Generalized Mixed Modeling in Massive Electronic Health Record Databases: What is a Healthy Serum Potassium?

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Title:

Generalized Mixed Modeling in Massive Electronic Health Record Databases: what is a healthy serum potassium?

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Abstract:

Background: Converting electronic health record (EHR) entries to useful clinical inferences requires one to address the poor scalability of existing implementations of Generalized Linear Mixed Models (GLMM) for repeated measures. The major computational bottleneck concerns the numerical evaluation of multivariable integrals, which even for the simplest EHR analyses may involve millions of dimensions (one for each patient). The hierarchical likelihood (h-lik) approach to GLMMs is a methodologically rigorous framework for the estimation of GLMMs that is based on the Laplace Approximation (LA), which replaces integration with numerical optimization, and thus scales very well with dimensionality.

Methods: We present a high-performance implementation of the h-lik for GLMMs in the R package TMB. Using this approach, we examined the relation of repeated serum potassium measurements and survival in the Cerner Real World Data (CRWD) EHR database. Analyzing this data requires the evaluation of an integral in over 3 million dimensions, putting this problem beyond the reach of conventional approaches. We also assessed the scalability and accuracy of LA in smaller samples of 1 and 10% size of the full dataset that were analyzed via the a) original, interconnected Generalized Linear Models (iGLM), approach to h-lik, b) Adaptive Gaussian Hermite (AGH) and c) the gold standard of Markov Chain Monte Carlo (MCMC) for multivariate integration.

Results: Random effects estimates generated by the LA were within 10% of the values obtained by the iGLMs, AGH and MCMC techniques. The H-lik approach was 4-30 times faster than AGH and nearly 800 times faster than MCMC. The major clinical inferences in this problem are the establishment of the non-linear relationship between the potassium level and the risk of mortality, as well as estimates of the individual and health care facility sources of variations for mortality risk in CRWD.

Conclusions: We found that the combination of the LA and AD offers a computationally efficient, numerically accurate approach for the analysis of extremely large, real world repeated measures data

38 via the *h-lik* approach to GLMMs. The clinical inference from our analysis may guide choices of
39 threatment thresholds for treating potassium disorders in the clinic.

40

41 **Keywords:** Generalized Linear Mixed Models, Laplace Approximation, Adaptive Gaussian Hermite
42 Quadrature, Electronic Health Records, Dyskalemias, Markov Chain Monte Carlo

Background:

Electronic Health Records (EHR) have been adopted near universally in medical practices across the United States. They contain information about vital signs, lab results, medical procedures, diagnoses, medications, admissions, healthcare facility features (e.g., type, location and practice) and individual subject outcomes (e.g., death or hospitalizations). Due to the large number of patients, and the equally large number of features collected in each subject, EHR “big data” is increasingly being mined hoping to gain useful clinical insights that enhance patient safety, improve health care quality and even manage costs [1–4]. A unique feature of EHR data that complicates analytics is the repeated measures and unbalanced nature of the data, featuring multiple and unequal number of observations in individual patients (IP), seen by different healthcare practitioners (HCPs) across healthcare facilities (HCFs). However existing approaches to big data such as deep learning[5] overlook this feature of EHR data, missing on a unique opportunity to mine variation at the level of IP/HCPs or HCFs. Subject or healthcare facility focused inference requires the deployment of conventional Generalized Linear Mixed Models (GLMM) for the analyses of repeated measures at the group (IP/HCP/HCF) level. GLMMs can tackle the entire spectrum of questions that a clinical researcher would want to examine using EHR data. Such questions typically involve the analyses of continuous (e.g., biomarker values, vital signs), discrete (e.g., development of specific diagnoses), time to event (e.g., survival) or joint biomarker-discrete/time-event data.

Addressing these questions with GLMMs necessitates the evaluation of high-dimensional integrals, which even for the simplest EHR analyses may involve millions of dimensions (e.g., one for each patient). The implementation of GLMMs in existing statistical environments (e.g. SAS, R) has been shown to scale poorly, when repeated measures for more than a few thousand individuals are analyzed [6, 7]; due to the “curse of dimensionality” numerical integration is no longer tractable either analytically or numerically in these high dimensional spaces. This lack of scalability presents a major barrier in the

application of formal statistical methods to big datasets. Approximate methods for fitting large GLMMs within the computational constraints of standard multicore workstations [6–8] or even parallel architectures (e.g. LinkedIn’s GLMix[9]) have been proposed in the literature. Most commonly analyses rely on specific features of the datasets to speed up calculations through data partitioning and meta-analytic techniques[6]. Other proposals revisit older approaches to statistical inference by applying the method of moments during estimation [7], fitting the models through summary statistics[8] and revisiting unsophisticated but rather robust optimization methods such as coordinate block relaxation and the more recent reincarnation of stochastic gradient descent. Empirical analyses [7] demonstrates that such approaches invariably trade statistical efficiency for speed, effectively discarding valuable information hidden in big data. Finally, quantification of uncertainty about model estimates becomes extremely challenging theoretically and, in some cases, it is not addressed at all in publications (as in GLMix).

The ideal approach to the analyses of EHR big data with GLMMs, would seek to eliminate or reduce the need for statistically inefficient approximations, while retaining the rigor, numerical precision, and uncertainty quantification measures (e.g., standard errors) that one has come to expect and trust from analyses of small to medium sized data. In this work we show how these ideals can be retained in big data analytics, by deploying theoretically rigorous estimation methods for GLMMs in a computationally efficient manner. The theoretical background for achieving these goals is based on the *Hierarchical likelihood (h-lik)* approach to GLMM estimation[10–12]. The *h-lik* was initially introduced as a theoretical framework for understanding the statistical properties of GLMMs, and later received attention for numerical work. In the context of *h-lik*, the Laplace approximation (LA) is used to replace multivariate integration with optimization, paving the road for computationally efficient implementations that are uniquely suited to tackle the challenges posed by EHR big data. However this potential is not realized in current implementations of the *h-lik* because of the reliance on the original,

interconnected General Linear Model (iGLM) formulation [12] which can be challenging to correctly implement[13] and which we may not even for large numbers of random effects as we show below. In this work, we circumvent these limitations by directly implementing the *h-lik* method in the R package TMB[14]. TMB combines the LA for the numerical evaluation of multivariate integrals, with Algorithmic Differentiation (AD) for the fast calculation of objective (log-likelihood) functions. TMB itself implements an approximate estimation method for the marginal likelihood of GLMMs [15, 16] but to date has not been adopted to implement *h-lik* calculations. TMB provides the key missing ingredients for fast, scalable *h-lik* calculations: AD, parallel computations to speed up the most computationally challenging steps and built-in uncertainty quantification features.

Motivating example

The analyses reported in this paper were motivated by the following clinical considerations from the physician author's subspecialty (nephrology):

- Abnormalities in the serum potassium levels (K^+ , dyskalemia), i.e., either low (hypokalemia) or high (hyperkalemia) are commonly encountered in clinical practice[17]. Aberrations in serum potassium will in turn interfere with the electrical conduction and cell membrane function in many tissues, including muscle, bowel and heart leading to muscle weakness/small bowel ileus, cardiac arrhythmias and even death.
- The precise relationship of K^+ with mortality across the spectrum of kidney function, remains poorly defined. The largest to date repeated measures study in the US examined a cohort of 55,266 individuals from a single Managed Care organization in California[18]. It demonstrated a "U" shaped curve suggesting that mortality was higher for both hypokalemia and hyperkalemia. However, this analysis was limited in examining outcomes from a single health care organization and discretized the K^+ measurements prior to analysis. Therefore, a continuous risk relationship that generalizes across the entire United States is difficult to infer from this publication.

- This lack of precision limits rational use of both potassium replacement in patients with low K^+ (hypokalemia) and potassium binding drugs in those with elevated K^+ (hyperkalemia). Existing and emerging therapies for hypertension[19], congestive heart failure[20–22] and therapies for diabetic kidney disease[23, 24], require the use of drugs e.g. the mineralocorticoid receptor antagonists that will variably elevate the potassium level[25]. By leveraging the EHR we hope to inform future practice guidelines for the management of potassium disorders in clinical practice. For example, these guidelines could link initiation of therapies to treat dyskalemias to the prevailing K^+ level, using the risk relation identified in real world data to specify treatment thresholds.

Contributions

These can be summarized as follows:

- 1) We provide a roadmap for the direct, accurate and scalable implementation of GLMMs using the *h-lik* approach. This implementation effectively maps the core concepts of the statistical theory behind *h-lik*, to calls to software libraries that use the LA to approximate marginal likelihoods. Rather than having to worry about manually encoding a high-performance implementation, the analyst can leave the numerical subtleties to be decided by the library. This implementation is scalable enough to be deployed in standard multicore workstations available to most clinical epidemiologists and as we show below yields answers to clinically meaningful questions in an acceptable timescale. Using real world big data, we show that the results obtained by our implementation are very similar to those obtained via theoretically more accurate techniques for GLMM estimation, i.e. Adaptive Gaussian Hermite (AGH) or Markov Chain Monte Carlo (MCMC) or even the original iGLM approach to the *h-lik*.
- 2) We demonstrate the deployment of *h-lik* to fit Poisson GLMMs in datasets derived from the Cerner Healthfacts Electronic Health Record (EHR) database (now referred as Cerner Real World Data and abbreviated as “CRWD” in this work). Cerner is one of the major EHR used in the United States. It

contains laboratory, clinical and outcomes data from nearly a third of US healthcare facilities over a period of more than 10 years.

3) We address the gap in the clinical knowledge about the relation between K^+ with mortality adjusting for the effect of kidney function on this relation.

4) We quantify the interindividual and healthcare facility variation around the curve that relates the K^+ level to survival. Assessment of such variability is a major advantage of GLMMs over other analytical approaches, e.g., deep learning and has implications for both policy and clinical practice.

This paper is organized as follows. In the methods section we introduce CRWD and the dataset used for our analyses. We will also review *h-lik* for GLMMs, and alternative methodologies for estimating GLMMs (AGH and MCMC) , the original (iGLM) approach for fitting the *h-lik* and describe our own implementation of the *h-lik* calculations in the R package TMB. In the results section we compare the results obtained by TMB and the referent GLMM implementation in R using iGLMs, AGH and MCMC.

Unlike the direct implementation of the *h-lik* we consider here, these three alternatives have difficulties in running to conclusion within a reasonable time scale when used in big datasets. Therefore, we used small random samples (1% and 10%) of the complete dataset to compare our method against competing approaches. After contrasting these alternatives, we will then present our analyses of the clinical scenario focusing on the relative risk of an abnormal K^+ level adjusting for the prevailing level of renal function (eGFR), as well as individual and facility sources of variation. We conclude by considering the impact of the proposed computational methodology for EHR big data, applications outside the narrow field of EHR analytics, and the path towards fully parallel implementations of the *h-lik* approach for GLMMs. Parts of this work have been presented in preprint [26] and in abstract/poster form presented during the American Society of Nephrology 2018 meeting [27].

Methods

Cerner Real World Data.

Cerner is a comprehensive source of de-identified, real-world data that is collected as a by-product of patient care from over 700 healthcare facilities across the United States. The relational database contains clinical records with time-stamped information on pharmacy, laboratory, admission, and billing data for over 69 million unique patients. Types of data available include demographics, encounters, diagnoses, procedures, lab results, medication orders, medication administration, vital signs, microbiology, surgical cases, other clinical observations, and health systems attributes. Detailed pharmacy, laboratory, billing, and registration data go back as far as 2000 and contain more than 630 million pharmacy orders for nearly 3,500 drugs by generic name and brand. The two largest tables in the database contain more than 4.3 billion laboratory results and 5.6 billion clinical events linked to more than 460 million patient visits. For our analyses, we used the entire CRWD from inception until September 1st, 2016 and extracted the first K⁺ measurement that had been obtained within 24 hours of a clinical encounter. We restricted attention to adult (older than 18-year-old) patients who were not receiving chronic dialysis and had received at least two K⁺ measurements in two clinical encounters. Individuals were observed until the resolution of the clinical encounter for a total of 29,787,791 days (~81,610 patient years). After excluding missing data, this dataset included 9,935,812 observations in 3,123,457 individuals and 327 facilities. During the observation period there were 48,578 deaths, corresponding to an event rate of 59.5/100 patient years. The median/interquartile range number of repeated observations per patient were 2/1 (mean and standard deviations were 3.18/2.72) and only 25% of patients had three or more repeated measurements. The limited number of observations per patient, a-priori disadvantages the LA, since the latter requires many more observations per individual to converge. Most patients in our analyses had observations from a single HCF (2,886,375/3,123,457 or 92.4%). Hence, even though most patients were “nested” inside HCF, those who had “crossed” to

multiple facilities complicate analyses when random effects at both the IP and the HCF facility are considered.

Modeling the risk of dyskalemia in CRWD via Poisson GLMM.

The data y_i for these analyses were death events ($y_i = 1$) recorded in CRWD. This outcome was modelled as a Poisson variable, by exploiting the link between Poisson models and analysis of survival time [28], using the duration of each clinical encounter as an offset. Predictors that were coded as *fixed effects* included the K⁺ level, the Charlson Comorbidity Index, a well validated instrument of the comorbid conditions affecting an individual, the prevailing level of kidney function (estimated Glomerular Rate, eGFR, computed by the validated CKD-Epi formula), patient's age, type of healthcare facility (e.g., hospital, nursing home, outpatient clinic), patient's age, race and gender. Natural splines were used to probe non-linear relationships between the outcome of interest, kidney function (eGFR) and the potassium level as well as age. During the comparative evaluation of methods for fitting the dataset, we run two separate analyses with different random effects specifications: one in which the grouping level was the individual (IP) and one in which the grouping level was the facility (HCF). These analyses allowed us to explore the scaling of performance of various estimation methods for GLMMs against the increasing dimensionality of the problem. The latter is largely determined by the number of random effects, since the vector of fixed effect coefficients is low dimensional, i.e., $p=18$ in all analyses. Clinical inference about the relation between the K⁺ level and the risk of death was based on the full dataset using random effects at both the IP and HCF level.

GLMMs estimation requires high-dimensional integrations.

Let y_i , $i = 1 \dots n$ denote data and let x_i and z_i stand for vectors of covariates for each data element (IP) in the model. The x_i vector is multiplied by the global ("*fixed effects*") p dimensional coefficient vector β that models the overall response, while the z_i by a group specific, q dimensional vector u of random effects. In the simplest case, the random effects feature vector indicates the group membership of the

data, e.g., which observations came from the same individual, but more complex scenarios are possible dependent on the repeated measures and clustering structure of the data. A GLMM is defined by the following properties:

1. The probability density function of the data ($f_{Y|U}$), conditional on the random and fixed effects vectors, is a member of the exponential family. The nature of the data determines the exponential family, e.g. for binary classification this would be the binomial distribution, for continuous data the Gaussian distribution, and for the analysis of time-to-event or counts of events (as in the present case) the Poisson distribution[28].

2. The expectation of the data μ_i conditional on the random effects is given by the equation:

$g(\mu_i) = x_i^T \beta + z_i^T u$. The function $g(\cdot)$ is the *link* function and is determined by the nature of the regression e.g., it is the logistic map for binary classification, or the logarithmic function when modeling count data. The variance of the data is determined as a product of a *dispersion parameter* (conventionally indicated as ϕ) and a variance function that is strictly a function of the conditional mean. For the Poisson GLMM we are considering here, the dispersion parameter is equal to one and the variance function is equal to the mean (see Table in p45 of [12] for variance functions of other generalized models). For the remainder, and without loss of generality we will assume that the dispersion parameters are known.

3. The random effects vector is assumed to have a zero mean multivariate normal distribution and covariance matrix $G = G(\gamma)$ where γ are the *variance* components, i.e., $f_{U|\gamma} \sim N(0, G)$. We stress that the specification of random effects in the *h-lik* is not restricted to the normal distribution, yet this choice is implicitly made in the comparator AGH methods.

Learning in a GLMM context corresponds to estimating the values of the variance components (γ), the fixed (β) and the random effects (u). *Maximum likelihood estimation* (MLE) for the variance components and the fixed effects involves maximization of the marginal likelihood $L(\beta, \gamma)$:

$$\max_{\beta, \gamma} L(\beta, \gamma) = \max_{\beta, \gamma} \int \exp(\log f_{Y|U} + \log f_{U|\gamma}) du \quad (1)$$

The integral in (1) is typically over the high dimensional space of the random effects and can only be approximated numerically. In particular, evaluation of such integrals in closed form are typically available for only a few combinations of random effects and response distributions. *Quadrature* approximations replace integrals via *weighted* sums over predefined abscissas (“nodes”) that are placed over the domain of integration. The quality of the approximation and the computational resources required to evaluate the integral will scale up with the number of nodes (order) used by the quadrature rule. However, the *curse-of-dimensionality* makes the use of higher order (more accurate) approximations impractical: applying an l order rule in m dimensions will require m^l evaluations of the integrand $\exp(\log f_{Y|U} + \log f_{U|\gamma})$, thus quickly exhausting computational resources. Integration of GLMMs in most statistical computing environments is based on *Adaptive Gauss-Hermite* quadrature[29–32]. In contrast to its non-adaptive version that places the nodes around zero, AGH carefully *centers* the location of the nodes by finding the values of the random effects (conditional modes, $\hat{u}$) that maximize the function $\log f_{Y|U} + \log f_{U|\gamma}$ and *scales* them according to the curvature of that function around its mode. These scaling factors are determined from the second derivatives (entries of the Hessian matrix) of $\log f_{Y|U} + \log f_{U|\gamma}$ around its maximum. While a significant advance in numerical mathematics for GLMMs, the combination of MLE and AGH is not exactly problem free:

- a. AGH is still as subject to the curse of dimensionality as the non-adaptive versions of Gaussian quadrature: it provides a more efficient way to spend one’s fixed computational budget, by focusing on the area of the integrand that is substantially different from zero. For all intents and

purposes, estimation of GLMMs with large number of random effects will be limited to a single node (AGH1) which is just the Laplace Approximation see ([33–35] and below)

- b. The variance components will often be estimated with considerable bias, especially for discrete outcome (e.g. logistic or Poisson) models and few observations per random effect [13, 36], leading to proposals that replace MLE with Restricted Maximum Likelihood (REML) estimation[37, 38]. REML maximizes the integral $\int \exp(\log f_{Y|U} + \log f_{U|Y}) du d\beta$ and reduces the bias when estimating the variance components. However, REML also requires the evaluation of a multidimensional integral, and thus its use is typically limited to linear mixed models. In the latter case, REML is available in closed form. Nevertheless, the H-likelihood of the next section directly applies the REML when estimating non-Gaussian GLMMs, forcing the analyst to consider the numerical evaluation of multivariate integrals.

H-likelihood for GLMMs

The *h-lik* is a statistical procedure for estimating GLMMs, in which the relevant calculations proceed in stages[10, 10, 11, 38, 39]. The starting point for *h-lik* is the *joint* likelihood of the data i.e., the product of $f_{Y|U}$ and $f_{U|Y}$. The *h-likelihood function* (h) is the logarithm of this product and it is the object used during computations [11] that are based on the function class $p_w(l(h))$ defined as:

$$p_w(l(h)) = \left[l(h) - \frac{1}{2} \log | -H(l(h), \hat{w}) / 2\pi | \right]_{w=\hat{w}} \quad (2)$$

where $l(h)$ is a functional of the h-likelihood function, $|\cdot|$ is the determinant, $H(l(h), \hat{w})$ is the Hessian (matrix of second derivatives) of the function $l(h)$ with respect to the argument w , evaluated at the point $\hat{w}$ verifying the (non-linear) system of the score equations $\partial l(h) / \partial w = 0$. The functional $l(h)$ depends on the nuisance parameters w , as well as other parameters of inferential interest, i.e., $l(h) = l(h(q, w))$. In the context of the statistical theory, $p_w(l(h))$ is an adjusted profile log-likelihood [40] that

allows the elimination of the nuisance effects w , through marginalization (random effects) or conditioning (fixed effects)[11]. These eliminations are required during steps 1-2 of the *h-lik* inferential procedure:

1. Inference about the variance components is based on the conditional density:

$$y|\hat{\beta}, \gamma \sim \exp(\log L(\beta, \gamma)) / \exp(\log L(\hat{\beta}, \gamma)) \quad (3)$$

with $\hat{\beta}$ the maximizer of the marginal likelihood in (1). This conditional density approximates the REML functional $\iint \exp(\log f_{Y|U} + \log f_{U|Y}) du d\beta$ [12].

2. Inference about the fixed effects is based on the marginal likelihood $L(h) = L(\beta, \gamma)$.
3. Inference about the random effects is based on the *h-likelihood function* $h(\beta, \gamma, u) = \log f_{Y|U} + \log f_{U|Y}$.

While optimization of the *h-likelihood* function is straightforward, multivariate integrations are required when making inferences about the fixed effects and variance components. Computationally the *h-lik* uses the LA to carry out the relevant integrations for the restricted (3) and marginal likelihoods, thus replacing multivariate integration by the much simpler problem of numerical optimization. For a general p dimensional integral, the LA for a function in the variables q , $I(q)$, defined via the integral of an exponentiated function $h(q, w)$, over the variables w , is given by:

$$I(q) = \int \exp(h(q, w)) dw \approx (2\pi)^{p/2} \exp\left(h(q, \hat{w}_q)\right) \left| -H(h, \hat{w}_q) \right|^{-1/2} \equiv \exp(p_w(h)) \quad (4)$$

where $\hat{w}_q$ is the optimum of the function $h(q, w)$ for a given value of q and $| -H(h, \hat{w}_q) |$ is the determinant of the Hessian matrix of the function $h(q, w)$ with respect to w , evaluated at the optimum. Direct comparison of (2) and (4) shows that the adjusted profile likelihood used by the *h-lik* is the logarithm of the LA to the integrals defining marginal likelihoods. The relevant profile likelihoods used by *h-lik* to estimate the fixed effects and the variance components are denoted by $p_u(h)$ and $p_{u,\beta}(h) \approx$

$p_{\beta}(\log L)$ respectively. The predicted values of the random effects may be derived as conditional expectations given the observed data (BLUP: Best Linear Unbiased Predictor). The values of these may also be obtained by optimizing the h-likelihood function $h(\beta, \hat{\gamma}, u)$ given β and the estimate of the variance parameters $\hat{\gamma}$ [10]. Applying the LA to compute the $p_u(h)$ obtains estimates of the BLUPs for “free”.

The interconnected GLM algorithm for H-likelihood estimation

While the theory of the *h-lik* is presented in terms of the LA, the actual numerical computations as introduced [10] and latter extended by numerous authors [11, 12, 41] is based on an additional approximation. Specifically, an Extended Quasi-Likelihood (EQL) approach [42] is used to model the mean and the variance of the response variable (y) and the random effects (u). Replacing the original GLM of the response variable and the probability density random effects by an approximation based on their first two moments, would appear a poorly justified choice given the loss of accuracy and potential for bias. However, this choice also allows the analyst to use the deviance (residuals) of a Generalized Linear Model (GLM) as data. This feature of the EQL reduces estimation of fixed, random effects, dispersion parameters and variance components to a clever, iterative fitting algorithm of interconnected GLMs (iGLM, see Chapter 7 in [12] and the documentation of the R implementations[43, 44]). The steps of this algorithm are:

1. Initialize starting values for β, u, γ and ϕ (if the GLM for the response includes a dispersion)
2. Construct an augmented model with $y_{aug} = \begin{pmatrix} y \\ E(u) \end{pmatrix}$, by stacking the observed data y and the expected values (mean) of the random effects $E(u)$. In the case of multivariate normal effects these expectations are identically zero.
3. Construct the double EQL approximation to the components $\log f_{Y|U}$, $\log f_{U|Y}$ of the *h-likelihood* function.

4. Fit the EQL approximation to the augmented data, by using the Iterative Weighted Least Squares (IWLS) algorithm for estimating GLMs. In this augmented GLM, each element of the augmented response is weighted inversely by a dispersion parameter. The latter is equal to ϕ_i for y_i and to the corresponding diagonal element of the covariance matrix $G(\gamma)$ of the random effects.
5. Compute the deviances d_i and leverages h_i for the augmented model using the corresponding formulas implied by the EQL approximation in Step 3. Form the adjusted deviances $d_i^* = d_i/(1 - h_i)$ and prior weights $(1 - h_i)/2$ for each augmented observation.
6. If the model includes a dispersion parameter, use the adjusted deviances and weights corresponding to the y component of y_{aug} to fit a Gamma GLM. Per EQL, the mean and variance of this gamma GLM will be related to the unknown dispersion parameter as: $E(d_i^*) = \phi_i$ and $var(d_i^*) = 2\phi_i^2/(1 - h_i)$. For a model with single dispersion parameter, all ϕ_i are equal to this unknown parameter. However, the model is more general, and one can use it to specify a regression on the dispersion to yield a structured dispersion model. Fitting this gamma GLM will thus yield an updated estimate for the dispersion components.
7. A Gamma GLM is then fit to the adjusted deviances and prior weights corresponding to the random effects' component of the augmented response to obtain updated estimates for the variance components. For models with multiple, single random effects components (e.g. independent univariate normal distributions), one can fit these Gamma models (one for each random component) sequentially, or deploy a regression structure to estimate them all together. Upon convergence, one obtains the appropriate diagonal entries in the covariance matrix $G(\gamma)$.
8. Iterate steps 4-7 until values no longer change and obtain standard errors using the final iteration of the IWLS for each GLM fit.

346 Variations of this algorithm have been proposed to correct for errors introduced by the various
347 approximations and the dependence of the random effects on dispersion parameters [12, 13, 39]. If
348 correctly implemented, the iGLM approach is very fast to converge, as is typical of block-coordinate
349 optimization algorithms[45, 46], in which one keeps certain parameters fixed, while sequentially
350 updating others and cycling through the parameter list until estimates no longer change.

351 Pitfalls in the high performance implementation of the iGLM have been previously described [13] : they
352 include errors in the implementation of the update equations and the derivatives (gradients) for the
353 various GLMs, sparse representations for the matrices appearing in the gradients and updating
354 equations, numerical imprecisions when finite differences are used to calculate the gradients and the
355 large computational burden if finite differencing is used to calculate the Hessian, from which standard
356 errors of estimates are computed. Current implementations of the iGLM algorithms are available in R
357 package hglm[43] and the (archived) package HGLMMM[44] as well as GenStat. To our knowledge, a
358 scalable, direct implementation of the hierarchical likelihood estimation for GLMMs that is not based on
359 the rather complex, error-prone coding of the iGLM algorithm has not been reported. Our
360 implementation designated as *h-lik* for the remainder of this paper is discussed below.

361 **A scalable implementation of the *h-lik* using AD and the LA.**

362 For a software implementation of *h-lik* to align with the corresponding methodology, it is only required
363 that inferences about the variance components be based on $p_{u,\beta}(h)$ and for the fixed and random
364 effects on $p_u(h)$ and h respectively. To implement *h-lik* for very large datasets, one needs ways to
365 calculate and optimize general functions of the form $p_w(h)$ in a manner that scales favorably with
366 problem size. Scalability is afforded by a) bypassing finite differences for gradients during numerical
367 optimization of the adjusted profile likelihoods, b) automatic detection of the sparsity (zero elements) in
368 the Hessian and gradient matrices used in the optimization and c) parallelization of calculations of the

value of the log-likelihood. The availability of all three features would free the analyst to concentrate on model (or equivalently the joint likelihood) specification and let the computer organize calculations in an efficient, expedient manner.

The benefits of AD in this context are clear: a) the gradients used during optimization are computed with numerical accuracy that rivals that of hand-coded analytical expressions b) computational cost for obtaining these gradients is of the same order as evaluating the original function (in contrast to finite differencing, in which the cost increases with the number of dimensions) [47–49] c) optimized software code for the Hessians also becomes available to the analyst at zero cost. The benefit of automatic generation of code for the Hessian is two-fold a) it allows the use of second order optimization methods (e.g., Newton algorithm) and b) provides standard errors for estimated parameters, by computing the Hessian computed at the optimum. For GLMM applications, the Hessian matrix will be a sparse one (i.e., only a few entries will be non-zero). Computer science algorithms such as graph coloring[50, 51] can be used to automatically detect the sparsity pattern of the Hessian *for each specific dataset* analyzed and tremendously speed up calculations and reduce memory requirements by ignoring elements that are zero.

Scalable optimization of marginal likelihoods as previously outlined, was initially proposed in the context of MLE (rather than REML) estimation for mixed models [15, 16] and provided the initial use case of the R library TMB [14]. *Implementation* of any statistical model in TMB requires the writing of code in two languages: C++ and R. Using C++ macros, the user specifies the joint log-likelihood, receives parameters, random effects, data, and initial values from R. R is used to prepare data, generate initial values, generate a computational tape (see below), invoke the optimizer, and post process the results. An analyst can use TMB to correctly implement *h-lik* by following a few simple steps:

391 1. Specify the *h-likelihood function* $h(\beta, \gamma, u)$ in C++ and compile it into a dynamic library. This is done
392 only once since the dynamic library may be used with different data for the same general model.
393 Hence TMB code for GLMMs is reusable across application domains.

394 2. Generate a computational graph (“tape”) of the calculations required to analyze a *specific* dataset
395 designating parameters as either fixed or random by calling the TMB package from within R. During
396 tape generation, explicit dependencies between the parameters are identified by TMB and code is
397 automatically generated for the evaluation of the gradient of the log-likelihood and its Hessian.

398 3. Call an optimizer of one’s choice which repeatedly evaluates the adjusted profile likelihood and its
399 gradient until convergence (we typically used a constrained quasi Newton method for the variance
400 components and unconstrained quasi Newton for fixed effects). During this optimization, TMB will
401 internally calculate the values of the parameters that are being eliminated by the profile likelihood
402 using a second order optimization method (Newton’s algorithm). Constraining the variance
403 components to be greater than zero is typically required only if these parameters are close to the
404 boundary value of zero, otherwise one may use any unconstrained optimization algorithm.
405 Regardless of the choice of the optimizer, the latter must be able to utilize gradients (computed by
406 AD) and fully leverage the potential of our implementation.

407 4. Runs the *report* function of TMB from within R to generate standard error of all estimates to
408 quantify uncertainty upon convergence. There are various ways to generate these standard errors of
409 variable speed and potential accuracy: a) numerically invert an estimate of the Hessian, obtained in
410 step 3 if a quasi-Newton optimizer (e.g., BFGS) was used for step 3 (this is the approach we followed
411 here), b) numerical (finite differencing) differentiation of the Jacobian and c) multiplication of the
412 Jacobian from the last point prior to convergence with its transpose.

413 In our direct implementation of the *h-lik* in TMB, steps 2 and 3 must be called twice. First, we integrate
414 over β, u by designating both as “random” when generating the tape. Using this tape during

optimization amounts to optimizing $p_{u,\beta}(h)$ to obtain a point estimate (and a covariance matrix) for the variance components. Then fixing the value of the variance components, one generates the tape a second time designating only u as random. Optimizing this tape, is equivalent to optimizing $p_u(h)$ to obtain point estimates and covariance matrices for the fixed and random effects. In the *h-lik* theory, a third optimization conditional on the values of the variance components and the fixed effects would be required to value of the random effects. We forwent this step, by noting that the estimates of u from the LA to $p_u(h)$ will often be numerically similar those obtained from the conditional maximization of the hierarchical likelihood. The major bottlenecks in large datasets involve the computation of the determinant of the Hessian e.g., through a sparse Cholesky decomposition in (3) and the evaluation of the joint log-likelihood. In our analyses we used the high performance implementation of the BLAS libraries[52] (MKL[®] by Intel that are distributed with Microsoft R Open) as suggested by the creators of the TMB package. We also evaluated the speed up afforded by the parallel calculation of the *h-likelihood* function, a feature which is natively supported by TMB in multicore platforms through OpenMP.

It has been previously pointed [11, 13, 53] out that the *h-lik* approach can be viewed as an approximation to a Bayesian analysis that uses non-informative priors for the fixed effects , dispersion parameters (if they are not known) and variance components. This connection allows one to check any method implementing the *h-lik* (e.g., the iGLM or our direct implementation) by comparing its computations against those obtained by MCMC integration of the corresponding Bayesian model. While MCMC may be considered the gold standard for high dimensional integration, it is a much more computationally demanding technique. Hence, while one can apply MCMC to small problems, one will wait for a very long time for MCMC to finish for datasets of the size we are considering. However, one can compare the results in smaller datasets that are representative of the big dataset. Such datasets may be obtained by simple random sampling without replacement from the final dataset that one would like to analyze.

Comparative evaluations

To compare different approaches (AGH, iGLM, and the direct implementation of *h-lik*) for the integration of marginal likelihoods in GLMMs, we randomly sampled our full dataset and created two subsets that included 1% and 10% of patients. We used the R package lme4 [54] for AGH based inference (function glmer) and utilized quadrature with 1, 5 and 9 nodes to explore the tradeoffs incurred between accuracy and speed. Note that the LA is formally equivalent to an AGH with a single quadrature node, so that the comparison between AGH1 and *h-lik* reflect the speedup due to the LA/AD combination. Bayesian analyses were carried out by invoking the Poisson GLMM in the STAN programming language [55] as implemented in the R package rstanarm [56]. Like TMB, STAN codes the statistical model into a C++ language template, which is also compiled into a dynamic library that implements the calculations for the posterior probability kernel of the model. In this case, the kernel coincides with the *h-likelihood* function. STAN also utilizes AD to compute the gradient of the model that are used during MCMC with the No U Turn Sampler [57]. Therefore, the comparison against STAN allows an assessment of the accuracy-speed trade-off of MCMC against the *h-lik* computations when the latter are interpreted as modal approximations to a full Bayesian analysis.

Hardware and timing

Timing information was generated in a high-end consumer workstation equipped with the i7-5960x octacore Intel Processor equipped with 32 GB of DDR4 RAM clocked at 2133MHz. The base frequency of the i7-5960x is at 3GHz, but the processor was overclocked to 3.8 GHz for the timing experiments. For the analyses of the full dataset, we utilized a Dual 16-core Xeon Gold 5218 clocked at 2.3 GHz (turbo single core frequency of 3.9 GHz) equipped with 512GB of DDR4 RAM (clocked at 2666MHz) running Windows 10 Pro for Workstations. Large memory requirements did not allow us to fit the parallel version to the full dataset, even in this large memory machine. For the comparative evaluation of

execution timing in the smaller datasets we ran the iGLM and the parallel TMB analyses thrice on the i7-5960x and the Xeon. To compare parallel and serial implementations of the *h-lik* in the TMB environment, we ran analyses of the 1% and 10% datasets on the i7-5960x using both parallel and serial versions of the code that incorporated the two random effects. In addition, we run all three datasets with the serial code on the dual Xeon. Analysis of variance was used to explore the relative impact of dataset size, parallel vs serial version of the code and computing platform, on execution (“wall”) times. We collected timing information for all the steps of the TMB *h-lik* calculation e.g., the generation of the tape, optimization, and calculation of the Hessian at convergence, only the total wall time is reported. All analyses were run using Microsoft R Open v 3.5.3 and v4.02 and TMB package v1.7.14-1.7.15.

Results:

Estimates of *h-lik* against AGH and MCMC based methods for single random effects Poisson models.

Analyses of the 1% and 10% datasets with glmer generated warnings about at least one non-positive definitive Hessian matrix suggesting that the optimization algorithm got stuck close to the true global optimum. Furthermore, AGH1 failed to converge at all, when the measurements were grouped at the IP level. In contrast to previous reports [6], we could obtain a solution from glmer for the 10% dataset for very large number of random effects but only if the AGH5 or AGH9 method were used. Convergence failure of the AGH1-9 methods implied that their estimates may not be reliable. We thus considered an alternative: a “zero” order method that is also available from within glmer [7]. This method effectively ignores the integral for the random effects and thus its estimates will contain a variable and unknown amount of bias. Nevertheless, this approximation usually converges without warnings as we found in our datasets. The results of the direct implementation of *h-lik* with TMB, AGH0, and AGH9 are shown in **Figure 1** as estimate (point) and 95% confidence interval for the two groupings and the two datasets. In

general, the estimates of our *h-lik* implementation were numerically similar to the AGH methods, suggesting that the nonconvergence reported by the latter would not affect inferences about the fixed effects. The difference among the different methods lies within the uncertainty of the estimate from each method; in fact, estimates were identical for most covariates up to two significant digits. Nevertheless, there were substantial differences among the methods when the estimate of the single variance component was examined. **Table 1** shows the estimates for the direct implementation of *h-lik* in TMB, the iGLM implementation in the R package *hglm*, AGH0 and AGH9. The variance of the estimates could not be obtained for the AGH methods and thus are not reported. Furthermore, we could not fit the iGLM to any dataset with IP random effects due to large memory requirements (i7-5960x) and numerical errors in platforms not limited by memory (Xeon).

Table 1 : Estimates of the standard deviation of the variance components for single random effects Poisson models.

Dataset	Group	h-lik	iGLM	AGH0	AGH9
1%	Individual	0.306 (0.289)		0.253	0.260
10%	Individual	0.469 (0.074)	—	0.505	0.504
1%	Facility	0.422 (0.085)	0.395 (0.047)	0.401	0.414
10%	Facility	0.703 (0.061)	0.669 (0.042)	0.699	0.701

Increasing the size of the dataset results in a greater agreement among the three methods and reduction in the magnitude of uncertainty in the estimates of the proposed *h-lik* method. Estimates by the AGH5 method were identical to the AGH9 to three significant digits (not shown). Bayesian analyses may be considered the benchmark against which other methods of integration for GLMMs should be judged. However only the 1% dataset with grouping at the facility level could be fit in reasonable time (see timing below). The Bayesian point estimate (posterior mean) of the variance component was 0.426

(standard deviation 0.089), an estimate that was in rough agreement with the estimates generated by all the methods in **Table 2** but was numerically closer to the direct *h-lik* estimate of 0.422. The Bayesian model estimates (posterior mean and standard deviation) for the fixed effects against the direct *h-lik* and iGLM implementations are shown in **Table 2**. Point estimates and standard errors returned by the two *h-lik* implementations were in close numerical agreement. Many of the MCMC estimates, including the coefficients for the natural splines used to model the effects of age and eGFR were close to those obtained by the *h-lik* implementations. Notable exceptions were the coefficient for some of the racial groups and the coefficients for the natural splines of the potassium level. Despite the differences in the numerical values of the spline coefficients, the splines estimated by the proposed *h-lik* implementation and the MCMC method were nearly identical (**Figure 2**).

Table 2 : Fixed effect estimates, summarized by the mean(standard error) from Bayesian and h-lik (as implemented in this paper and the iGLM algorithm) analyses for the 1% dataset with grouping at the facility level.

Fixed Effects	Bayesian (MCMC)	h-lik	iGLM
Intercept	-6.214 (0.961)	-6.218 (0.994)	-6.168 (0.992)
Potassium (natural spline coefficient 1)	8.062 (1.979)	6.808 (2.462)	6.805 (2.461)
Potassium (natural spline coefficient 2)	-38.03 (31.12)	-9.491 (40.24)	-10.00 (40.23)
Potassium (natural spline coefficient 3)	-75.33 (61.7)	-18.50 (79.78)	-19.51 (79.76)
eGFR (natural spline coefficient 1)	-0.406 (0.255)	-0.43 (0.251)	-0.435 (0.251)
eGFR (natural spline coefficient 2)	-1.872 (0.492)	-1.839 (0.505)	-1.839 (0.505)
eGFR (natural spline coefficient 3)	-1.141 (0.502)	-1.091 (0.509)	-1.089 (0.509)
Age (natural spline coefficient 1)	0.305 (0.332)	0.309 (0.329)	0.306 (0.329)
Age (natural spline coefficient 2)	-0.086 (0.938)	-0.227 (0.913)	-0.227 (0.913)
Age (natural spline coefficient 3)	0.924 (0.199)	0.906 (0.198)	0.902 (0.198)
Male Gender	0.214 (0.093)	0.214 (0.093)	0.214 (0.093)
White Race	0.155 (0.143)	0.158 (0.146)	0.160 (0.145)
Hispanic Race	-0.745 (0.853)	-0.457 (0.723)	-0.452 (0.723)
Native American	-0.233 (0.829)	0.031 (0.731)	0.040 (0.730)
Other Race	-0.618 (0.321)	-0.580 (0.323)	-0.571 (0.322)
Unknown Race	-0.347 (0.488)	-0.242 (0.472)	-0.238 (0.471)
Inpatient status	2.404 (0.198)	2.390 (0.194)	2.397 (0.194)

Charlson Comorbidity Score	0.098 (0.014)	0.099 (0.014)	0.099 (0.014)
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The predicted random effects for the 1% dataset grouped at the facility level obtained by all non- Bayesian methods were rather like those obtained by MCMC (

Figure 3), as evidenced by the high correlations. Bland Altman plots (lower diagonal panels in **Figure 3**) indicated that the difference between *h-lik* and the other methods were within 10% of each other.

In summary, all methods appear to generate similar estimates for the fixed effects, rather similar estimates of the variance components, with the proposed direct *h-lik* implementation demonstrating the closest numerical agreement to MCMC.

Timing comparisons between *h-lik* and the AGH methods for single random effect models

Figure 4 contrasts the execution times between *h-lik* and the AGH methods in the i7-5960x platform. Irrespective of the size of the dataset and the grouping structure, the *h-lik* implementation was much faster than the AGH implementation in glmer. The smallest speedup was observed for the 10% dataset with grouping at the IP level (3.7x faster), but the speedup could range up to 32.5x (1% dataset, grouping at the HCF level). The direct *h-lik* implementation was only slightly slower than the iGLM in the datasets we could analyze with the iGLM. Analysis of Variance (ANOVA) showed that the size of the dataset (F statistic 68.07) and the estimation method (F statistic 18.1) were much stronger predictors of these timing differences than the grouping structure of the data (F statistic 3.68). Examination of the timing of the three steps of the *h-lik* method showed that the greatest amount of time was spent on optimization, e.g., for the 10% dataset with random effects at the IP level, tape generation took 137sec, optimization 3327 sec and Hessian calculation/uncertainty quantification 1,844 sec. For the 1% dataset with random effects at the HCF level, the corresponding times were: 8 sec (tape generation), 17 sec (optimization), 1.7sec (uncertainty quantification). In sharp contrast, Bayesian methods were much

544 slower than any of the other methods considered. Therefore, our analyses were limited to the 1%
545 dataset at the HCF level. Parallel simulation of 1,000 samples from each of four independent Markov
546 Chains took 20,517 seconds of wall time, thus was nearly three orders of magnitude slower than either
547 of the two *h-lik* implementations.

548 **Potassium level, interindividual and interfacility sources of variation in the risk of death in CRWD**

549 Predictors of mortality in the CRWD accounting for both IP and HCF variability by a two random effects
550 model and for the various datasets considered here are shown in **Table 2**. Increasing the dataset size,
551 stabilized model estimates of the (log) relative risk of death associated with each of the covariates.
552 Increasing the dataset size was associated with a substantial decrease in the standard error of these
553 estimates. There was considerable interindividual and (to a larger extent) interfacility variation in the
554 relative risk of death, as evidenced by the magnitude of the variance components in the full CRWD
555 dataset. The point estimate (standard error) was 0.234 (0.034) and 1.11 (0.067) for the IP and HCF
556 components, respectively. These estimates imply that individual factors not captured by the covariates
557 considered in Table 1 will be associated with 2.5-fold variation in individual risk between the 2.5% and
558 the 97.5% risk quantiles of patients with the exact same values of these covariates. Similarly, facility
559 level factors are an important source of variation, though in this case the relative risk of an individual
560 evaluated in a facility at the 97.5% quantile vs. a facility in the 2.5% quantile is 77.5-fold higher.

561 The coefficients of the spline associated with the K^+ level appear rather different among the three
562 datasets. Nevertheless, the predicted relative risk of death for a given K^+ level was essentially identical
563 between the 10% and the 100% datasets (

564 **Figure 5**). Utilizing the full (100%) dataset resulted in a substantial reduction in the uncertainty (95%
565 pointwise confidence interval) for a given K^+ level. The relative risk associated was numerically close to
566 one for a broad range of K^+ between 3.3 to 4.5 meq/l, i.e., in the vicinity of the “normal” level of 4.0
567 meq/l.

Table 3 : Fixed effects estimates summarized by the mean(standard error) from the direct *h-lik* implementation for the 1% , 10% and 100% dataset with random effects at both the IP and HCF levels.

Parameter	1%	10%	100%
Fixed Effects			
Intercept	-6.22(0.99)	-5.22(0.31)	-3.21(0.16)
Potassium (natural spline coefficient 1)	6.81(2.46)	8.65(0.74)	11.98(0.32)
Potassium (natural spline coefficient 2)	-9.49(40.24)	-39.56(12.39)	-77.79(7.97)
Potassium (natural spline coefficient 3)	-18.5(79.78)	-74.64(24.57)	-146.92(15.84)
eGFR (natural spline coefficient 1)	-0.43(0.25)	-0.66(0.08)	-0.59(0.02)
eGFR (natural spline coefficient 2)	-1.84(0.51)	-1.41(0.15)	-1.44(0.05)
eGFR (natural spline coefficient 3)	-1.09(0.51)	-0.32(0.15)	-0.26(0.05)
Age (natural spline coefficient 1)	0.31(0.33)	0.6(0.12)	0.78(0.04)
Age (natural spline coefficient 2)	-0.23(0.91)	1.43(0.32)	2.08(0.11)
Age (natural spline coefficient 3)	0.91(0.2)	1.1(0.07)	1.22(0.02)
Male Gender	0.21(0.09)	0.17(0.03)	0.17(0.01)
White Race	0.16(0.15)	0.06(0.05)	0.1(0.02)
Hispanic Race	-0.46(0.72)	0.14(0.15)	0.16(0.05)
Native American	0.03(0.73)	-0.08(0.2)	0.16(0.06)
Other Race	-0.58(0.32)	-0.12(0.09)	0.08(0.03)
Unknown Race	-0.24(0.47)	-0.09(0.15)	0.02(0.05)
Inpatient status	2.39(0.19)	2.13(0.06)	2.21(0.02)
Charlson Comorbidity Score	0.10(0.01)	0.10(0.00)	0.10(0.00)

Analysis of performance of *h-lik* computations in large datasets with multiple random effects

Total wall time (in log10 space) for triplicate executions of the parallel and serial versions of the proposed implementations of *h-lik* are shown in

Figure 6 and clearly illustrate the exponential increase in execution time with the size of the dataset irrespective of the machine used. ANOVA identified the size of the dataset (F statistic 1950.474) and the parallel implementation (F statistic 78.030) as more influential predictors than the machine executing the code (F statistic 2.694). A linear regression analysis of the data showed that execution on the Xeon was 16% faster than the i7-5960x (95% confidence interval -38.4% to +2.8% $p=0.114$). The serial code was 11.5% faster (95% confidence interval -25.8% to +5.6%, $p=0.129$) slower to execute than the parallel code. In

Figure 7 we illustrate the time spent in various activities when running the *h-lik* programs. Optimization of the $p_{u,\beta}(h)$ profile likelihood took the longest, followed closely by optimization of $p_u(h)$. These time-consuming tasks only slightly benefited from parallelization. Tape generation was notably slower when

done in parallel. The divergent effects of parallelization on these two tasks, underline the small effect of parallelization on execution speed.

Discussion

In this report we demonstrate the initial feasibility of fitting GLMMs to mine large clinical EHR databases by combining the LA with AD into a direct implementation of the *h-lik* approach to GLMMs. Analysis of very large datasets is an area in which many existing approaches to numerical integration for GLMM, e.g., those based on AGH or MCMC methods, are impractical because they execute slowly for big datasets with large number of random effects. In contrast, the proposed technical advance can reliably and reasonably fast fit such datasets. Our implementation differs from the original iGLM algorithm for fitting the hierarchical likelihood. The direct implementation of adjusted profile likelihoods avoids programming errors in the hand coding of matrix operations, as well as numerical errors when calculating derivatives by finite differences speeding up calculations. There are several implications for future work and practice as noted below.

Random effects modeling in very big datasets

GLMMs are one of the most versatile modeling techniques in statistics. In recent years, it has been noted that numerous models used for the non-parametric, flexible modeling of data can be viewed as special cases of the GLMMs. Such models include penalized spline approaches in statistics, but also “workhorses” of Machine Learning such as kernel based methods [58]. However, the applications of GLMMs to big data to date has been limited by the computational bottlenecks inherent in evaluating the high dimensional integrals that arise in their mathematical formulation. A previous biomedically oriented paper reported difficulties in fitting random effects models with 890,934 random effects using AGH in glmer in 2012. The authors resorted to a “divide and conquer” technique to fit separate models to chunks of this dataset followed by meta-regression to synthesize evidence from the smaller datasets.

However, because of their approximative nature, any “divide and conquer” technique will be accompanied by a non-negligible amount of bias. Furthermore, certain approximation approaches may exhibit a dramatic loss in statistical efficiency, discarding information and essentially converting a “big”, information-rich dataset to a much smaller one[7]. Having the ability to fit a large dataset with the same rigorous techniques that work in small datasets would thus represent a major advantage, because of the preservation of statistical efficiency. In our analyses we effortlessly fit a problem that was 4 times as large as the largest one reported in the biomedical literature by fitting the GLMM using the *h-lik*. Although GLMMs are frequently encountered in the analyses of biomedical data, their scope of application is rather broad. For example, an implementation of GLMMs by the LinkedIn software engineers[9] showed that the random effect modeling performed among the top 5 to 10 methods in numerous nonmedical datasets used in the KDD Cup competitions. Taken together these results suggest that GLMMs deserve a closer examination by other fields that deal with massive datasets using various ad hoc Machine Learning or Artificial Intelligence approaches.

H-lik offers a theoretically rigorous, computational friendly method for estimation of GLMMs

The *h-lik* was originally introduced as a unified framework for several common models e.g. Poisson-gamma, binomial-beta with the intention to resolve apparent differences between subject specific and population averaged models[10]. *h-lik* was latter extended to models with structured and unknown dispersion parameters (e.g. the (inverse) Gaussian GLMM) [11] and even the so called “double HGLM” in which random effects can be specified for both mean and variance parameters. The reliance of *h-lik* on the LA would appear to be an area of concern, especially in datasets similar to our own, with few repeated measurements per individual and a binary outcome[38, 39, 59]. Nevertheless, the LA based *h-lik* inferences for fixed and random effects were numerically close to those obtained via the alternative AGH approach. In the case of varying estimates between *h-lik* and AGH, we found the former to be closer to the gold standard of MCMC integration. This observation suggests that higher order LA

introduced in extensions of the basic *h-lik* theory [11–13, 38, 39] may not be required for the size of datasets considered in this paper. At first, this conclusion appears to contradict previous literature arguing that higher order LA are required to avoid biases in the estimation of variance components[13, 39, 60–64]. However, this apparent contradiction disappears if one considers the asymptotic order behavior of the LA to integrals over *very high* dimensional spaces[65]. The error (and thus potential inferential bias) introduced by foregoing corrections is of the order of $o(k^{-(1+d)/2})$, where d is the dimensionality of the space and k a scaling factor of the Hessian at the optimum. Therefore, for analyses of datasets with large number of random effects (large d), in which the underlying model is reasonably identified by the data (large k), the approximation error of the LA will decline rapidly to zero because of the “little o” asymptotics. Consequently, while the curse of dimensionality renders higher order AGH approximations impractical, it simultaneously makes the ordinary LA highly accurate in the same settings. Finally, our implementation of the *h-lik* corresponds to method HL(1,1) in the theory of the hierarchical likelihood, which appears to not be as susceptible to bias as lower order approximations [13, 39, 66, 67].

The *h-lik* approach may be viewed as Empirical Bayes/modal approximations to a non-informative Bayesian analysis of the same data, allowing the analyst to invoke a Bayesian interpretation of the results obtained through the *h-lik* if non-informative priors are appropriate for the problem at hand. In the opinion of the authors, this is a rather significant development since bona fide Bayesian analyses of large datasets via MCMC can be orders of magnitude slower than their likelihood counterparts. Future studies should explore the use (and abuse) of *h-lik* as approximations to full Bayesian analyses in other datasets and define the range of problems and random effects structures for which *h-lik* will give numerical answers that don’t differ much from those given by MCMC. A particularly interesting application would explore non-Gaussian random effect distributions, which are trivial to estimate both by the iGLM algorithm and the implementation considered herein.

655 Scalable alternatives to the proposed *h-lik* implementation, include the R package glmmTMB and the
656 original iGLM algorithm for fitting the hierarchical likelihood approach. glmmTMB was recently
657 introduced [68] for GLMMs and uses an interface similar to R's glmer. However, to our knowledge this
658 package does not implement the *h-lik* approach, although it does appear to be able to estimate non-
659 gaussian GLMMs via REML. The precise definition of the REML implemented in glmmTMB is not
660 explicitly stated in the package documentation. Examination of the R source code of the latter package
661 suggests that REML estimation in glmmTMB amounts to optimization of the $p_{u,\beta}(h)$ function, i.e., the
662 first stage in the hierarchical likelihood approach. Limited comparisons in subsets of CRWD and
663 simulations showed that while the variance components returned by glmmTMB and our approach were
664 identical, estimates of the fixed and random effects could differ, particularly when the number of
665 random effects in the dataset were small. Future work should thus concentrate on investigating
666 alternative ways to optimize the adjusted profile likelihood functions of *h-lik* theory that can offer higher
667 speed advantages to our naïve implementation.

668 The original iGLM approach offers an alternative to the direct implementation of the *h-lik* approach with
669 comparable performance in small datasets. This alternative is also a candidate for a high-performance
670 implementation, since the underlying operations (iterative solutions of weighted linear regression and
671 numerical optimization) are available in many high-performance scientific computing platforms. Future
672 work may even consider implementing either of the two implementations of the *h-lik* explored in this
673 work within mainstream Machine Learning platforms such as TensorFlow[69]. R research in alternative
674 implementations of the *h-lik* has the potential to make the rigor of GLMMs available to a wider audience
675 of data scientists in addition to statisticians.

676

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What did we learn about the potassium level and EHR analyses?

This work was motivated by a clinical question that the authors posed internally a few years ago. We believe that the analysis presented herein answered the question by re-confirming the “U” shaped curve between the K^+ level and mortality previously suggested [18], but dramatically reducing the uncertainty about this relationship. Based on our data, potassium levels close to the normal level of 4meq/l are not associated with excess mortality. Hence, our bracketing of a globally valid reference range for potassium levels could be used to inform the design of *clinical trials* to guide the proper use of potassium supplements and potassium lowering drugs. The individual and facility level variation detected here is of relevance to future investigations that use EHRs; unless such variation can be captured and modelled through covariates available in the EHRs, inferences from such data will be contaminated by significant bias.

Conclusions

Combining the Laplace Approximation with Automatic Differentiation results in a direct implementation of the *h-lik* that can efficiently fit very large EHR datasets, with accuracy that is equivalent if not better than the state-of-the-art AGH methods and the original iGLM algorithm for GLMMs. For the problems we examined, the *h-lik* gave results that are indistinguishable from the gold standard of MCMC integration, but the results were obtained much faster.

List of abbreviations:

AD: Algorithmic Differentiation

AGH: Adaptive Gaussian Hermite Quadrature

ANOVA: Analysis of Variance

BLAS: Basic Linear Algebra Subprograms

701 **BLUP:** Best Linear Unbiased Predictor

702 **CRWD:** Cerner Real World Data

703 **eGFR:** Estimated Glomerular Filtration Rate

704 **EHR:** Electronic Health Record

705 **EQL:** Extended Quasi Likelihood

706 **GLM:** Generalized Linear Model

707 **GLMM:** Generalized Linear Mixed Model

708 **HCP:** Healthcare Practitioners

709 **HCF:** Healthcare Facilities

710 **h-lik:** Hierarchical Likelihood

711 **K⁺:** Serum potassium level

712 **iGLM:** Interconnected Generalized Linear Models

713 **IWLS:** Iterative Weighted Linear Squares

714 **IP:** Individual Patients

715 **LA:** Laplace Approximation

716 **MCMC:** Markov Chain Monte Carlo

717 **MLE:** Maximum Likelihood Estimation

718 **REML:** Restricted Maximum Likelihood

Declarations:

Ethics approval and consent to participate: Analyses with CRWD are considered “Not Human Research” by the Human Research Protection Office (ethics committee and Institutional Review Board) of the University of New Mexico Health Sciences Center

Consent for publication: Not applicable

Availability of data and materials: The data that support the findings of this study are available from Cerner Corporation, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. The Cerner Health Facts Database (now referred to as the Cerner Real World Data, CRWD) is available to researchers at contributing hospitals (and their research affiliates) upon request made directly to Cerner Corporation. Software code for the implementation of the LA for a Poisson regression with one and two random effects is available from the repository: <https://bitbucket.org/chrisarg/laplaceapproximationandhyperkalemia/>

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Author’s contributions: CB extracted and preprocessed the data from the CRWD database used in this analysis, VSP, JC and CA designed the comparative evaluations used in the manuscript and programmed the analysis in R. MLU, MER, VS, SKS, SA and CA interpreted the clinical analyses of hyperkalemia and the risk of death.

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889 **Figure Legends**

890 **Figure 1:** Estimates and 95% confidence intervals for the fixed effect components

891 **Figure 2:** Estimated cubic splines relating the relative risk of death to potassium level and their associated
892 95% confidence (*h-lik*) and credible (MCMC) intervals using the 1% dataset and a single random effect at
893 the healthcare facility level

894 **Figure 3:** Comparison of the predicted random effects (BLUPs) as estimated by the *h-lik*, the various AGH
895 and the MCMC methods

896 **Figure 4:** GLMM execution timings for different datasets for single random effects models, either at the
897 individual patient or the healthcare facility level

898 **Figure 5:** Estimated cubic splines relating the relative risk of death to potassium level and their associated
899 95% confidence by the direct *h-lik* implementation for various dataset sizes. Poisson models included
900 random effects at both the individual and the healthcare facility levels (gray lines demarcate the zone in
901 which RR is between 0.9 and 1.1).

902 **Figure 6:** Performance (total wall time) of *h-lik* computations using serial and parallel codes.

903 **Figure 7:** Execution times of the steps of *h-lik* calculations for serial and parallel codes.

Figures

Figure 1

Estimates and 95% confidence intervals for the fixed effect components

Figure 2

Estimated cubic splines relating the relative risk of death to potassium level and their associated 95% confidence (h-lik) and credible (MCMC) intervals using the 1% dataset and a single random effect at the healthcare facility level

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Comparison of the predicted random effects (BLUPs) as estimated by the h.lik, the various AGH and the MCMC methods

Figure 4

GLMM execution timings for different datasets for single random effects models, either at the individual patient or the healthcare facility level

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Estimated cubic splines relating the relative risk of death to potassium level and their associated 95% confidence by the direct h-lik implementation for various dataset sizes. Poisson models included random effects at both the individual and the healthcare facility levels (gray lines demarcate the zone in which RR is between 0.9 and 1.1).

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Performance (total wall time) of h-lik computations using serial and parallel codes.

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Execution times of the steps of h-lik calculations for serial and parallel codes.