf{Z}^T = \mathbf{I}$, which is inaccurate in the presence of a small number of covariates.

We also examined the behavior of the methods under modeling misspecification. To do this, we introduced noise into the standardization procedure of the covariates. Specifically, we multiplied the estimated frequency of every binary variable $j$ by $r_j \sim U \left( \frac{1}{1+e}, 1 + e \right)$ prior to standardizing it, where $e \in [0,1]$ is the standardization error magnitude, and
Figure 6: Estimating the heritability of various complex disorders from (Wellcome Trust Case Control Consortium et al., 2007). Shown are the variance component estimates according to three examined methods, which can be interpreted as the heritability of a complex trait (the fraction of liability variance explained by genetic factors). The error bars are the standard deviation multiplied by 1.96, as estimated via jackknife. The complex disorders are Crohns disease (CD), rheumatoid arthritis (RA), bipolar disorder (BD), type 1 diabetes (T1D), type 2 diabetes (T2D), coronary artery disease (CAD) and hypertension (HT). The population prevalence of each trait is shown below its name, as provided in (Golan and Rosset, 2014). The estimates of AEP and PCGC are relatively concordant, whereas the estimated of APL are significantly down-biased, in agreement with the results of simulations of misspecified covariance matrices.

used this value for estimation, but not for the true generative model. This noise model is motivated by GWAS, where genetic variants are often standardized according to (somewhat noisy) estimates of their population frequency rather than their sample frequency, to prevent bias due to ascertainment. The results indicate that AEP is highly robust to such modeling misspecification, whereas PCGC is moderately sensitive and APL is highly sensitive to such misspecification (Figure 5 c). These experiments indicate that AEP is more reliable than the other methods under a wide variety of modeling assumptions, and is thus the method of choice for likelihood-based variance component estimation in case-control studies.

Finally, we examined the computational speed of the evaluated methods. Our analysis shows that PCGC and APL are very efficient as compared to AEP, because they scale quadratically with the sample size whereas AEP scales cubically, just like standard EP (Nickisch and Rasmussen, 2008). Nevertheless, AEP can still perform maximum likelihood estimation in data sets with 3,000 units in less than two hours, and is thus applicable to solve reasonably sized real-world problems.
6.3 Real Data Analysis

Finally, we evaluated the ability of the proposed methods to estimate variance components in real data sets. To this end, we estimated the heritability of seven complex disorders, having population prevalence between 0.1% and 6%, based on large data sets with \( \sim 3,700 \) individuals and \( \sim 280,000 \) genetic variants from the Wellcome Trust 1 case-control consortium (Wellcome Trust Case Control Consortium et al., 2007). We performed stringent preprocessing to avoid artifacts from biasing our results, as reported in our previous publication (Weissbrod et al., 2016). We modeled sex, which is strongly associated with several of these traits, as a binary covariate associated with a fixed effect, and estimated its effect via AGEE as done in the simulation studies. Standard errors were computed via jackknife sampling.

Our results indicate that the heritability explained by measured genotypes for all investigated disorders lies between 20%-60% (Figure 6). We additionally see a high degree of concordance between PCGC and AEP, whereas the estimates of APL are substantially lower. This behavior is consistent with the one seen in the simulation studies of covariance misspecification, and suggests that the use of APL in practice may be highly sensitive to model misspecification. To conclude, AEP appears to be more accurate than the state of the art (PCGC) under simulations and yields similar estimates under real data analysis, and is thus the first reliable method we are aware of for likelihood-based inference in GLMMs with unit-level ascertainment and a dense and full-rank covariance matrix.

7. Discussion

This study presents several methods for parameter estimation and inference in settings with unit-level ascertainment, a large number of random effects, and a dense correlation structure. This was done by combining the ascertained likelihood framework with GLMMs, which form the statistical backbone of likelihood based analysis of non-iid data.

We proposed two approximate likelihood-based methods for the ascertained GLMM framework, AEP and APL, and empirically compared them with PCGC – the current state of the art method for estimating variance components in genetic case-control studies, which uses a moment-based rather than a likelihood-based estimator. APL is very computationally efficient but appears to be highly sensitive to model misspecification. AEP, which is the most complex and best approximation of maximum likelihood we propose, is slower and is more technically complex than the other methods, but is consistently more accurate than PCGC, and is less sensitive to modeling assumptions in our simulations. AEP additionally has the advantage of providing a full probabilistic model with a well-defined likelihood, and it recovers standard EP as a special case under random ascertainment. On the other hand, PCGC has a principled underlying approximation, whereas APL and AEP are less well understood. We thus believe that the three methods are complementary in terms of their strengths and weaknesses, and we encourage future case-control studies to use multiple methods to gain a deeper understanding of high dimensional dependency structures.

The combination of unit-level ascertainment, a large number of random effects and a dense correlation structure is very common in statistical genetics (Golan et al., 2014), but is often encountered in other scientific domains, such as geostatistics and GP classification (Diggle et al., 1998; Chu et al., 2010; Ziegler et al., 2014; Young et al., 2013). Ascertaine
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sampling is almost inevitable when studying rare phenomena, and the increasing dimensionality of studied data often necessitates the introduction of random rather than fixed effects, which in turn induce dense dependency structures. Additionally, it is often more convenient to perform dense sampling in a small number of clusters rather than collecting a large number of clusters (Bellamy et al., 2005; Zhang, 2004; Glidden and Vittinghoff, 2004) leading to dense, full-rank dependency structures at the cluster level. Hence, we expect our work to be applicable in diverse scientific fields.

One limitation of the dense dependency structure setting is that statistical theory is relatively undeveloped for this case. Specifically, assuming a study with $r$ mutually independent clusters of $m$ units, statistical theory is well developed for the asymptotic behavior $r/m \to \infty$, but is limited for $r/m \to 0$, which is our setting of interest (as $r=1$ when the covariance matrix is dense). The consistency of estimators in such cases has been established in limited settings, including GEEs (Xie and Yang, 2003), maximum penalized quasi likelihood (Bellamy et al., 2005), composite likelihood approximation (Heagerty and Lele, 1998) Laplace approximations (Shun and McCullagh, 1995), and specific geostatistical models (Zhang and Zimmerman, 2005; Du et al., 2009). Several recent studies have established the consistency of maximum likelihood estimators for linear mixed models in similar settings using random matrix theory (Bonnet et al., 2015; Jiang et al., 2016b; Dicker and Erdogdu, 2016), but to our knowledge such results have not been derived for GLMMs. We conclude that there is a major gap in statistical theory regarding $r/m \to 0$ asymptotics, representing questions of both theoretical and practical importance.

In this study we extend the well-known EP algorithm (Minka, 2001) to approximate the GLMM likelihood. Another common approach utilizes Gauss Hermite quadrature (Pinheiro and Bates, 1995; Pinheiro and Chao, 2006), but this approach is computationally infeasible in our settings because it scales exponentially with the number of random effects. Another approach performs Markov chain Monte Carlo (MCMC) sampling combined with an integration scheme such as thermodynamic integration (Kuss and Rasmussen, 2005; Nickisch and Rasmussen, 2008; Gelman and Meng, 1998), but in our experience such approaches are in practice too slow and complex for use with modern sized data sets. Other approaches include analytical approximations such as penalized quasi likelihood (Breslow and Clayton, 1993; Wolzinger and O’Connell, 1993), Laplace approximations (Tierney and Kadane, 1986; Raudenbush et al. 2000) and variational approximations (Opper and Archambeau, 2009). Of these, EP has proven to consistently outperform the alternatives in terms of accuracy-computation tradeoff (Kuss and Rasmussen, 2005; Nickisch and Rasmussen, 2008), and thus forms the basis for our proposed improvement.

In recent years, Bayesian approaches have proven to be potential alternatives to likelihood based approaches in GLMMs (Ferkingstad and Rue, 2015). However, such approaches can be sensitive to the choice of prior distribution, and require using extremely computationally expensive MCMC integration. Several analytical approximations exist, but these are often relatively inaccurate in the presence of binary data (Fong et al., 2010). Hence, the potential use of Bayesian approaches for inference in GLMMs under case-control ascertainment remains to be explored.

Several topics that remain unexplored in this work are GLMMs with multiple variance components, outcome prediction and testing of fixed effects, for which several heuristic methods have been proposed in the statistical genetics literature (Hayeck et al., 2015; Weiss-
brod et al., 2015; Chen et al., 2016; Jiang et al., 2016a). Extending our approach to handle these topics is a potential avenue for future work.

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Appendix A

Here we describe a fast Taylor expansion-based approximation to ascertained pairwise likelihood in the common settings where we have (a) a probit likelihood function; (b) covariates with a unit magnitude (i.e. $Z_i^T Z_i = 1$); and (c) iid random effects. Specifically, denoting $Z_i^T Z_j = \rho$, we have $\text{cov}(g_i, g_j) = \rho \sigma^2$ (where $g_i = Z_i^T b$ is the latent variable of unit $i$). We can therefore expand the pairwise likelihood around $\rho = 0$.

We first write the joint likelihood of each pair of units as

$$P(y_i = a, y_j = b \mid X_i, X_j, Z_i, Z_j, s_i, s_j) = \frac{A_{ab}(\rho)}{B(\rho)} P(s_i \mid y_i) P(s_j \mid y_j),$$

(5)

where $A_{ab}(\rho) \triangleq P(y_i = a, y_j = b \mid X_i, X_j, \rho)$, $B(\rho) \triangleq P(s_i, s_j \mid X_i, X_j, \rho)$. Using the law of total probability, we can write: $B(\rho) = (s^1)^2 A_{11}(\rho) + s^1 s^0 (A_{10}(\rho) + A_{01}(\rho)) + (s^0)^2 A_{00}(\rho)$, where $s^i = P(s_i \mid y_i = i)$. Next, we explicitly evaluate these quantities at $\rho = 0$: $A_{ab}(0) = K_i^a (1 - K_j)^{1-a} K_j^{1-b}$, $B(0) = (s^0(1 - K_i) + s^1 K_i) (s^0(1 - K_j) + s^1 K_j)$, where $K_i = P(y_i = 1 \mid X_i)$, and we omitted the dependence on $Z_i$ because of the assumptions $Z_i^T Z_i = 1$, $b \sim \mathcal{N}(0, \sigma^2 I)$. The above equations hold because $y_i, y_j$ and $s_i, s_j$ are independent given $\rho = 0$.

We next compute the partial derivatives of both expressions with respect to $\rho$ at $\rho = 0$. Following (Golan et al., 2014), we have:

$$\frac{d}{d\rho} A_{ab}(\rho)_{\rho=0} = \phi(t_i) \phi(t_j) \sigma^2 (-1)^{a\neq b}$$

$$\frac{d}{d\rho} B(\rho)_{\rho=0} = (s^1)^2 \frac{d}{d\rho} A_{11}(\rho)_{\rho=0} + 2 s^1 s^0 \frac{d}{d\rho} A_{ab}(\rho)_{\rho=0} + (s^0)^2 \frac{d}{d\rho} A_{00}(\rho)_{\rho=0}$$

$$= \phi(t_i) \phi(t_j) \sigma^2 \left((s^1)^2 + (s^0)^2 - 2 s^1 s^0\right),$$

where $\phi(\cdot)$ is the standard normal density, and $t_i = \Phi^{-1}(1 - K_i) - X_i^T \beta$ is the liability cutoff for unit $i$, with $\Phi(\cdot)$ representing the standard normal cumulative density and $K$ being the prevalence of cases in the population.

Finally, we plug in the above expressions into the Taylor expansion of Equation 5 at $\rho = 0$, given by:

$$\frac{A_{ab}(\rho)}{B(\rho)} P(s_i \mid y_i) P(s_j \mid y_j) = \left(\frac{A_{ab}(0) B(0) - B'(0) A_{ab}(0)}{B(0)^2} \rho + O(\rho^2)\right) P(s_i \mid y_i) P(s_j \mid y_j).$$

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Appendix B

Here we provide proofs of Propositions 1-2 from Section 5.3.2, using Assumptions 1-3.

**Proposition 1** \( q_{-i}(g_i) \approx P(g_i, X, Z, y_{-i}) \).

**Proof** Our proof consists of two stages. First, we define the unnormalized cavity distribution \( q_{-i}^*(g_i) \triangleq \int P(g|Z) \prod_{j \neq i} t_j(g_j) dg_{-i} \), and show that \( q_{-i}^*(g_i) \approx C(X, Z) \cdot P(g_i, y_{-i}|X, Z, s_{-i}) \):

\[
q_{-i}^*(g_i) \triangleq \int P(g|Z) \prod_{j \neq i} t_j(g_j) dg_{-i}
\]

Assumption 2 \( \approx \int P(g|Z) \prod_{j \neq i} \frac{P(y_j, s_j|g_j, X_j)}{P(s_j|X, Z, s_{-j})} dg_{-i} \)

Assumption 1 \( \approx C(X, Z) \int \frac{P(g|Z)}{P(s_{-i}|X, Z)} \prod_{j \neq i} P(y_j, s_j|g_j, X_j) dg_{-i} \)

\[
= C(X, Z) \int \frac{P(g_{-i}|Z)P(g_i|g_{-i}, Z)}{P(s_{-i}|X, Z)} P(y_{-i}, s_{-i}|g_{-i}, X_{-i}) dg_{-i}
\]

rearrangement \( \approx C(X, Z) \int \frac{P(g_{-i}|Z)P(s_{-i}|g_{-i}, X_{-i})}{P(s_{-i}|X, Z)} P(y_{-i}, s_{-i}, X_{-i}) P(g_i|g_{-i}, Z) dg_{-i} \)

Bayes rule \( \approx C(X, Z) \int P(g_{-i}|X, Z, s_{-i}) P(y_{-i}, s_{-i}, X_{-i}) P(g_i|g_{-i}, Z) dg_{-i} \)

graphical model \( \approx C(X, Z) \int P(g_{-i}, y_{-i}|X, Z, s_{-i}) P(g_i|g_{-i}, X, Z, s_{-i}) dg_{-i} \)

\[
= C(X, Z) \int P(g_i, y_{-i}|X, Z, s_{-i}) dg_{-i}
\]

\[
= C(X, Z) \cdot P(g_i, y_{-i}|X, Z, s_{-i})
\]

Next, we note that since \( q_{-i}(g_i) \triangleq \frac{q_{-i}^*(g_i)}{\int q_{-i}^*(g_i) dg_i} \) is a normalized distribution over \( g_i \), we have \( q_{-i}(g_i) \approx P(g_i|X, Z, y_{-i}, s_{-i}) \). Finally, we note that \( g_i \) is conditionally independent of \( s_{-i} \) given \( y_{-i} \) due to the graphical model structure, yielding \( q_{-i}(g_i) \approx P(g_i|X, Z, y_{-i}) \).  

**Proposition 2** \( \int q_{-i}(g_i) \frac{P(y_i, s_i|g_i, X_i)}{P(s_i|X, Z, s_{-i})} dg_i \approx P(y_i|X, Z, y_{-i}, s_i) \).
Proof First, we invoke Proposition 1 and the graphical model structure to obtain the following approximation:

\[
\int q_i(g_i) \frac{P(y_i, s_i | g_i, X_i)}{P(s_i | X, Z, s_{-i})} dg_i \approx \int P(g_i | X, Z, y_{-i}) \frac{P(y_i, s_i | g_i, X_i)}{P(s_i | X, Z, s_{-i})} dg_i
\]

\[
= \int \frac{P(g_i | X, Z) P(y_{-i} | g_i, X_i, Z) P(y_i, s_i | g_i, X_i)}{P(y_{-i} | X, Z) P(s_i | X, Z, s_{-i})} dg_i
\]

\[
= \int \frac{P(g_i | X, Z) P(s_i | X, Z, s_{-i})}{P(y_{-i} | X, Z) P(s_i | X, Z, s_{-i})} \frac{P(y_i | g_i, X, Z, y_{-i}) P(s_i | y_i)}{P(s_i | X, Z, s_{-i})} \frac{P(y_i | X, Z)}{P(s_i | X, Z, s_{-i})} \approx \frac{P(y_i | X, Z) P(s_i | y_i)}{P(y_{-i} | X, Z) P(s_i | X, Z, s_{-i})}.
\]

(6)

Next, we multiply the rhs of Equation 6 by \( \frac{P(s_{-i} | y_i) P(s_{-i} | X, Z)}{P(s_{-i} | y_{-i}) P(s_{-i} | X, Z)} \) and invoke Assumption 3 to obtain:

\[
\frac{P(y_i | X, Z) P(s_i | y_i)}{P(y_{-i} | X, Z) P(s_i | X, Z, s_{-i})} \frac{P(s_{-i} | y_i) P(s_{-i} | X, Z)}{P(s_{-i} | y_{-i}) P(s_{-i} | X, Z)} = \frac{P(y_i | X, Z) P(s_i | y_i) P(s_{-i} | X, Z)}{P(y_{-i} | X, Z) P(s_i | X, Z, s_{-i})}
\]

\[
= \frac{P(y_i | X, Z) P(s_i | y_i)}{P(y_{-i} | X, Z) P(s_i | X, Z, s_{-i})} = \frac{P(y_i | X, Z) P(s_i | y_i)}{P(y_{-i} | X, Z) P(s_i | X, Z, s_{-i})}
\]

\[
= \frac{P(y_i | X, Z) P(s_i | y_i)}{P(y_{-i} | X, Z) P(s_i | X, Z, s_{-i})}
\]

\[
= \frac{P(y_i | X, Z) P(s_i | y_i)}{P(y_{-i} | X, Z) P(s_i | X, Z, s_{-i})}
\]

\[
= \frac{P(y_i | X, Z, y_{-i}, s_i)}{P(y_{-i} | X, Z, s_{-i})}
\]

\[
= \frac{P(y_i | X, Z, y_{-i}, s_i)}{P(y_{-i} | X, Z, s_{-i})}
\]

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Appendix C

Here we describe our novel development of ascertained generalized estimating equations (AGEE). GEEs are extensions of generalized linear models that can estimate fixed effects while accounting for dependencies without requiring a probabilistic model (Liang and Zeger, 1993). GEEs require a correct specification of the mean of the outcome conditional on the covariates, \( \mu_i = E[y_i | X_i; \beta] \), and a (possibly misspecified) working covariance matrix of the outcomes, denoted as \( \Omega(\theta^\Omega) \) and parameterized by \( \theta^\Omega \). Given these, \( \beta \) is estimated by solving the estimating equation \( \frac{\partial}{\partial \theta^\Omega} \Omega(\theta^\Omega)^{-1}(y - \mu(\beta)) = 0 \). GEEs yield consistent
estimates of $\beta$ and its sampling variance even if the covariance structure is misspecified and is dense (Xie and Yang, 2003).

GEEs can naturally be adapted to case-control settings by using the ascertained conditional mean function $E[y_i|X_i, s_i = 1] = P(y_i = 1|X_i, s_i = 1)$.

We now show how the GEE fixed effect estimates can be plugged into GLMMs. In the general case it is not possible to reconcile fixed effect estimates of GEEs and GLMMs, because GEEs assume that the conditional mean of the outcome is affected only by the fixed effects, whereas GLMMs assume that it is affected by both the fixed and random effects. Fortunately, the probit likelihood function provides a convenient way to reconcile the two approaches. Denote $\beta_{\text{GEE}}$ and $\beta_{\text{GLMM}}$ as the vectors of fixed effects used by GEE and GLMM, respectively. When using a probit likelihood, the GEE conditional mean is given by $\Phi(X_i^T \beta_{\text{GEE}})$, where $\Phi(\cdot)$ is the standard normal cumulative density. In contrast, the GLMM conditional mean is given by $\Phi\left(\frac{X_i^T \beta_{\text{GLMM}}}{(\text{var}(g_i)+1)^{1/2}}\right)$. If the variance of $g_i$ is constant for every unit $i$ (which corresponds to a constant value on the diagonal of the covariance matrix of $g$), the two approaches can be reconciled by defining $\beta_{\text{GLMM}} = \beta_{\text{GEE}} (\text{var}(g_i) + 1)^{1/2}$. In practice, the diagonal of the covariance matrix $g$ is often exactly or is almost exactly constant, which enables exploiting the above relation. Therefore, we can use the GEE estimates in a GLMM by setting $\beta_{\text{GLMM}} = \beta_{\text{GEE}} (\text{var}(g_i) + 1)^{1/2}$.

Our implementation of AGEE closely followed that of (Jiang et al., 2016a), with a suitable modification of the likelihood function to encode ascertainment, as described above.

References
Scarlett L. Bellamy, Yi Li, Xihong Lin, and Louise M. Ryan. Quantifying PQL bias in estimating cluster-level covariate effects in generalized linear mixed models for group-randomized trials. *Stat. Sin.*, 15(4):1015–1032, 2005.

Benjamin M. Bolker, Mollie E. Brooks, Connie J. Clark, Shane W. Geange, John R. Poulsen, M. Henry H. Stevens, and Jada-Simone S. White. Generalized linear mixed models: a practical guide for ecology and evolution. *Trends Ecol. Evol.*, 24(3):127–35, 2009.

Anna Bonnet, Elisabeth Gassiat, and Cline Levy-Leduc. Heritability estimation in high dimensional sparse linear mixed models. *Electron. J. Stat.*, 9(2):2099–2129, 2015.

Norman E. Breslow. Statistics in epidemiology: the case-control study. *J. Am. Stat. Assoc.*, 91(433):14–28, 1996.

Norman E. Breslow and David G. Clayton. Approximate inference in generalized linear mixed models. *J. Am. Stat. Assoc.*, 88(421):9–25, 1993.

Paul R. Burton, Katrina J. Tiller, Lyle C. Gurrin, William OCM Cookson, A. William Musk, and Lyle J. Palmer. Genetic variance components analysis for binary phenotypes using generalized linear mixed models (GLMMs) and Gibbs sampling. *Genet. Epidemiol.*, 17(2):118–140, 1999.

William S. Bush and Jason H. Moore. Chapter 11: Genome-Wide Association Studies. *PLOS Comput. Biol.*, 8(12):e1002822, 2012.
Han Chen, Chaolong Wang, Matthew P. Conomos, Adrienne M. Stilp, Zilin Li, Tamar Sofer, Adam A. Szpiro, Wei Chen, John M. Brehm, Juan C. Celédón, et al. Control for population structure and relatedness for binary traits in genetic association studies via logistic mixed models. *Am. J. Hum. Genet.*, 98(4):653–666, 2016.

Carlton Chu, Peter Bandettini, John Ashburner, Andre Marquand, and Stefan Kloeppel. Classification of neurodegenerative diseases using Gaussian process classification with automatic feature determination. In *Proceedings of the first workshop on brain decoding: Pattern recognition challenges in neuroimaging (WBD)*, 2010, pages 17–20. IEEE, 2010.

David R. Cox and Nancy Reid. A note on pseudolikelihood constructed from marginal densities. *Biometrika*, 91(3):729–737, 2004.

Alexander Philip Dawid. Selection paradoxes of Bayesian inference. *Lecture Notes-Monograph Series*, pages 211–220, 1994.

Guillaume Dehaene and Simon Barthelmé. Bounding errors of Expectation-Propagation. In *Proceedings of the twenth-eighth conference on advances in neural information processing systems*, pages 244–252, 2016.

Guillaume Dehaene and Simon Barthelmé. Expectation propagation in the large data limit. *J. R. Stat. Soc. B*, 80(1):199–217, 2018.

Everett R. Dempster and I. Michael Lerner. Heritability of threshold characters. *Genetics*, 35(2):212–36, 1950.

Lee H. Dicker and Murat A. Erdogdu. Maximum likelihood for variance estimation in high-dimensional linear models. In *Proceedings of the nineteenth international conference on artificial intelligence and statistics*, pages 159–167, 2016.

Peter J. Diggle, Jonathan A. Tawn, and Rana Moyeed. Model-based geostatistics. *J. R. Stat. Soc. C*, 47(3):299–350, 1998.

Juan Du, Hao Zhang, and Vidyadhar Mandrekar. Fixed-domain asymptotic properties of tapered maximum likelihood estimators. *Ann. Stat.*, 37(6A):3330–3361, 2009.

Georg B. Ehret, Patricia B. Munroe, Kenneth M. Rice, Murielle Bochud, Andrew D. Johnson, Daniel I. Chasman, Albert V. Smith, Martin D. Tobin, Germaine C. Verwoert, Shih-Jen Hwang, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*, 478(7367):103–109, 2011.

Michael P. Epstein, Xihong Lin, and Michael Boehnke. Ascertainment-adjusted parameter estimates revisited. *Am. J. Hum. Genet.*, 70(4):886–95, 2002.

Ludwig Fahrmeir and Gerhard Tutz. *Multivariate Statistical Modelling Based on Generalized Linear Models*. Springer Series in Statistics. Springer New York, Berlin, 2nd edition, 2001. ISBN 978-0-387-95187-4.

Egil Ferkingstad and Håvard Rue. Improving the INLA approach for approximate Bayesian inference for latent Gaussian models. *Electron. J. Stat.*, 9(2):2706–2731, 2015.
Youyi Fong, Håvard Rue, and Jon Wakefield. Bayesian inference for generalized linear mixed models. *Biostatistics*, 11(3):397–412, 2010.

Andrew Gelman and Xiao-Li Meng. Simulating normalizing constants: From importance sampling to bridge sampling to path sampling. *Stat. Sci.*, 13(2):163–185, 1998.

David V. Glidden and Kung-Yee Liang. Ascertaintment adjustment in complex diseases. *Genet. Epidemiol.*, 23(3):201–208, 2002.

David V. Glidden and Eric Vittinghoff. Modelling clustered survival data from multicentre clinical trials. *Stat. Med.*, 23(3):369–88, 2004.

David Golan and Saharon Rosset. Effective genetic-risk prediction using mixed models. *Am. J. Hum. Genet.*, 95(4):383–93, 2014.

David Golan, Eric Lander, and Saharon Rosset. Measuring missing heritability: Inferring the contribution of common variants. *Proc. Natl. Acad. Sci. USA*, 111(49):E5272–81, 2014.

Tristan J. Hayeck, Noah A. Zaitlen, Po-Ru Loh, Bjarni Vilhjalmsson, Samuela Pollack, Alexander Gusev, Jian Yang, Guo-Bo Chen, Michael E. Goddard, Peter M. Visscher, et al. Mixed model with correction for case-control ascertainment increases association power. *Am. J. Hum. Genet.*, 96(5):720–730, 2015.

Patrick J Heagerty and Subhash R Lele. A composite likelihood approach to binary spatial data. *J. Am. Stat. Assoc.*, 93(443):1099–1111, 1998.

Leonhard Held, Isabel Natrio, Sarah Elaine Fenton, Håvard Rue, and Nikolaus Becker. Towards joint disease mapping. *Stat. Methods Med. Res.*, 14(1):61–82, 2005.

Brian D Hobbs, Margaret M Parker, Han Chen, Taotao Lao, Megan Hardin, Dandi Qiao, Iwona Hawrylkiewicz, Pawel Sliwinski, Jae-Joon Yim, Woo Jin Kim, et al. Exome array analysis identifies a common variant in IL27 associated with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.*, 194(1):48–57, 2016.

David A Hsieh, Charles F Manski, and Daniel McFadden. Estimation of response probabilities from augmented retrospective observations. *J. Am. Stat. Assoc.*, 80(391):651–662, 1985.

Duo Jiang, Joelle Mbatchou, and Mary Sara McPeek. Retrospective association analysis of binary traits: overcoming some limitations of the additive polygenic model. *Hum. Hered.*, 80(4):187–195, 2015.

Duo Jiang, Sheng Zhong, and Mary Sara McPeek. Retrospective Binary-Trait Association Test Elucidates Genetic Architecture of Crohn Disease. *Am. J. Hum. Genet.*, 98(2):243–255, 2016a.

Jiming Jiang, Cong Li, Debashis Paul, Can Yang, and Hongyu Zhao. On high-dimensional misspecified mixed model analysis in genome-wide association study. *Ann. Stat.*, 44(5):2127–2160, 2016b.
Julia E Kelsall and Peter J. Diggle. Spatial variation in risk of disease: a nonparametric binary regression approach. *J. Royal Stat. Soc. C*, 47(4):559–573, 1998.

Holly J Kramer, Adrienne M. Stilp, Cathy C. Laurie, Alex P. Reiner, James Lash, Martha L. Daviglus, Sylvia E. Rosas, Ana C. Ricardo, Bamidele O. Tayo, Michael F. Flessner, et al. African ancestry–specific alleles and kidney disease risk in Hispanics/Latinos. *J. Am. Soc. Nephrol.*, 28(3):915–922, 2017.

Malte Kuss and Carl Edward Rasmussen. Assessing approximate inference for binary Gaussian process classification. *J. Mach. Learn. Res.*, 6:1679–1704, 2005.

Sang Hong Lee, Naomi R. Wray, Michael E. Goddard, and Peter M. Visscher. Estimating missing heritability for disease from genome-wide association studies. *Am. J. Hum. Genet.*, 88(3):294–305, 2011.

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

Kung-Yee Liang and Scott L Zeger. Regression analysis for correlated data. *Annu. Rev. Public Health*, 14(1):43–68, 1993.

Po-Ru Loh, Gaurav Bhatia, Alexander Gusev, Hilary K Finucane, Brendan K Bulik-Sullivan, Samuela J Pollack, Teresa R de Candia, Sang Hong Lee, Naomi R Wray, Kenneth S Kendler, et al. Contrasting genetic architectures of schizophrenia and other complex diseases using fast variance-components analysis. *Nat. Genet.*, 47(12):1385–1392, 2015.

Charles F Manski and Daniel McFadden. *Alternative estimators and sample designs for discrete choice analysis*. MIT Press, Cambridge, MA, 1981.

Charles E McCulloch, Shayle R Searle, and John M Neuhaus. *Generalized, Linear, and Mixed Models*. Wiley Series in Probability and Statistics, 2nd edition, 2008. ISBN 0-470-01181-5.

Thomas P Minka. Expectation propagation for approximate Bayesian inference. In *Proceedings of the seventeenth conference on incertainty in artificial intelligence*, pages 362–369. Morgan Kaufmann Publishers Inc., 2001. ISBN 1-55860-800-1.

Gerhard Moser, Sang Hong Lee, Ben J. Hayes, Michael E. Goddard, Naomi R. Wray, and Peter M. Visscher. Simultaneous discovery, estimation and prediction analysis of complex traits using a Bayesian mixture model. *PLoS Genet.*, 11(4):e1004969, 2015.

J. M. Neuhaus, Alastair J. Scott, Chris J. Wild, Y. Jiang, C. E. McCulloch, and R. Boylan. Likelihood-based analysis of longitudinal data from outcome-related sampling designs. *Biometrics*, 70(1):44–52, 2014.

John M. Neuhaus and Nicholas P. Jewell. The effect of retrospective sampling on binary regression models for clustered data. *Biometrics*, 46(4):977–990, 1990.
John M. Neuhaus, Alastair H. Scott, and Chris J. Wild. The analysis of retrospective family studies. *Biometrika*, 89(1):23–37, 2002.

John M. Neuhaus, Alastair J. Scott, and Chris J. Wild. Family-specific approaches to the analysis of case-control family data. *Biometrics*, 62(2):488–94, 2006.

Hannes Nickisch and Carl Edward Rasmussen. Approximations for binary Gaussian process classification. *J. Mach. Learn. Res.*, 9:2035–2078, 2008.

Yukinori Okada, Di Wu, Gosia Trynka, Towfiqke Raj, Chikashi Terao, Katsunori Ikari, Yuta Kochi, Koichiro Ohmura, Akari Suzuki, Shinji Yoshida, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*, 506(7488):376–381, 2014.

Manfred Opper and Cédric Archambeau. The variational Gaussian approximation revisited. *Neural Comput.*, 21(3):786–92, 2009.

Manfred Opper and Ole Winther. Gaussian processes for classification: Mean-field algorithms. *Neural computation*, 12(11):2655–2684, 2000.

Dirk Pfeiffer. *Spatial Analysis in Epidemiology*. Oxford University Press, 2008.

Jos C Pinheiro and Douglas M Bates. Approximations to the log-likelihood function in the nonlinear mixed-effects model. *J. Comp. Graph. Stat.*, 4(1):12–35, 1995.

Jos C Pinheiro and Edward C Chao. Efficient Laplacian and Adaptive Gaussian Quadrature Algorithms for Multilevel Generalized Linear Mixed Models. *J. Comp. Graph. Stat.*, 15(1):58–81, 2006.

Alkes L. Price, Chris C. A. Spencer, and Peter Donnelly. Progress and promise in understanding the genetic basis of common diseases. *Proc Biol Sci*, 282(1821), 2015.

Qibin Qi, Adrienne M Stilp, Tamar Sofer, Jee-Young Moon, Bertha Hidalgo, Adam A Szpiro, Tao Wang, Maggie CY Ng, Xiuqing Guo, Yii-Der Ida Chen, et al. Genetics of type 2 diabetes in US Hispanic/Latino individuals: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Diabetes*, 66(5):1419–1425, 2017.

Yuan Alan Qi, Thomas P Minka, Rosalind W Picard, and Zoubin Ghahramani. Predictive automatic relevance determination by expectation propagation. In *Proceedings of the twenty-first international conference on machine learning*, page 85. ACM, 2004. ISBN 1-58113-838-5.

Sophia Rabe-Hesketh, Anders Skrondal, and Andrew Pickles. Generalized multilevel structural equation modeling. *Psychometrika*, 69(2):167–190, 2004.

Sophia Rabe-Hesketh, Anders Skrondal, and Andrew Pickles. Maximum likelihood estimation of limited and discrete dependent variable models with nested random effects. *J. Econom.*, 128(2):301–323, 2005.

Carl E. Rasmussen and Christopher K. I. Williams. *Gaussian Processes for Machine Learning*. The MIT Press, 2006. ISBN 978-0-262-18253-9.
Stephen W. Raudenbush, Meng-Li Yang, and Matheos Yosef. Maximum likelihood for generalized linear models with nested random effects via high-order, multivariate Laplace approximation. *J. Comp. Graph. Stat.*, 9(1):141–157, 2000.

Didier Renard, Geert Molenberghs, and Helena Geys. A pairwise likelihood approach to estimation in multilevel probit models. *Comput. Stat. Data Anal.*, 44(4):649–667, 2004.

Stephan Ripke, Benjamin M Neale, Aiden Corvin, James TR Walters, Kai-How Farh, Peter A Holmans, Phil Lee, Brendan Bulik-Sullivan, David A Collier, Hailiang Huang, et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, 511(7510):421–427, 2014.

AE Sanders, D Jain, T Sofer, KF Kerr, CC Laurie, JR Shaffer, ML Marazita, LM Kaste, GD Slade, RB Fillingim, et al. GWAS identifies new loci for painful temporomandibular disorder: Hispanic Community Health Study/Study of Latinos. *J. Dent. Res.*, 96(3):277–284, 2017.

Stephen Sawcer, Garrett Hellenthal, Matti Pirinen, Chris CA Spencer, Nikolaos A Patsopoulos, Loukas Moutsianas, Alexander Dilthey, Zhan Su, Colin Freeman, Sarah E Hunt, et al. Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature*, 476(7359):214–9, 2011.

Alastair J Scott and Chris J Wild. Fitting regression models to case-control data by maximum likelihood. *Biometrika*, 84(1):57–71, 1997.

Alastair J. Scott and Chris J. Wild. Maximum likelihood for generalised case-control studies. *J. Stat. Plan. Inference*, 96(1):3–27, 2001.

Matthias Seeger. Low rank updates for the cholesky decomposition. Technical report, 2004.

Stephen Senn. A note concerning a selection paradox of Dawid’s. *Am. Stat.*, 62(3):206–210, 2008.

Zhenming Shun and Peter McCullagh. Laplace approximation of high dimensional integrals. *J. R. Stat. Soc. B*, 57(4):749–760, 1995.

Luke Tierney and Joseph B Kadane. Accurate approximations for posterior moments and marginal densities. *J. Am. Stat. Assoc.*, 81(393):82–86, 1986.

Christian Timmann, Thorsten Thye, Maren Vens, Jennifer Evans, Jürgen May, Christa Ehnen, Jürgen Sievertsen, Birgit Muntau, Gerd Ruge, Wibke Loag, et al. Genome-wide association study indicates two novel resistance loci for severe malaria. *Nature*, 489(7416):443, 2012.

Cristiano Varin, Nancy Reid, and David Firth. An overview of composite likelihood methods. *Stat. Sin.*, 21(1):5–42, 2011.

Aki Vehtari, Tommi Mononen, Ville Tolvanen, Tuomas Sivula, and Ole Winther. Bayesian leave-one-out cross-validation approximations for Gaussian latent variable models. *J. Mach. Learn. Res.*, 17(1):3581–3618, 2016.
Likelihood for GPs under Case-Control Sampling

Peter M. Visscher, Naomi R. Wray, Qian Zhang, Pamela Sklar, Mark I. McCarthy, Matthew A. Brown, and Jian Yang. 10 years of GWAS discovery: biology, function, and translation. *Am. J. Hum. Genet.*, 101(1):5–22, 2017.

Omer Weissbrod, Christoph Lippert, Dan Geiger, and David Heckerman. Accurate liability estimation improves power in ascertained case-control studies. *Nat. Methods*, 12(4):332–4, 2015.

Omer Weissbrod, Dan Geiger, and Saharon Rosset. Multikernel linear mixed models for complex phenotype prediction. *Genome Res.*, 26(7):969–79, 2016.

Wellcome Trust Case Control Consortium et al. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*, 447(7145):661–678, 2007.

Chris J. Wild. Fitting prospective regression models to case-control data. *Biometrika*, 78(4):705–717, 1991.

Russ Wolfinger and Michael O’Connell. Generalized linear mixed models a pseudo-likelihood approach. *J. Stat. Comput. Simul.*, 48(3-4):233–243, 1993.

Minge Xie and Yaning Yang. Asymptotics for generalized estimating equations with large cluster sizes. *Ann. Stat.*, 31(1):310–347, 2003.

Jian Yang, Beben Benyamin, Brian P. McEvoy, Scott Gordon, Anjali K. Henders, Dale R. Nyholt, Pamela A. Madden, Andrew C. Heath, Nicholas G Martin, Grant W. Montgomery, et al. Common SNPs explain a large proportion of the heritability for human height. *Nat. Genet.*, 42(7):565–569, 2010.

Jian Yang, Noah A. Zaitlen, Michael E. Goddard, Peter M. Visscher, and Alkes L. Price. Advantages and pitfalls in the application of mixed-model association methods. *Nat. Genet.*, 46(2):100–106, 2014.

Jonathan Young, Marc Modat, Manuel J. Cardoso, Alex Mendelson, Dave Cash, Sebastien Ourselin, the Alzheimer’s Disease Neuroimaging Initiative, et al. Accurate multimodal probabilistic prediction of conversion to Alzheimer’s disease in patients with mild cognitive impairment. *Neuroimage Clin.*, 2:735–745, 2013.

Hao Zhang. Inconsistent estimation and asymptotically equal interpolations in model-based geostatistics. *J. Am. Stat. Assoc.*, 99(465):250–261, 2004.

Hao Zhang and Dale L. Zimmerman. Towards reconciling two asymptotic frameworks in spatial statistics. *Biometrika*, 92(4):921–936, 2005.

Xiang Zhou, Peter Carbonetto, and Matthew Stephens. Polygenic modeling with Bayesian sparse linear mixed models. *PLoS Genet.*, 9(2):e1003264, 2013.

Gabriel Ziegler, Gerard R. Ridgway, Robert Dahnke, Christian Gaser, the Alzheimer’s Disease Neuroimaging Initiative, et al. Individualized Gaussian process-based prediction and detection of local and global gray matter abnormalities in elderly subjects. *Neuroimage*, 97:333–348, 2014.