

General methods for evolutionary quantitative genetic inference from generalised mixed models

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Abstract

Methods for inference and interpretation of evolutionary quantitative genetic parameters, and for prediction of the response to selection, are best developed for traits with normal distributions. Many traits of evolutionary interest, including many life history and behavioural traits, have inherently non-normal distributions. The generalised linear mixed model (GLMM) framework has become a widely used tool for estimating quantitative genetic parameters for non-normal traits. However, whereas GLMMs provide inference on a statistically-convenient latent scale, it is sometimes desirable to express quantitative genetic parameters on the scale upon which traits are expressed. The parameters of a fitted GLMMs, despite being on a latent scale, fully determine all quantities of potential interest on the scale on which traits are expressed. We provide expressions for deriving each of such quantities, including population means, phenotypic (co)variances, variance components including additive genetic (co)variances, and parameters such as heritability. We demonstrate that fixed effects have a strong impact on those parameters and show how to deal for this effect by averaging or integrating over fixed effects. The expressions require integration of quantities determined by the link function, over distributions of latent values. In general cases, the required integrals must be solved numerically, but efficient methods are available and we provide an implementation in an R package, QGGLMM. We show that known formulae for quantities such as heritability of traits with Binomial and Poisson distributions are special cases of our expressions. Additionally, we show how fitted GLMM can be incorporated into existing methods for predicting evolutionary trajectories. We demonstrate the accuracy of the resulting method for evolutionary prediction by simulation, and apply our approach to data from a wild pedigreed vertebrate population.

26 Introduction

27 Additive genetic variances and covariances of phenotypic traits determine the response to se-
28 lection, and so are key determinants of the processes of adaptation in response to natural
29 selection and of genetic improvement in response to artificial selection (Fisher, 1918; Falconer,
30 1960; Lynch and Walsh, 1998; Walsh and Lynch, forthcoming). While the concept of additive
31 genetic variance (Fisher, 1918; Falconer, 1960) is very general, being applicable to any type of
32 character with any arbitrary distribution, including, for example, fitness (Fisher, 1930), tech-
33 niques for estimating additive genetic variances and covariances are best developed for Gaussian
34 traits (i.e., traits that follow a normal distribution; Henderson 1950; Lynch and Walsh 1998).
35 Furthermore, quantitative genetic theory for predicting responses to selection are also best
36 developed and established for Gaussian characters (Walsh and Lynch, forthcoming), but see
37 Morrissey (2015). Consequently, although many characters of potential evolutionary interest
38 are not Gaussian (e.g. survival or number of offspring), they are not well-handled by existing
39 theory and methods. Comprehensive systems for estimating genetic parameters and predict-
40 ing evolutionary trajectories of non-Gaussian traits will hence be very useful for quantitative
41 genetic studies of adaptation.

42 For the analysis of Gaussian traits, linear mixed model-based (LMM) inferences of genetic
43 parameters, using the ‘animal model’, have become common practice in animal and plant
44 breeding (Thompson, 2008; Hill and Kirkpatrick, 2010), but also in evolutionary studies on
45 wild populations (Kruuk, 2004; Wilson *et al.*, 2010). Recently, the use of generalised linear
46 mixed models (GLMMs) to analyse non-Gaussian traits has been increasing (e.g. Milot *et al.*,
47 2011; Wilson *et al.*, 2011; Morrissey *et al.*, 2012; de Villemereuil *et al.*, 2013; Ayers *et al.*,
48 2013). Whereas LMM analysis directly estimates additive genetic parameters on the scale on
49 which traits are expressed and selected, and upon which we may most naturally consider their
50 evolution, this is not the case for GLMMs. In this paper, we offer a comprehensive description
51 of the assumptions of GLMMs and their consequences in terms of quantitative genetics and a
52 framework to infer quantitative genetic parameters from GLMMs output. This work applies and
53 extends theory in Morrissey (2015), to handle the effects of (non-linear) relationships among the
54 scale upon which inference is conducted in a GLMM and the scale of data, and to accommodate

55 the error structures that arise in GLMM analysis. These results generalise existing expressions
56 for specific models (threshold model and Poisson with a log-link, Dempster and Lerner, 1950;
57 Robertson, 1950; Foulley and Im, 1993). We show that fixed effects in GLMMs raise special
58 complications and we offer some efficient approaches for dealing with this issue.

59 While it will undoubtedly be desirable to develop a comprehensive method for making data-
60 scale inferences of quantitative genetic parameters with GLMMs, such an endeavour will not
61 yield a system for predicting evolution in response to natural or artificial selection, even if a
62 particular empirical system is very well served by the assumptions of a GLMM. This is because
63 systems for evolutionary prediction, specifically the Breeder's equation (Lush, 1937; Fisher,
64 1924) and the Lande equation (Lande, 1979; Lande and Arnold, 1983), assume that breeding
65 values (and in most applications, phenotypes) are multivariate normal or make assumptions
66 such as linearity of the parent-offspring regression, which are unlikely to hold for non-normal
67 traits (Walsh and Lynch, forthcoming). Even if it is possible to estimate additive genetic vari-
68 ances of traits on the scale upon which traits are expressed, we will show that these quantities
69 will not strictly be usable for evolutionary prediction. However, we will see that the scale on
70 which estimation is performed in a GLMM does, by definition, satisfy the assumptions of the
71 Breeder's and Lande equations. Thus, for the purpose of predicting evolution, it may be useful
72 to be able to express selection of non-Gaussian traits on this scale. Such an approach will yield
73 a system for evolutionary prediction of characters that have been modelled with a GLMM,
74 requiring no more assumptions than those that are already made in applying the statistical
75 model.

76 The main results in this paper are arranged in four sections. First, we describe the GLMM
77 framework: its relationship to the more general (Gaussian) LMM and especially to the Gaussian
78 animal model (Henderson, 1973; Kruuk, 2004; Wilson *et al.*, 2010), how GLMMs can be usefully
79 viewed as covering three scales and how some special interpretational challenges arise and are
80 currently dealt with. Second, we propose a system for making inferences of quantitative genetic
81 parameters on the scale upon which traits are expressed for arbitrary GLMMs. We show how
82 to estimate genotypic and additive genetic variances and covariances on this scale, accounting
83 for fixed effects as necessary. We lay out the formal theory underlying the system, apply it to
84 an empirical dataset. The relationships between existing analytical formulae and our general

85 framework are also highlighted. Third, we illustrate the issues when inferring quantitative
86 genetic parameters using a GLMM with an empirical example on Soay sheep (*Ovis aries*) and
87 how our framework can help to overcome them. Fourth, we outline a system of evolutionary
88 prediction for non-Gaussian traits that capitalises on the fact that the latent scale in a GLMM
89 satisfies the assumptions of available equations for the prediction of evolution. We show in
90 a simulation study that (i) evolutionary predictions using additive genetic variances on the
91 observed data scale represent approximations, and can, in fact, give substantial errors, and
92 (ii) making inferences via the latent scale provides unbiased predictions, insofar as a GLMM
93 may provide a pragmatic model of variation in non-Gaussian traits. The framework introduced
94 here (including both quantitative genetic parameters inference and evolutionary prediction) has
95 been implemented in a package for the R software (R Core Team, 2015) available at <https://github.com/devillemereuil/qgglm>.

97 **The generalised linear mixed model framework**

98 **Linear mixed models for Gaussian traits**

99 For Gaussian traits, a linear mixed model allows various analyses of factors that contribute to
100 the mean and variance of phenotype. In particular, a formulation of a linear mixed model called
101 the ‘animal model’ provides a very general method for estimating additive genetic variances and
102 covariances, given arbitrary pedigree data, and potentially accounting for a range of different
103 types of confounding variables, such as environmental effects, measurement error or maternal
104 effects. A general statement of an animal model analysis decomposing variation in a trait, \mathbf{z} ,
105 into additive genetic and other components would be

$$\mathbf{z} = \mu + \mathbf{X}\mathbf{b} + \mathbf{Z}_a\mathbf{a} + \mathbf{Z}_1\mathbf{u}_1 + \dots + \mathbf{Z}_k\mathbf{u}_k + \mathbf{e}, \quad (1)$$

106 where μ is the model intercept, \mathbf{b} is a vector of fixed effects such as sex and age, relating
107 potentially both continuous and categorical effects to observations via the fixed effects design
108 matrix \mathbf{X} , just as in an ordinary linear model, and \mathbf{e} is the vector of normally-distributed
109 residuals. An arbitrary number of random effects can be modelled, with design matrices \mathbf{Z} ,

110 where effects (\mathbf{a} , $\mathbf{u}_1 \dots \mathbf{u}_k$) are assumed to be drawn from normal distributions with variances
111 to be estimated. The key feature of the animal model is that it includes individual additive
112 genetic effects, or breeding values, conventionally denoted \mathbf{a} . These additive genetic effects
113 and, critically, their variance, are estimable given relatedness data, which can be derived from
114 pedigree data, or, more recently, from genomic estimates of relatedness (Sillanpää, 2011). The
115 covariances of breeding values among individuals can be modelled according to

$$\mathbf{a} \sim N(\mathbf{0}, \mathbf{A}V_A), \quad (2)$$

116 where \mathbf{A} is the additive genetic relatedness matrix derived from the pedigree and V_A is the
117 genetic additive variance.

118 **Common issues with non-Gaussian traits**

119 Many non-Gaussian traits, however, cannot be strictly additive on the scale on which they are
120 expressed. Consider, for example, survival probability that is bounded at 0 and 1 so that effects
121 like the substitution effect of one allele for another necessarily must be smaller when expressed
122 in individuals that otherwise have expected values near zero or one. In such a scenario, it may
123 be reasonable to assume that there exists an underlying scale, related to survival probability,
124 upon which genetic and other effects are additive.

125 In addition to inherent non-additivity, many non-Gaussian traits will have complex patterns
126 of variation. Over and above sources of variation that can be modelled with fixed and random
127 effects, as in a LMM (e.g., using Eqs. 1 and 2), residual variation may include both inherently
128 stochastic components, and components that correspond to un-modelled systematic differences
129 among observations. In a LMM, such differences are not distinguished, but contribute to resid-
130 ual variance. However, for many non-Gaussian traits it may be desirable to treat the former
131 as arising from some known statistical distribution, such as the binomial or Poisson distribu-
132 tion, and to deal with additional variation via a latent-scale residual (i.e. an overdispersion
133 term). Separation of these two kinds of variation in residuals may be very generally useful in
134 evolutionary quantitative genetic studies.

135 The scales of the generalised linear mixed model

136 Generalised linear mixed model (GLMM) analysis can be used for inference of quantitative
137 genetic parameters, and provides pragmatic ways of dealing with inherent non-additivity and
138 with complex sources of variation. The GLMM framework can be thought of as consisting of
139 three distinct scales on which we can think of variation in a trait occurring (see Fig. 1). A *latent*
140 *scale* is assumed (Fig. 1, top), on which effects on the propensity for expression of some trait
141 are assumed to be additive. A function, called a ‘link function’ is applied that links expected
142 values for a trait to the latent scale. For example, a trait that is expressed in counts, say,
143 number of behaviours expressed in a unit time, is a strictly non-negative quantity. As depicted
144 in Fig. 1, a strictly positive distribution of expected values may related to latent values ranging
145 from $-\infty$ to $+\infty$ by a function such as the log link. Finally, a distribution function (e.g.
146 Binomial, Poisson, etc.) is required to model the “noise” of observed values around expected
147 value (Fig. 1, bottom). Different distributions are suitable for different traits. For example,
148 with a count trait such as that depicted in Fig. 1, observed values may be modelled using the
149 Poisson distribution, with expectations related to the latent scale via the log link function.

150 More formally, these three scales of the GLMM can be written:

$$\ell = \mu + \mathbf{X}\mathbf{b} + \mathbf{Z}_a\mathbf{a} + \mathbf{Z}_1\mathbf{u}_1 + \dots + \mathbf{Z}_k\mathbf{u}_k + \mathbf{o}, \quad (3a)$$

151

$$\boldsymbol{\eta} = g^{-1}(\ell), \quad (3b)$$

152

$$\mathbf{z} \sim \mathcal{D}(\boldsymbol{\eta}, \boldsymbol{\theta}), \quad (3c)$$

153 where Eq. 3a is just as for a LMM (Eq. 1), except that it describes variation on the *latent*
154 *scale* ℓ , rather than the response directly. Note that we now refer to the “residual” (noted \mathbf{e} in
155 Eq. 1) as “overdispersion” (denoted \mathbf{o} , with a variance denoted V_O), since residuals (variation
156 around expected values) are defined by the distribution function, \mathcal{D} , in this model. Just as for
157 the LMM (Eq. 1), all random effects are assumed to follow normal distributions with variances
158 to be estimated on the latent scale. Particularly, the variance of additive genetic effects \mathbf{a} is
159 assumed to follow Eq. 2 on the latent scale.

160 Eq. 3b formalises the idea of the link function. Any link function has an associated inverse

161 link function, g^{-1} , which is often useful for converting specific latent values to expected values.
162 The expected values $\boldsymbol{\eta}$ constitute what we call the *expected data scale*. For example, where
163 the log link function translates expected values to the latent scale, its inverse, the exponential
164 function, translates latent values to expected values. Finally, Eq. 3c specifies the distribution
165 by which the observations \mathbf{z} scatter around the expected values according to some distribution
166 function, that may involve parameters (denoted $\boldsymbol{\theta}$) other than the expectation. We call this
167 the *observed data scale*. Some quantities of interest, such as the mean, are the same on the
168 expected data scale and on the observed data scale. When parameters are equivalent on these
169 two scales, we will refer to them together as the *data scales*.

170 The distinction we make between the expected and observed data scales is one of convenience
171 as they are not different scales *per se*. However, this distinction allows for more biological
172 subtlety when interpreting the output of a GLMM. The expected data scale can be thought
173 of as the “intrinsic” value of individuals (shaped by both the genetic and the environment),
174 but this intrinsic value can only be studied through random realisations. As we will see,
175 because breeding values are intrinsic individual values, the additive genetic variance is the
176 same for both scales, but, due to the added noise in observed data, the heritabilities are not.
177 Upon which scale to calculate heritability depends on the underlying biological question. For
178 example, individuals (given their juvenile growth and genetic value) might have an intrinsic
179 annual reproductive success of 3.4, but can only produce a integer number of offspring each
180 year (say 2, 3, 4 or 5): heritabilities of both intrinsic expectations and observed numbers can
181 be computed, but their values and interpretations will differ.

182 **Current practices and issues to compute genetic quantitative parameters from** 183 **GLMM outputs**

184 Genetic variance components estimated in a generalised animal model are obtained on the
185 latent scale. Hence, the “conventional” formula to compute heritability:

$$h_{\text{lat}}^2 = \frac{V_{A,\ell}}{V_{A,\ell} + V_{\text{RE}} + V_{\text{O}}}, \quad (4)$$

186 where V_{RE} is the summed variance of all random effects apart from the additive genetic variance,
187 and V_O is the overdispersion variance, is the heritability on the latent scale, not on the observed
188 data scale (Morrissey *et al.*, 2014). Here, and throughout this paper, $V_{A,\ell}$ stands for the additive
189 genetic variance on the latent scale. Although it might sometimes be sensible to measure the
190 heritability of a trait on the latent scale (for example, in animal breeding, where selection might
191 be based on latent breeding values), it is natural to seek inferences on the scale upon which the
192 trait is expressed, and on which we may think of selection as acting. Some expressions exist
193 by which various parameters can be obtained or approximated on the observed data scale. For
194 example, various expressions for the intra-class correlation coefficients on the data scale exist
195 (reviewed in Nakagawa and Schielzeth, 2010), but, contrary to LMM, heritabilities on the data
196 scales within a GLMM framework cannot be considered as intra-class correlation coefficients.
197 Exact analytical expressions exist for the additive genetic variance and heritability on the
198 observed data scale for two specific and important families of GLMMs (i.e. combinations of
199 link functions and distribution functions): for a binomial model with a probit link function (i.e.,
200 the “threshold model,” Dempster and Lerner, 1950) and for a Poisson model with a logarithm
201 link function (Foulley and Im, 1993). A general system for calculating genetic parameters on
202 the expected and observed data scales for arbitrary GLMMs is currently lacking.

203 In addition to handling the relationship between observed data and the latent trait via
204 the link and distribution functions, any system for expected and observed scale quantitative
205 genetic inference with GLMMs will have to account for complex ways in which fixed effects
206 can influence quantitative genetic parameters. It is currently appreciated that fixed effects
207 in LMMs explain variance, and that variance associated with fixed effects can have a large
208 influence on summary statistics such as repeatability (Nakagawa and Schielzeth, 2010) and
209 heritability (Wilson, 2008). This principle holds for GLMMs as well, but fixed effects cause
210 additional, important complications for interpreting GLMMs. While random and fixed effects
211 are independent in a GLMM on the latent scale, the non-linearity of the link function renders
212 them inter-related on the expected and observed scales. Consequently, and unlike in a LMM
213 or in a GLMM on the latent scale, variance components on the observed scale in a GLMM
214 depend on the fixed effects. Consider, for example, a GLMM with a log link function. Because
215 the exponential is a convex function, the influence of fixed and random effects will create more

216 variance on the expected and observed data scales for larger values than for smaller values.

217 Quantitative genetic parameters in GLMMs

218 Although all examples and most equations in this article are presented in a univariate form, all
219 our results are applicable to multivariate analysis, which is implemented in our software. Unless
220 stated otherwise, the equations below assume that no fixed effect (apart from the intercept)
221 were included in the GLMM model.

222 Phenotypic mean and variances

223 **Expected population mean** The expected mean phenotype \bar{z} on the data scale (i.e., applying
224 to both the mean expected value and mean observed value) is given by

$$\bar{z} = \int g^{-1}(\ell) f_{\mathcal{N}}(\ell, \mu, V_{A,\ell} + V_{RE} + V_O) d\ell, \quad (5)$$

225 where $f_{\mathcal{N}}(\ell, \mu, V_{A,\ell} + V_{RE} + V_O)$ is the probability density of a Normal distribution with mean
226 μ and variance $V_{A,\ell} + V_{RE} + V_O$ evaluated at ℓ .

227 **Expected-scale phenotypic variance** Phenotypic variance on the expected data scale can be
228 obtained analogously to the data scale population mean. Having obtained \bar{z} , the phenotypic
229 variance is

$$V_{P,\text{exp}} = \int (g^{-1}(\ell) - \bar{z})^2 f_{\mathcal{N}}(\ell, \mu, V_{A,\ell} + V_{RE} + V_O) d\ell. \quad (6)$$

230 **Observed-scale phenotypic variance** Phenotypic variance of observed values is the sum of the
231 variance in expected values and variance arising from the distribution function. Since these
232 variances are independent by construction in a GLMM, they can be summed. This distribution
233 variance is influenced by the latent trait value, but might also depend on additional distribution
234 parameters included in θ (see Eq. 3c). Given a distribution-specific variance function v :

$$V_{P,\text{obs}} = V_{P,\text{exp}} + \int v(\ell, \theta) f_{\mathcal{N}}(\ell, \mu, V_{A,\ell} + V_{RE} + V_O) d\ell. \quad (7)$$

235 **Genotypic variance on the data scales, arising from additive genetic variance on**
236 **the latent scale**

237 Because the link function is non-linear, additive genetic variance on the latent scale is manifested
238 as a combination of additive and non-additive variance on the data scales. Following Falconer
239 (1960) the total genotypic variance on the data scale is the variance of genotypic values on
240 that scale. Genotypic values are the expected data scale phenotypes, given latent scale genetic
241 values. The expected phenotype of an individual with a given latent genetic value a , i.e., its
242 genotypic value on the data scales $E[z|a]$, is given by

$$E[z|a] = \int g^{-1}(\ell) f_{\mathcal{N}}(\ell, \mu + a, V_{\text{RE}} + V_{\text{O}}) d\ell. \quad (8)$$

243 The total genotypic variances on the expected and observed data scales are the same, since
244 genotypic values are expectations that do not change between the expected and observed scales.
245 The total genotypic variance on both the expected and observed data scales is then

$$V(E[z|a]) = \int (E[z|a] - \bar{z})^2 f_{\mathcal{N}}(a, 0, V_{\text{A},\ell}) da. \quad (9)$$

246 This is the total genotypic variance on the data scale, arising from strictly additive genetic
247 variance on the latent scale. If non-additive genetic effects are modelled on the latent scale,
248 they would be included in the expectations and integrals in Eqs. 8 and 9.

249 **Additive genetic variance on the data scales**

250 The additive variance on the data scales is the variance of breeding values computed on the
251 data scales. Following Robertson (1950; see also Fisher 1918), breeding values on the data
252 scales, i.e., a_{exp} and a_{obs} , are the part of the phenotype z that depends linearly on the latent
253 breeding values. The breeding values on the data scale can then be defined as the predictions
254 of a least-squares regression of the observed data on the latent breeding values,

$$a_{\text{obs}} = \hat{z}|a = m + ba, \quad (10)$$

255 where \hat{z} is the value of z predicted by the regression, a the latent breeding value and m and b
256 the parameters of the regression. Thus, we have $V_{A,\text{obs}} = b^2 V_{A,\ell}$ and, from standard regression
257 theory:

$$b = \frac{\text{cov}(z, a)}{V_{A,\ell}}. \quad (11)$$

258 Because of the independence between the expected values of z (i.e. the expected data scale
259 $g^{-1}(\ell)$) and the distribution “noise” (see Eq. 7), we can obtain the result that $\text{cov}(z, a) =$
260 $\text{cov}(g^{-1}(\ell), a)$, hence:

$$b = \frac{\text{cov}(g^{-1}(\ell), a)}{V_{A,\ell}}. \quad (12)$$

261 Stein’s (1973) lemma states that if X and Y are bivariate normally distributed random variables,
262 then the covariance of Y and some function of X , $f(X)$, is equal to the expected value of $f'(X)$
263 times the covariance between X and Y , so,

$$\text{cov}(g^{-1}(\ell), a) = E \left[\frac{dg^{-1}(\ell)}{d\ell} \right] \text{cov}(\ell, a) = E \left[\frac{dg^{-1}(\ell)}{d\ell} \right] V_{A,\ell}, \quad (13)$$

264 noting that the covariance of latent breeding values and latent values is the variance of latent
265 breeding values. Finally, combining Eq. 12 with Eq. 13, we obtain:

$$b = E \left[\frac{dg^{-1}(\ell)}{d\ell} \right]. \quad (14)$$

266 To avoid confusion with various uses of b as other forms of regression coefficients, and for
267 consistency with Morrissey (2015), we denote the average derivative of expected value with
268 respect to latent value as Ψ :

$$\Psi = E \left[\frac{dg^{-1}(\ell)}{d\ell} \right] = \int \frac{dg^{-1}(\ell)}{d\ell} f_{\mathcal{N}}(\ell, \mu, V_{A,\ell} + V_{\text{RE}} + V_{\text{O}}) d\ell. \quad (15)$$

269 The additive genetic variance on the expected and observed scales are still the same and are
270 given by

$$V_{A,\text{obs}} = V_{A,\text{exp}} = \Psi^2 V_{A,\ell}. \quad (16)$$

271 Including fixed effects in the inference

272 **General issues** Because of the non-linearity introduced by the link function in a GLMM, all
273 quantitative genetic parameters are directly influenced by the presence of fixed effects. Hence,
274 when fixed effects are included in the model, it will often be important to marginalise over them
275 to compute accurate population parameters. There are different approaches to do so. We will
276 first describe the simplest approach (i.e. directly based on GLMM assumptions).

277 **Averaging over predicted values** In a GLMM, no assumption is made about the distribution of
278 covariates in the fixed effects. Given this, we can marginalise over fixed effects by averaging over
279 predicted values (marginalised over the random effects, i.e. $\mathbf{X}\hat{\mathbf{b}}$, where $\hat{\mathbf{b}}$ are the fixed effects
280 estimates). Note that, doing so, we implicitly make the assumption that our sample is repre-
281 sentative of the population of interest. Using this approach, we can compute the population
282 mean in Eq. 5 as:

$$\bar{z} = \frac{1}{N} \sum_{i=1}^N \int g^{-1}(\ell) f_{\mathcal{N}}(\ell, \mu + \hat{\ell}_i, V_{A,\ell} + V_{RE} + V_O) d\ell, \quad (17)$$

283 where N is the number of predicted latent values in $\hat{\ell} = \mathbf{X}\hat{\mathbf{b}}$. Typically, \mathbf{X} will be the fixed
284 effects design matrix used when fitting the generalised animal model (Eqs. 1, 2, and 3), and
285 N will be the number of data observations. Furthermore, this assumes that all fixed effects
286 represent biologically relevant variation, rather than being corrections for the observation pro-
287 cess or experimental condition. From this estimate of \bar{z} , we can compute the expected-scale
288 phenotypic variance:

$$V_{P,\text{exp}} = \frac{1}{N} \sum_{i=1}^N \int (g^{-1}(\ell) - \bar{z})^2 f_{\mathcal{N}}(\ell, \mu + \hat{\ell}_i, V_{A,\ell} + V_{RE} + V_O) d\ell. \quad (18)$$

289 Note that we are not averaging over variances computed for each predicted values, since the
290 value of the mean \bar{z} is the same across the computation. Eqs. 7, 8, 9 and 15 are to be modified
291 accordingly to compute all parameters, including Ψ . This approach has the advantages of being
292 simple and making a direct use of the GLMM inference without further assumptions.

293 **Sampled covariates are not always representative of the population** The distribution of covariate
294 values in \mathbf{X} may not be representative of the population being studied. In such cases, integration
295 over available values of fixed effects may be inappropriate. For example, a population may be
296 known (or assumed) to have an equal sex ratio, but one sex may be easier to catch, and
297 therefore over-represented in any given dataset. In such a situation, incorporation of additional
298 assumptions or data about the distribution of covariates (e.g., of sex ratio) may be useful.
299 A first approach is to predict values according to a new set of covariates constructed to be
300 representative of the population (e.g. with balanced sex ratio). Given these new predicted
301 values, the above approach can readily be used to compute quantitative genetic parameters
302 of interest. A drawback of this approach is that it requires one to create a finite sample of
303 predicted values instead of a full distribution of the covariates. A second approach will require
304 one to specify such a distribution for fixed covariates, here noted $f_X(\mathbf{X})$. In that case, Eq. 17
305 can be modified as follows

$$\bar{z} = \iint g^{-1}(\ell) f_{\mathcal{N}}(\ell, \mu + \mathbf{X}\hat{\mathbf{b}}, V_{A,\ell} + V_{RE} + V_O) f_X(\mathbf{X}) d\mathbf{X} d\ell. \quad (19)$$

306 All relevant equations (Eqs. 6, 7, 8, 9 and 15) are to be modified accordingly. This approach is
307 the most general one, but requires the ability to compute $f_X(\mathbf{X})$. Note that this distribution
308 should also account for potential covariance between covariates.

309 **Summary statistics and multivariate extensions**

310 Eqs. 5 through 16 give the values of different parameters that are useful for deriving other
311 evolutionary quantitative genetic parameters on the observed data scale. Hence, from them,
312 other parameters can be computed. The narrow-sense heritability on the observed data scale
313 can be written as

$$h_{\text{obs}}^2 = \frac{V_{A,\text{obs}}}{V_{P,\text{obs}}}. \quad (20)$$

314 Replacing $V_{P,\text{obs}}$ by $V_{P,\text{exp}}$ will lead to the heritability on the expected data scale h_{exp}^2 :

$$h_{\text{exp}}^2 = \frac{V_{A,\text{exp}}}{V_{P,\text{exp}}}. \quad (21)$$

315 Recalling that $V_{A,obs} = V_{A,exp}$, but $V_{P,obs} \neq V_{P,exp}$, note that the two heritabilities above differ.
316 Parameters such as additive genetic coefficient of variance and evolvability (Houle, 1992) can
317 be just as easily derived. The coefficient of variation on the expected and observed data scales
318 are identical and can be computed as

$$CV_{A,obs} = CV_{A,exp} = 100 \frac{\sqrt{V_{A,obs}}}{\bar{z}}, \quad (22)$$

319 and the evolvability on the expected and observed data scales will be

$$I_{A,obs} = I_{A,exp} = \frac{V_{A,obs}}{\bar{z}^2}. \quad (23)$$

320 The multivariate genetic basis of phenotypes, especially as summarised by the \mathbf{G} matrix,
321 is also often of interest. For simplicity, all expressions considered to this point have been pre-
322 sented in univariate form. However, every expression has a fairly simple multivariate extension.
323 Multivariate phenotypes are typically analysed by multi-response GLMMs. For example, the
324 vector of mean phenotypes in a multivariate analysis on the expected data scale is obtained by
325 defining the link function to be a vector-valued function, returning a vector of expected values
326 from a vector of values on the latent scale. The phenotypic variance is then obtained by inte-
327 grating the vector-valued link function times the multivariate normal distribution total variance
328 on the latent scale, as in Eq. 5 and Eq. 7. Integration over fixed effects for calculation of the
329 multivariate mean is directly analogous to either of the extensions of Eq. 5 given in Eqs. 17
330 or 19. Calculation of other parameters, such as multivariate genotypic values, additive-derived
331 covariance matrices, and phenotypic covariance matrices, have directly equivalent multivariate
332 versions as well. The additive genetic variance-covariance matrix (the \mathbf{G} matrix) on the ob-
333 served scale is simply the multivariate extension of Eq. 16, i.e., $\mathbf{G}_{obs} = \mathbf{\Psi} \mathbf{G}_\ell \mathbf{\Psi}^T$. Here, \mathbf{G}_ℓ is the
334 latent \mathbf{G} matrix and $\mathbf{\Psi}$ is the average gradient matrix of the vector-valued link function, which
335 is a diagonal matrix of Ψ values for each trait (simultaneously computed from a multivariate
336 version of Eq. 15).

337 Relationships with existing analytical formulae

338 Binomial distribution and the threshold model

339 Heritabilities of binary traits have a long history of analysis with a threshold model (Wright,
340 1934; Dempster and Lerner, 1950; Robertson, 1950), whereby an alternate trait category is
341 expressed when a trait on a latent “liability scale” exceeds a threshold. Note that this liability
342 scale is not the same as the latent scale hereby defined for GLMM (see Fig. S1 in Supplementary
343 Information). However, it can be shown (see Supplementary Information, section A) that
344 a GLMM with a binomial distribution and a probit link function is exactly equivalent to
345 such a model, only with slightly differently defined scales. For threshold models, heritability
346 can be computed on this liability scale by using adding a so-called “link variance” V_L to the
347 denominator (see for example Nakagawa and Schielzeth, 2010; de Villemereuil *et al.*, 2013):

$$h_{\text{liab}}^2 = \frac{V_{A,\ell}}{V_{A,\ell} + V_{\text{RE}} + V_{\text{O}} + V_L}. \quad (24)$$

348 Because the probit link function is the inverse of the cumulative standard normal distribution
349 function, the “link variance” V_L is equal to one in this case. One can think of the “link variance”
350 as arising in this computation because of the reduction from three scales (in case of a GLMM)
351 to two scales (liability and observed data in the case of a threshold model): the liability scale
352 includes the link function.

353 When the heritability is computed using the threshold model, Dempster and Lerner (1950)
354 and Robertson (1950) derived an exact analytical formula relating this estimate to the observed
355 data scale:

$$h_{\text{obs}}^2 = \frac{t^2}{p(1-p)} h_{\text{liab}}^2, \quad (25)$$

356 where p is the probability of occurrence of the minor phenotype and t is the density of a
357 standard normal distribution at the p th quantile (see also Roff, 1997). It can be shown (see
358 SI, section A) that this formula is an exact analytical solution to Eqs. 5 to 21 in the case of
359 a GLMM with binomial distribution and a probit link. When fixed effects are included in the
360 model, it is still possible to use these formulae by integration over the marginalised predictions
361 (see SI, section A). Note that Eq. 25 applies only to analyses conducted with a probit link, it

362 does not apply to a binomial model with a logit link function.

363 **Poisson distribution with a logarithm link**

364 For a log link function and a Poisson distribution, both the derivative of the inverse link function,
365 and the variance of the distribution, are equal to the expected value. Consequently, analytical
366 results are obtainable for a log/Poisson model for quantities such as broad- and narrow-sense
367 heritabilities. Foulley and Im (1993) derived an analytical formula to compute narrow-sense
368 heritability on the observed scale:

$$h_{\text{obs}}^2 = \frac{\lambda^2 V_{A,\ell}}{\lambda^2 [\exp(V_{A,\ell} + V_{\text{RE}} + V_{\text{O}}) - 1] + \lambda} = \frac{\lambda V_{A,\ell}}{\lambda [\exp(V_{A,\ell} + V_{\text{RE}} + V_{\text{O}}) - 1] + 1}, \quad (26)$$

369 where λ is the data scale phenotypic mean, computed analytically as:

$$\lambda = \exp\left(\mu + \frac{V_{A,\ell} + V_{\text{RE}} + V_{\text{O}}}{2}\right). \quad (27)$$

370 Again, it can be shown (see SI, section B) that these formulae are exact solutions to Eq. 5 to
371 21 when assuming a Poisson distribution with a log link. The inclusion of fixed effects in the
372 model make the expression slightly more complicated (see SI, section B). These results can also
373 be extended to the Negative-Binomial distribution with log link with slight modifications of
374 the analytical expressions (see SI, section B).

375 The component of the broad-sense heritability on the observed data scale that arises from
376 additive genetic effects on the latent scale can be computed as an intra-class correlation coefficient (i.e. repeatability) for this kind of model (Foulley and Im, 1993; Nakagawa and Schielzeth,
377 2010):

$$H_{\text{obs}}^2 = \frac{V(E[z|a])}{V_{\text{P,obs}}} = \frac{\lambda(\exp(V_{A,\ell}) - 1)}{\lambda [\exp(V_{A,\ell} + V_{\text{RE}} + V_{\text{O}}) - 1] + 1}. \quad (28)$$

379 If non-additive genetic component were fitted in the model (e.g. dominance variance), they
380 should be added to $V_{A,\ell}$ in Eq. 28 to constitute the total genotypic variance, and thus obtain
381 the actual broad-sense heritability. Note that the Eqs. 28 and 26 converge together for small
382 values of $V_{A,\ell}$.

383 **Example analysis: quantitative genetic parameters of a non-normal** 384 **character**

385 We modelled the first year survival of Soay sheep (*Ovis aries*) lambs on St Kilda, Outer He-
386 brides, Scotland. The data are comprised of 3814 individuals born between 1985 and 2011,
387 and that are known to either have died in their first year, defined operationally as having died
388 before the first of April in the year following their birth, or were known to have survived be-
389 yond their first year. Months of mortality for sheep of all ages are generally known from direct
390 observation, and day of mortality is typically known. Furthermore, every lamb included in this
391 analysis had a known sex and twin status (whether or not it had a twin), and a mother of a
392 known age.

393 Pedigree information is available for the St Kilda Soay sheep study population. Maternal
394 links are known from direct observation, with occasional inconsistencies corrected with genetic
395 data. Paternal links are known from molecular data. Most paternity assignments are made
396 with very high confidence, using a panel of 384 SNP markers, each with high minor allele
397 frequencies, and spread evenly throughout the genome. Details of marker data and pedigree
398 reconstruction are given in Bérénos *et al.* (2014). The pedigree information was pruned to
399 include only phenotyped individuals and their ancestors. The pedigree used in our analyses
400 thus included 4687 individuals with 4165 maternal links and 4054 paternal links.

401 We fitted a generalised linear mixed model of survival, with a *logit* link function and a
402 binomial distribution function. We included fixed effects of individual's sex and twin status,
403 and linear, quadratic, and cubic effects of maternal age ($matAge_i$). Maternal age was mean-
404 centred by subtracting the overall mean. We also included an interaction of sex and twin status,
405 and an interaction of twin status with maternal age. We included random effects of breeding
406 value (as for Eq. 2), maternal identity, and birth year. Because the overdispersion variance V_O
407 in a binomial GLMM is unobservable for binary data, we set its variance to one. The model was
408 fitted in MCMCGLMM (Hadfield, 2010), with diffuse independent normal priors on all fixed
409 effects, and parameter-expanded priors for the variances of all estimated random effects.

410 We identified important effects on individual survival probability, i.e., several fixed effects
411 were substantial, and also, each of the additive genetic, maternal, and among-year random

412 effects explained appreciable variance (Table 1). The model intercept corresponds to the ex-
413 pected value on the latent scale of a female singleton (i.e. not a twin) lamb with an average
414 age (4.8 years) mother. Males have lower survival than females, and twins have lower survival
415 than singletons. There were also substantial effects of maternal age, corresponding to a rapid
416 increase in lamb survival with maternal age among relatively young mothers, and a negative
417 curvature, such that the maximum survival probabilities occur among offspring of mothers aged
418 6 or 7 years. The trajectory of maternal age effects in the cubic model are similar to those
419 obtained when maternal age is fitted as a multi-level effect.

420 To illustrate the consequences of accounting for different fixed effects on expected and ob-
421 served data scale inferences, we calculated several parameters under a series of different treat-
422 ments of the latent scale parameters of the GLMM. We calculated the phenotypic mean, the
423 additive genetic variance, the total variance of expected values, the total variance of observed
424 values, and the heritability of survival on the expected and observed scales.

425 First, we calculated parameters using only the model intercept (μ in Eq. 1 and 3a). This
426 intercept, under default settings, is arbitrarily defined by the linear modelling software imple-
427 mentation and is thus software-dependent. In the current case, due to the details of how the
428 data were coded, the intercept is the latent scale prediction for female singletons with average
429 aged (4.8 years) mothers. In an average year, singleton females with average aged mothers have
430 a probability of survival of about 80%. The additive genetic variance $V_{A,obs}$, calculated with
431 Eq. 16 is about 0.005, and corresponds to heritabilities on the expected and observed scales of
432 0.115 and 0.042 (Table 2).

433 In contrast, if we wanted to calculate parameters using a different (but equally arbitrary)
434 intercept, corresponding to twin males, we would obtain a mean survival rate of 0.32, an additive
435 genetic variance that is twice as large, but similar heritabilities (Table 1). Note that we have
436 not modelled any systematic differences in genetic parameters between females and males, or
437 between singletons and twins. These differences in parameter estimates arise from the exact
438 same estimated variance components on the latent scale, as a result of different fixed effects.

439 This first comparison has illustrated a major way in which the fixed effects in a GLMM
440 influence inferences on the expected and observed data scales. For linear mixed models, it
441 has been noted that variance in the response is explained by the fixed predictors, and that

442 this may inappropriately reduce the phenotypic variance and inflate heritability estimates for
443 some purposes (Wilson, 2008). However, in the example so far, we have simply considered two
444 different intercepts (i.e. no difference in explained variance): female singletons vs male twins,
445 in both cases, assuming focal groups of individuals are all born to average aged mothers. Again
446 these differences in phenotypic variances and heritabilities arise from differences in intercepts,
447 not any differences in variance explained by fixed effects. All parameters on the expected and
448 observed value scales are dependent on the intercept, including the mean, the additive genetic
449 variance and the total variance generated from random effects. Heritability is modestly affected
450 by the intercept, because additive genetic and total variances are similarly, but not identically,
451 influenced by the model intercept.

452 Additive genetic effects are those arising from the average effect of alleles on phenotype,
453 integrated over all background genetic and environmental circumstances in which alternate
454 alleles might occur. Fixed effects, where they represent biologically-relevant variation, are
455 part of this background. Following our framework (see Eq. 17), we can solve the issue of the
456 influence of the intercept by integrating our calculation of Ψ and ultimately $V_{A,obs}$ over all fixed
457 effects. This approach has the advantage of being consistent for any chosen intercept, as the
458 value obtained after integration will not depend on that intercept. Considering all fixed and
459 random effects, quantitative genetic parameters on the expected and observed scales are given
460 in table 2, third column. Note that additive genetic variance is not intermediate between the
461 two extremes (concerning sex and twin status), that we previously considered. The calculation
462 of $V_{A,obs}$ now includes an average slope calculated over a wide range of the steep part of the
463 inverse-link function (near 0 on the latent scale, and near 0.5 on the expected data scale), and so
464 is relatively high. The observed total phenotypic variance $V_{P,obs}$ is also quite high. The increase
465 in $V_{P,obs}$ has two causes. First the survival mean is closer to 0.5, so the random effects variance
466 is now manifested as greater total variance on the expected and observed scales. Second, there
467 is now variance arising from fixed effects that is included in the total variance.

468 Given this, which estimates should be reported or interpreted? We have seen that when
469 fixed effects are included in a GLMM, the quantitative genetic parameters calculated without
470 integration are sensitive to an arbitrary parameter: the intercept. Hence integration over fixed
471 effects may often be the best strategy for obtaining parameters that are not arbitrary. In

472 the case of survival analysed here, h_{obs}^2 is the heritability of realised survival, whereas h_{exp}^2 is
473 the heritability of “intrinsic” individual survival. Since realised survival is the one “visible”
474 by natural selection, h_{obs}^2 might be a more relevant evolutionary parameter. Nonetheless, we
475 recommend that $V_{\text{P,exp}}$ and $V_{\text{P,obs}}$ are both reported.

476 **Evolutionary prediction**

477 Systems for predicting adaptive evolution in response to phenotypic selection assume that the
478 distribution of breeding values is multivariate normal, and in most applications, that the joint
479 distribution of phenotypes and breeding values is multivariate normal (Lande, 1979; Lande and
480 Arnold, 1983; Morrissey, 2014; Walsh and Lynch, forthcoming). The distribution of breeding
481 values is assumed to be normal on the latent scale in a GLMM analysis, and therefore the
482 parent-offspring regression will also be normal on that scale, but not necessarily on the data
483 scale. Consequently, evolutionary change predicted directly using data-scale parameters may
484 be distorted. The Breeder’s and Lande equations may hold approximately, and may perhaps be
485 useful. However, having taken up the non-trivial task of pursuing GLMM-based quantitative
486 genetic analysis, the investigator has at their disposal inferences on the latent scale. On this
487 scale, the assumptions required to predict the evolution of quantitative traits hold. In this
488 section we will first demonstrate by simulation how application of the Breeder’s equation will
489 generate biased predictions of evolution. We then proceed to an exposition of some statistical
490 machinery that can be used to predict evolution on the latent scale (from which evolution on
491 the expected and observed scale can subsequently be calculated, using Eq. 5), given inference
492 of the function relating traits to fitness.

493 **Direct application of the Breeder’s and Lande equations on the data scale**

494 In order to explore the predictions of the Breeder’s equation applied at the level of observed
495 phenotype, we conducted a simulation in which phenotypes were generated according to a
496 Poisson GLMM (Eq. 3a to 3c, with a Poisson distribution function and a log link function), and
497 then selected the largest observed count values (positive selection) with a range of proportions
498 of selected individuals (from 5% to 95%, creating a range of selection differentials), a range

of latent-scale heritabilities (0.1, 0.3, 0.5 and 0.8, with a latent phenotypic variance fixed to 0.1), and a range of latent means μ (from 0 to 3). We simulated 10,000 replicates of each scenario, each composed of a different array of 10,000 individuals. For each simulation, we simulated 10,000 offspring. For each offspring, a breeding value was simulated according to $a_{\ell,i} \sim \mathcal{N}((a_{\ell,d} + a_{\ell,s})/2, V_{A,\ell}/2)$, where $a_{\ell,i}$ is the focal offspring's breeding value, $a_{\ell,d}$ and $a_{\ell,s}$ are the breeding values of simulated dams and sires and $V_{A,\ell}/2$ represents the segregational variance assuming parents are not inbred. Dams and sires were chosen at random with replacement from among the pool of simulated selected individuals. For each scenario, we calculated the realised selection differential arising from the simulated truncation selection, S_{obs} , and the average evolutionary response across simulations, R_{obs} . For each scenario, we calculated the heritability on the observed scale using Eq. 20. If the Breeder's equation was strictly valid for a Poisson GLMM on the observed scale, the realised heritability $R_{\text{obs}}/S_{\text{obs}}$ would be equal to the observed-scale heritability h_{obs}^2 .

The correspondence between $R_{\text{obs}}/S_{\text{obs}}$ and h_{obs}^2 is approximate (Fig. 2), and strongly depends on the selection differential (controlled here by the proportion of selected individuals). Note that, although the results presented here depict a situation where the ratio $R_{\text{obs}}/S_{\text{obs}}$ is very often larger than h_{obs}^2 , this is not a general result (e.g. this is not the case when using negative instead of positive selection, data not shown). In particular, evolutionary predictions are poorest in absolute terms for large μ and large (latent) heritabilities. However, because we were analysing simulation data, we could track the selection differential of latent value (by calculating the difference in its mean between simulated survivors and the mean simulated before selection). We can also calculate the mean latent breeding value after selection. Across all simulation scenarios, the ratio of the change in breeding value after selection, to the change in breeding value before selection was equal to the latent heritability (see Fig. 2), showing that evolutionary changes could be accurately predicted on the latent scale.

Evolutionary change on the latent scale, and associated change on the expected and observed scales

In an analysis of real data, latent (breeding) values are, of course, not measured. However, given an estimate of the effect of traits on fitness, say via regression analysis, we can derive

528 the parameters necessary to predict evolution on the latent scale. The idea is thus to relate
529 measured fitness on the observed data scale to the latent scale, compute the evolutionary
530 response on the latent scale and finally compute the evolutionary response on the observed
531 data scale.

532 To relate the measured fitness on the observed scale to the latent scale, we need to compute
533 the expected fitness W_{exp} given latent trait value ℓ , which is

$$W_{\text{exp}}(\ell) = \sum_k W_P(k)P(Z = k|\ell), \quad (29)$$

534 where $W_P(k)$ is the measure of fitness for the k th data scale category (assuming the observed
535 data scale is discrete as in most GLMMs). Population mean fitness, can then be calculated in
536 an analogous way to Eq. 5:

$$\bar{W} = \int W_{\text{exp}}(\ell)f_{\mathcal{N}}(\ell, \mu, V_{A,\ell} + V_{\text{RE}} + V_{\text{O}})d\ell. \quad (30)$$

537 These expressions comprise the basic functions necessary to predict evolution. Given a fitted
538 GLMM, and a given estimate of the fitness function $W_P(k)$, each of several approaches could
539 give equivalent results. For simplicity, we proceed via application of the breeder's equation at
540 the level of the latent scale.

541 The change in the mean genetic value of any character due to selection is equal to the
542 covariance of breeding value with relative fitness (Robertson, 1966, 1968). Using Stein's (1973)
543 lemma once more, this covariance can be obtained as the product of the additive genetic variance
544 of latent values and the average derivative of expected fitness with respect to latent value, i.e.,
545 $E \left[\frac{dW_{\text{exp}}}{d\ell} \right]$. Evolution on the latent scale can therefore be predicted by

$$\Delta\mu = V_A E \left[\frac{dW_{\text{exp}}}{d\ell} \right] \frac{1}{\bar{W}}. \quad (31)$$

546 In the case of a multivariate analysis, note that the derivative above should be a vector of
547 partial derivatives (partial first order derivative with respect to latent value for each trait) of
548 fitness.

549 If fixed effects need to be considered, the approach can be modified in the same way as

550 integration over fixed effects is accomplished for calculating other quantities, i.e. the expression

$$\bar{W} = \frac{1}{N} \sum_{i=1}^N \int W_{\text{exp}}(\ell) f_{\mathcal{N}}(\ell, \mu + \hat{\ell}_i, V_{A,\ell} + V_{\text{RE}} + V_{\text{O}}) d\ell \quad (32)$$

551 would be used in calculations of mean fitness and the average derivative of expected fitness
552 with respect to latent value.

553 Phenotypic change caused by changes in allele frequencies in response to selection is calcu-
554 lated as

$$\Delta \bar{z} = \int g^{-1}(\ell) f_{\mathcal{N}}(\ell, \mu + \Delta\mu, V_{A,\ell} + V_{\text{RE}} + V_{\text{O}}) d\ell - \bar{z}. \quad (33)$$

555 Or, if fixed effects are included in the model:

$$\Delta \bar{z} = \frac{1}{N} \sum_{i=1}^N \int g^{-1}(\ell) f_{\mathcal{N}}(\ell, \mu + \hat{\ell}_i + \Delta\mu, V_{A,\ell} + V_{\text{RE}} + V_{\text{O}}) d\ell - \bar{z}. \quad (34)$$

556 Note that, in this second equation, \bar{z} must be computed as in Eq. 17 and that this equation
557 assumes that the distribution of fixed effects for the offspring generation is the same as for the
558 parental one.

559 Another derivation of the expected evolutionary response using the Price-Robertson identity
560 (Robertson, 1966; Price, 1970) is given in the Supplementary Information (section C).

561 **The simulation study revisited**

562 Using the same replicates as in the simulation study above, we used Eqs. 29 to 34 to predict
563 phenotypic evolution. This procedure provides greatly improved predictions of evolutionary
564 change on the observed scale (Fig. 3, top row). However, somewhat less response to selection is
565 observed than is predicted. This deviation occurs because, in addition to producing a perma-
566 nent evolutionary response in the mean value on the latent scale, directional selection creates
567 a transient reduction of additive genetic variance due to linkage disequilibrium. Because the
568 link function is non-linear, this transient change in the variance on the latent scale generates
569 a transient change in the mean on the expected and observed scales. Following several genera-
570 tions of random mating, the evolutionary change on the observed scale would converge on the
571 predicted values. We simulated such a generation at equilibrium by simply drawing breeding

572 values for the post-selection sample from a distribution with the same variance as in the parental
573 generation. This procedure necessarily generated a strong match between predicted and simu-
574 lated evolution (Fig. 3, bottom row). Additionally, the effects of transient reduction in genetic
575 variance on the latent scale could be directly modelled, for example, using Bulmer's (1971)
576 approximations for the transient dynamics of the genetic variance in response to selection.

577 Discussion

578 The general approach outlined here for quantitative genetic inference with GLMMs has several
579 desirable features: *(i)* it is a general framework, which should work with any given GLMM
580 and especially, any link and distribution function, *(ii)* provides mechanisms for rigorously han-
581 dling fixed effects, which can be especially important in GLMMs, and *(iii)* it can be used for
582 evolutionary prediction under standard GLMM assumptions about the genetic architecture of
583 traits.

584 Currently, with the increasing applicability of GLMMs, investigators seem eager to convert
585 to the observed data scale. It seems clear that conversions between scales are generally useful.
586 However, it is of note that the underlying assumption when using GLMMs for evolutionary
587 prediction is that predictions hold on the latent scale. Hence, some properties of heritabilities
588 for additive Gaussian traits, particularly the manner in which they can be used to predict
589 evolution, do not hold on the data scale for non-Gaussian traits, even when expressed on the
590 data scale. Yet, given an estimate of a fitness function, no further assumptions are necessary to
591 predict evolution on the data scale, via the latent scale (as with Eqs. 29, 31, and 33), over and
592 above those that are made in the first place upon deciding to pursue GLMM-based quantitative
593 genetic analysis. Hence we recommend using this framework to produce accurate predictions
594 about evolutionary scenarios.

595 We have highlighted important ways in which fixed effects influence quantitative genetic in-
596 ferences with GLMMs, and developed an approach for handling these complexities. In LMMs,
597 the main consideration pertaining to fixed effects is that they explain variance, and some or all
598 of this variance might be inappropriate to exclude from an assessment of V_P when calculating
599 heritabilities (Wilson, 2008). This aspect of fixed effects is relevant to GLMMs, but further-

600 more, all parameters on the expected and observed scales, not just means, are influenced by
601 fixed effects in GLMMs; this includes additive genetic and phenotypic variances. This fact
602 necessitates particular care in interpreting GLMMs. Our work clearly demonstrates that con-
603 sideration of fixed effects is essential, and the exact course of action needs to be considered
604 on a case-by-case basis. Integrating over fixed effects would solve, in particular, the issue of
605 intercept arbitrariness illustrated with the Soay sheep example. Yet cases may often arise where
606 fixed effects are fitted, but where one would not want to integrate over them (e.g. because they
607 represent experimental rather than natural variability). In such cases, it will be important to
608 work with a biologically meaningful intercept, which can be achieved for example by centring
609 covariates on relevant values (Schielzeth, 2010). Finally, note that this is not an all-or-none
610 alternative: in some situations, it could be relevant to integrate over some fixed effects (e.g. of
611 biological importance) while some other fixed effects (e.g. those of experimental origins) would
612 be left aside.

613 One of the most difficult concepts in GLMMs seen as a non-linear developmental model
614 (Morrissey, 2015) is that an irreducible noise is attached to the observed data. This is the
615 reason why we believe that distinguishing between expected and observed data scale does have
616 a biological meaning. Researchers using GLMMs need to realise that this kind of model can
617 assume a large variance in the observed data with very little variance on the latent and expected
618 data scales. For example, a Poisson/log GLMM with a latent mean $\mu = 0$ and a total latent
619 variance of 0.5 will result in observed data with a variance $V_{P,obs} = 2.35$. Less than half of this
620 variance lies in the expected data scale ($V_{P,exp} = 1.07$), the rest is residual Poisson variation.
621 Our model hence assumes that more than half of the measured variance comes from totally
622 random noise. Hence, even assuming that the whole latent variance is composed of additive
623 genetic variance, the heritability will never reach a value above 0.5. Whether this random noise
624 should be accounted for when computing heritabilities (i.e. whether we should compute h_{exp}^2
625 or h_{obs}^2) depends on the evolutionary question under study. In many instances, it is likely that
626 natural selection will act directly on realised values rather than their expectations, in which case
627 h_{obs}^2 should be preferred. We recommend however, that, along with $V_{A,obs}$, all other variances
628 (including V_O , $V_{P,exp}$ and $V_{P,obs}$) are reported by researchers.

629 The expressions given here for quantitative genetic parameters on the expected and ob-

630 served data scales are exact, given the GLMM model assumptions, in two senses. First, they
631 are not approximations, such as might be obtained by linear approximations (Browne *et al.*,
632 2005). Second, they are expressions for the parameters of direct interest, rather than convenient
633 substitutes. For example, the calculation (also suggested by Browne *et al.* 2005) of variance
634 partition coefficients (i.e. intraclass correlations) on an underlying scale only provides a value
635 of the broad-sense heritability (e.g. using the genotypic variance arising from additive genetic
636 effects on the latent scale).

637 The framework developed here (including univariate and multivariate parameters computa-
638 tion and evolutionary predictions on the observed data scale) is implemented in the R package
639 QGGLMM available at <https://github.com/devillemereuil/qgglm>. Note that the package
640 does not perform any GLMM inference but only implements the hereby introduced framework
641 for analysis posterior to a GLMM inference. While the calculations we provide will often (i.e.
642 when no analytical formula exists) be more computationally demanding than calculations on
643 the latent scale, they will be direct ascertainments of specific parameters of interest, since the
644 scale of evolutionary interest is likely to be the observed data scale, rather than the latent
645 scale (unless some artificial selection is applied to predicted latent breeding values as in mod-
646 ern animal breeding). Most applications should not be onerous. Computations of means and
647 (additive genetic) variances took less than a second on a 1.7 GHz processor when using our
648 R functions on the Soay sheep data set. Summation over fixed effects, and integration over
649 1000 posterior samples of the fitted model took several minutes. When analytical expressions
650 are available (e.g. for Poisson/log, Binomial/probit and Negative-Binomial/log, see the sup-
651plementary information and R package documentation), these computations are considerably
652 accelerated.

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Table 1: Parameters from the GLMM-based quantitative genetic analysis of Soay sheep (*Ovis aries*) lamb first-year survival. All estimates are reported as posterior modes with 95% credible intervals. The intercept in this model is arbitrarily defined for female lambs without twins, born to average age (4.8 years) mothers.

Parameter	Posterior mode with 95% CI
(a) Fixed effects	
Intercept	2.686 (1.631 – 3.299)
Sex (male vs. female)	-1.185 (-1.436 – -0.932)
Twin (twin vs. singleton)	-2.383 (-3.315 – -1.760)
Maternal age, linear term	0.238 (0.092 – 0.384)
Maternal age, quadratic term	-0.169 (-0.196 – -0.148)
Maternal age, cubic term	0.014 (0.010 – 0.019)
Sex-twin interaction	0.497 (0.016 – 1.016)
Sex-maternal age interaction	-0.020 (-0.103 – 0.070)
(b) Random effects	
$V_{A,\ell}$	0.882 (0.256 – 1.542)
V_{mother}	0.467 (0.213 – 0.876)
V_{year}	3.062 (1.814 – 5.635)

Table 2: Estimates of expected and observed scale phenotypic mean and variances, and additive genetic variance, for three different treatments of the fixed effects, as modelled on the linear scale with a GLMM, and reported in table 1. Additive genetic variance and heritability on the latent scales are also reported for comparison. Note that h_{lat}^2 is slightly lower when averaging over fixed effects, since the variance they explain is then accounted for.

Quantity	Arbitrary intercept (singleton female)	Arbitrary intercept (twin male)	Averaging over all fixed effects
$V_{A,\ell}$	0.915 (0.275 – 1.66)	0.915 (0.275 – 1.66)	0.915 (0.275 – 1.66)
h_{lat}^2	0.159 (0.056 – 0.27)	0.159 (0.056 – 0.27)	0.117 (0.0417 – 0.194)
\bar{z}	0.838 (0.721 – 0.887)	0.352 (0.220 – 0.474)	0.446 (0.334 – 0.511)
$V_{A, \text{obs}}$	0.006 (0.002 – 0.015)	0.011 (0.005 – 0.023)	0.013 (0.005 – 0.021)
$V_{P, \text{exp}}$	0.060 (0.034 – 0.095)	0.098 (0.072 – 0.124)	0.123 (0.106 – 0.137)
$V_{P, \text{obs}}$	0.136 (0.108 – 0.206)	0.250 (0.183 – 0.250)	0.250 (0.227 – 0.250)
h_{exp}^2	0.109 (0.043 – 0.201)	0.122 (0.054 – 0.227)	0.102 (0.039 – 0.166)
h_{obs}^2	0.047 (0.017 – 0.085)	0.051 (0.022 – 0.101)	0.043 (0.020 – 0.087)

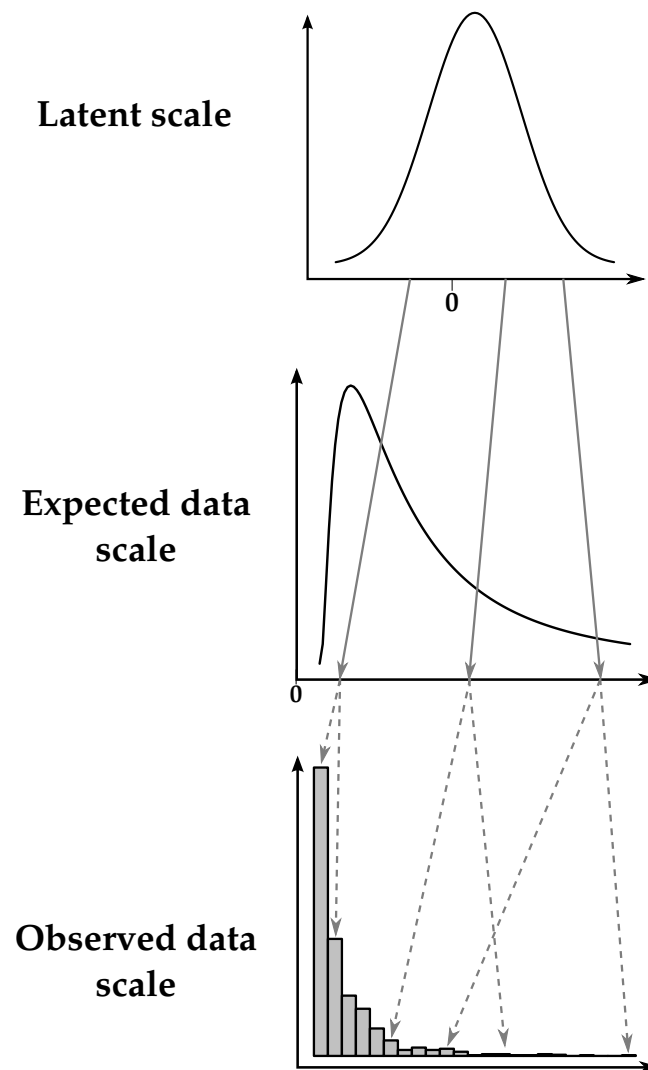


Figure 1: Example of the relationships between the three scales of the GLMM using a Poisson distribution and a logarithm link function. Deterministic relationships are denoted using grey plain arrows, whereas stochastic relationships are denoted using grey dashed arrows. Note that the latent scale is depicted as a simple Gaussian distribution for the sake of simplicity, whereas it is a mixture of Gaussian distributions in reality.

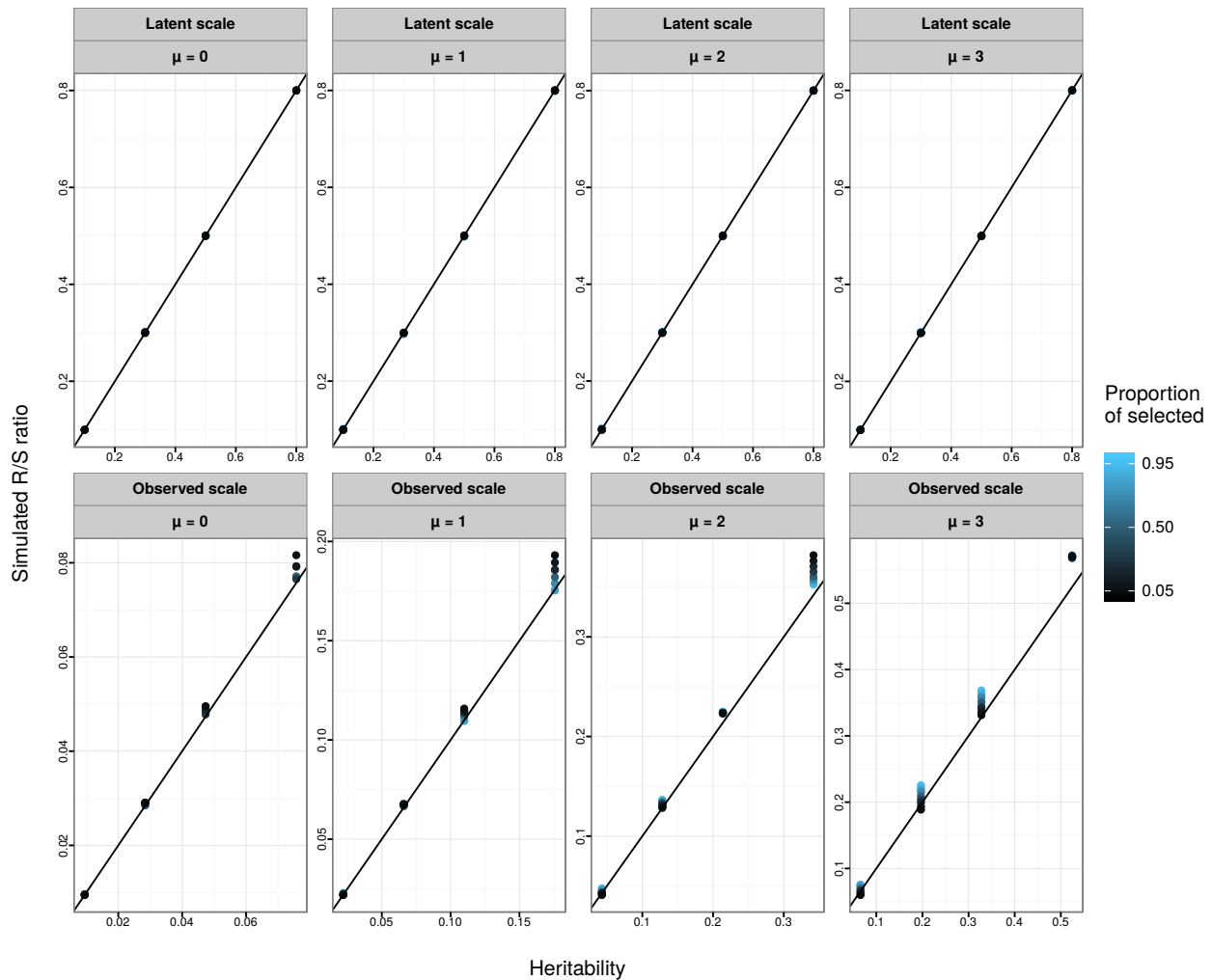


Figure 2: Simulated R/S (evolutionary response over selection differential, or the realised heritability) on the latent (upper panels) or observed data (lower panels) scales against the corresponding-scale heritabilities. Each data point is the average over 10,000 replicates of 10,000 individuals for various latent heritabilities h_{lat}^2 (0.1, 0.3, 0.5, 0.8), latent population mean (μ from 0 to 3, from left to right) and proportion of selected individuals (5%, 10%, 20%, 30%, 50%, 70%, 80%, 90%, 95%, varying from black to blue). The 1:1 line is plotted in black. The breeder's equation is predictive on the latent scale (upper panels), but approximate on the observed data scale (lower panels), because phenotypes and breeding values are not jointly multivariate normal on that scale.

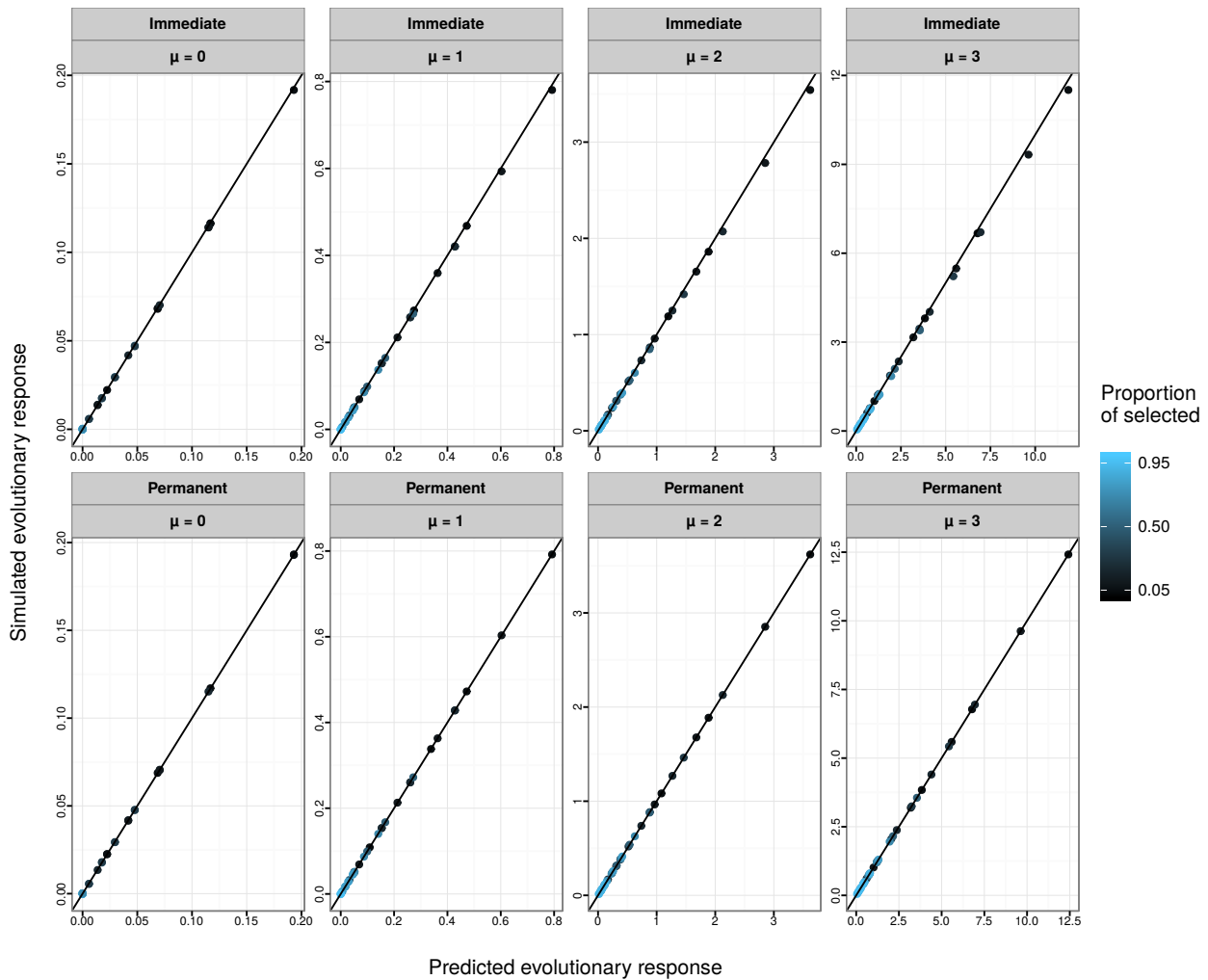


Figure 3: Predicted R_{obs} (phenotypic evolutionary response on the observed scale, see Eq. 34) against the simulated R_{obs} , via evolutionary predictions applied on the latent scale. Each data point is the average over 10,000 replicates of 10,000 individuals for various latent heritabilities h_{lat}^2 (0.1, 0.3, 0.5, 0.8), latent population mean (μ from 0 to 3) and proportion of selected individuals (5%, 10%, 20%, 30%, 50%, 70%, 80%, 90%, 95%, varying from black to blue). The 1:1 line is plotted in black. The upper panels (“Immediate”) show simulations for the response after a single generation, which include both a permanent and transient response to selection arising from linkage disequilibrium. The bottom panels (“permanent”) show simulation results modified to reflect only the permanent response to selection.