

**Supplementary Material**  
Twin Research and Human Genetics

EpiPen: An R package to investigate two-locus epistatic models

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## S1 Model Design Matrices

Each of the GLM model parameterizations is defined by the design matrix that links the parameters  $\beta$  to (a function of) the conditional expected values of the phenotype (Equation 7). The design matrices and parameters for each of the GLM models included in the EpiPen package are provided below. Additional details on the motivation and interpretation of each model can be found in their respective sources.

### $F_2$ Model

Adapting the notation of Zeng, Wang, and Zou (2005), the design matrix for the  $F_2$  model (Anderson & Kempthorne, 1954) is defined as

$$\begin{bmatrix} u_{AABB} \\ u_{AaBB} \\ u_{aaBB} \\ u_{AABb} \\ u_{AaBb} \\ u_{aaBb} \\ u_{AAbb} \\ u_{Aabb} \\ u_{aabb} \end{bmatrix} = \begin{bmatrix} 1 & -1 & -\frac{1}{2} & -1 & -\frac{1}{2} & 1 & \frac{1}{2} & \frac{1}{2} & \frac{1}{4} \\ 1 & 0 & \frac{1}{2} & -1 & -\frac{1}{2} & 0 & -\frac{1}{2} & 0 & -\frac{1}{4} \\ 1 & 1 & -\frac{1}{2} & -1 & -\frac{1}{2} & -1 & \frac{1}{2} & -\frac{1}{2} & \frac{1}{4} \\ 1 & -1 & -\frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 & -\frac{1}{2} & -\frac{1}{4} \\ 1 & 0 & \frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 & 0 & \frac{1}{4} \\ 1 & 1 & -\frac{1}{2} & 0 & \frac{1}{2} & 0 & 0 & \frac{1}{2} & -\frac{1}{4} \\ 1 & -1 & -\frac{1}{2} & 1 & -\frac{1}{2} & -1 & -\frac{1}{2} & \frac{1}{2} & \frac{1}{4} \\ 1 & 0 & \frac{1}{2} & 1 & -\frac{1}{2} & 0 & \frac{1}{2} & 0 & -\frac{1}{4} \\ 1 & 1 & -\frac{1}{2} & 1 & -\frac{1}{2} & 1 & -\frac{1}{2} & -\frac{1}{2} & \frac{1}{4} \end{bmatrix} \begin{bmatrix} \mu \\ a_a \\ d_a \\ a_b \\ d_b \\ aa_{ab} \\ da_{ab} \\ ad_{ab} \\ dd_{ab} \end{bmatrix}$$

This is a natural extension from coding the effects of a single locus as

$$\begin{bmatrix} u_{AA} \\ u_{Aa} \\ u_{aa} \end{bmatrix} = \begin{bmatrix} 1 & -1 & -\frac{1}{2} \\ 1 & 0 & \frac{1}{2} \\ 1 & 1 & -\frac{1}{2} \end{bmatrix} \begin{bmatrix} \mu \\ a \\ d \end{bmatrix}$$

## $F_\infty$ Model

Adapting the notation of Zeng et al. (2005), the design matrix for the  $F_\infty$  model (Hayman & Mather, 1955) is defined as

$$\begin{bmatrix} u_{AABB} \\ u_{AaBB} \\ u_{aaBB} \\ u_{AABb} \\ u_{AaBb} \\ u_{aaBb} \\ u_{AAAb} \\ u_{Aabb} \\ u_{aabb} \end{bmatrix} = \begin{bmatrix} 1 & -1 & 0 & -1 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & -1 & 0 & 0 & -1 & 0 & 0 \\ 1 & 1 & 0 & -1 & 0 & -1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 1 & 0 & 0 & -1 & 0 \\ 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 \\ 1 & 1 & 0 & 0 & 1 & 0 & 0 & 1 & 0 \\ 1 & -1 & 0 & 1 & 0 & -1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 1 & 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \mu \\ a_a \\ d_a \\ a_b \\ d_b \\ aa_{ab} \\ da_{ab} \\ ad_{ab} \\ dd_{ab} \end{bmatrix}$$

This is a natural extension of coding the effects of a single locus as

$$\begin{bmatrix} u_{AA} \\ u_{Aa} \\ u_{aa} \end{bmatrix} = \begin{bmatrix} 1 & -1 & 0 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \end{bmatrix} \begin{bmatrix} \mu \\ a \\ d \end{bmatrix}$$

## G2A Model

The General Two-Allele Model (Zeng et al., 2005) incorporates the marginal allele frequencies for each locus  $p_a$  and  $p_b$ , respectively. Similarly, denote the major allele frequencies as  $q_a$  and  $q_b$ , respectively. The resulting model is specified with the following design matrix.

$$\begin{bmatrix} u_{AABB} \\ u_{AaBB} \\ u_{aaBB} \\ u_{AABb} \\ u_{AaBb} \\ u_{aaBb} \\ u_{AAAb} \\ u_{Aabb} \\ u_{aabb} \end{bmatrix} = \begin{bmatrix} 1 & -2p_a & -2p_a^2 & -2p_b & -2p_b^2 & 4p_a p_b & 4p_a^2 p_b & 4p_a p_b^2 & 4p_a^2 p_b^2 \\ 1 & q_a - p_a & 2p_a q_a & -2p_b & -2p_b^2 & 2(p_a - q_a)p_b & -4p_a q_a p_b & 2(p_a - q_a)p_b^2 & -4p_a q_a p_b^2 \\ 1 & 2q_a & -2q_a^2 & -2p_b & -2p_b^2 & -4q_a p_b & 4q_a^2 p_b & -4q_a p_b^2 & 4q_a^2 p_b^2 \\ 1 & -2p_a & -2p_a^2 & q_b - p_b & 2p_b q_b & 2p_a(p_b - q_b) & 2p_a^2(p_b - q_b) & -4p_a p_b q_b & -4p_a^2 p_b q_b \\ 1 & q_a - p_a & 2p_a q_a & q_b - p_b & 2p_b q_b & (p_a - q_a)(p_b - q_b) & 2p_a q_a(q_b - p_b) & 2(q_a - p_a)p_b q_b & 4p_a q_a p_b q_b \\ 1 & 2q_a & -2q_a^2 & q_b - p_b & 2p_b q_b & -2q_a(p_b - q_b) & 2q_a^2(p_b - q_b) & 4q_a p_b q_b & -4q_a^2 p_b q_b \\ 1 & -2p_a & -2p_a^2 & 2q_b & -2q_b^2 & -4p_a q_b & -4p_a^2 q_b & 4p_a q_b^2 & 4p_a^2 q_b^2 \\ 1 & q_a - p_a & 2p_a q_a & 2q_b & -2q_b^2 & -2(p_a - q_a)q_b & 4p_a q_a q_b & 2(p_a - q_a)q_b^2 & -4p_a q_a q_b^2 \\ 1 & 2q_a & -2q_a^2 & 2q_b & -2q_b^2 & 4q_a q_b & -4q_a^2 q_b & -4q_a q_b^2 & 4q_a^2 q_b^2 \end{bmatrix} \begin{bmatrix} \mu \\ a_a \\ d_a \\ a_b \\ d_b \\ aa_{ab} \\ da_{ab} \\ ad_{ab} \\ dd_{ab} \end{bmatrix}$$

This corresponds to coding the effects at a single locus with allele frequency  $p$  as

$$\begin{bmatrix} u_{AA} \\ u_{Aa} \\ u_{aa} \end{bmatrix} = \begin{bmatrix} 1 & -2p & -2p^2 \\ 1 & 1 - 2p & 2p(1 - p) \\ 1 & 2(1 - p) & -2(1 - p)^2 \end{bmatrix} \begin{bmatrix} \mu \\ a \\ d \end{bmatrix}$$

## Unweighted Model

Cheverud and Routman (1995) proposed a model that uses the unweighted mean of the genotype values as the overall mean. The design matrix for this model is given by

$$\begin{bmatrix} u_{AABB} \\ u_{AaBB} \\ u_{aaBB} \\ u_{AABb} \\ u_{AaBb} \\ u_{aaBb} \\ u_{AAbb} \\ u_{Aabb} \\ u_{aabb} \end{bmatrix} = \begin{bmatrix} 1 & -1 & -\frac{1}{3} & -1 & -\frac{1}{3} & 1 & \frac{1}{3} & \frac{1}{3} & \frac{1}{9} \\ 1 & 0 & \frac{2}{3} & -1 & -\frac{1}{3} & 0 & -\frac{2}{3} & 0 & -\frac{2}{9} \\ 1 & 1 & -\frac{1}{3} & -1 & -\frac{1}{3} & -1 & \frac{1}{3} & -\frac{1}{3} & \frac{1}{9} \\ 1 & -1 & -\frac{1}{3} & 0 & \frac{2}{3} & 0 & 0 & -\frac{2}{3} & -\frac{2}{9} \\ 1 & 0 & \frac{2}{3} & 0 & \frac{2}{3} & 0 & 0 & 0 & \frac{4}{9} \\ 1 & 1 & -\frac{1}{3} & 0 & \frac{2}{3} & 0 & 0 & \frac{2}{3} & -\frac{2}{9} \\ 1 & -1 & -\frac{1}{3} & 1 & -\frac{1}{3} & -1 & -\frac{1}{3} & \frac{1}{3} & \frac{1}{9} \\ 1 & 0 & \frac{2}{3} & 1 & -\frac{1}{3} & 0 & \frac{2}{3} & 0 & -\frac{2}{9} \\ 1 & 1 & -\frac{1}{3} & 1 & -\frac{1}{3} & 1 & -\frac{1}{3} & -\frac{1}{3} & \frac{1}{9} \end{bmatrix} \begin{bmatrix} \mu \\ a_a \\ d_a \\ a_b \\ d_b \\ aa_{ab} \\ da_{ab} \\ ad_{ab} \\ dd_{ab} \end{bmatrix}$$

where effects for a single locus could be similarly coded as

$$\begin{bmatrix} u_{AA} \\ u_{Aa} \\ u_{aa} \end{bmatrix} = \begin{bmatrix} 1 & -1 & -\frac{1}{3} \\ 1 & 0 & \frac{2}{3} \\ 1 & 1 & -\frac{1}{3} \end{bmatrix} \begin{bmatrix} \mu \\ a \\ d \end{bmatrix}$$

## NOIA Model

Alvarez-Castro and Carlborg (2007) propose two forms of the NOIA model. Let  $p_{AA}$ ,  $p_{Aa}$  and  $p_{aa}$  be the genotype frequencies for the indicated genotypes at the first locus, and let  $\mu_a = p_{Aa} + 2p_{aa}$  be the mean genotype at the first locus. Similarly define  $p_{BB}$ ,  $p_{Bb}$ ,  $p_{bb}$ , and  $\mu_b$  for the second locus. Then the NOIA Functional model is defined by

$$\begin{bmatrix} u_{AABB} \\ u_{AaBB} \\ u_{aaBB} \\ u_{AABb} \\ u_{AaBb} \\ u_{aaBb} \\ u_{AAbb} \\ u_{Aabb} \\ u_{aabb} \end{bmatrix} = \begin{bmatrix} 1 & -\mu_a & -p_{Aa} & -\mu_b & -p_{Bb} & \mu_a\mu_b & p_{Aa}\mu_b & \mu_a p_{Bb} & p_{Aa}p_{Bb} \\ 1 & 1-\mu_a & 1-p_{Aa} & -\mu_b & -p_{Bb} & -(1-\mu_a)\mu_b & -(1-p_{Aa})\mu_b & -(1-\mu_a)p_{Bb} & -(1-p_{Aa})p_{Bb} \\ 1 & 2-\mu_a & -p_{Aa} & -\mu_b & -p_{Bb} & -(2-\mu_a)\mu_b & p_{Aa}\mu_b & -(2-\mu_a)p_{Bb} & p_{Aa}p_{Bb} \\ 1 & -\mu_a & -p_{Aa} & 1-\mu_b & 1-p_{Bb} & -\mu_a(1-\mu_b) & -p_{Aa}(1-\mu_b) & -\mu_a(1-p_{Bb}) & -p_{Aa}(1-p_{Bb}) \\ 1 & 1-\mu_a & 1-p_{Aa} & 1-\mu_b & 1-p_{Bb} & (1-\mu_a)(1-\mu_b) & (1-p_{Aa})(1-\mu_b) & (1-\mu_a)(1-p_{Bb}) & (1-p_{Aa})(1-p_{Bb}) \\ 1 & 2-\mu_a & -p_{Aa} & 1-\mu_b & 1-p_{Bb} & (2-\mu_a)(1-\mu_b) & -p_{Aa}(1-\mu_b) & (2-\mu_a)(1-p_{Bb}) & -p_{Aa}(1-p_{Bb}) \\ 1 & -\mu_a & -p_{Aa} & 2-\mu_b & -p_{Bb} & -\mu_a(2-\mu_b) & -p_{Aa}(2-\mu_b) & \mu_a p_{Bb} & p_{Aa}p_{Bb} \\ 1 & 1-\mu_a & 1-p_{Aa} & 2-\mu_b & -p_{Bb} & (1-\mu_a)(2-\mu_b) & (1-p_{Aa})(2-\mu_b) & -(1-\mu_a)p_{Bb} & -(1-p_{Aa})p_{Bb} \\ 1 & 2-\mu_a & -p_{Aa} & 2-\mu_b & -p_{Bb} & (2-\mu_a)(2-\mu_b) & -p_{Aa}(2-\mu_b) & -(2-\mu_a)p_{Bb} & p_{Aa}p_{Bb} \end{bmatrix} \begin{bmatrix} R \\ a_a \\ d_a \\ a_b \\ d_b \\ aa_{ab} \\ da_{ab} \\ ad_{ab} \\ dd_{ab} \end{bmatrix}$$

This is an extension of the following single-locus model

$$\begin{bmatrix} u_{AA} \\ u_{Aa} \\ u_{aa} \end{bmatrix} = \begin{bmatrix} 1 & -\mu_a & -p_{Aa} \\ 1 & 1 - \mu_a & 1 - p_{Aa} \\ 1 & 2 - \mu_a & -p_{Aa} \end{bmatrix} \begin{bmatrix} R \\ a \\ d \end{bmatrix}$$

The NOIA Statistical model is similarly defined by the same expansion of the single-locus model

$$\begin{bmatrix} u_{AA} \\ u_{Aa} \\ u_{aa} \end{bmatrix} = \begin{bmatrix} 1 & -\mu_a & -\frac{2p_{Aa}p_{aa}}{p_{AA}+p_{aa}-(p_{AA}-p_{aa})^2} \\ 1 & 1 - \mu_a & \frac{4p_{AA}p_{aa}}{p_{AA}+p_{aa}-(p_{AA}-p_{aa})^2} \\ 1 & 2 - \mu_a & -\frac{2p_{AA}p_{Aa}}{p_{AA}+p_{aa}-(p_{AA}-p_{aa})^2} \end{bmatrix} \begin{bmatrix} \mu \\ \alpha \\ \delta \end{bmatrix}$$

yielding a two-locus model with parameters  $\beta = [\mu, \alpha_a, \delta_a, \alpha_b, \delta_b, (\alpha\alpha)_{ab}, (\delta\alpha)_{ab}, (\alpha\delta)_{ab}, (\delta\delta)_{ab}]'$ . The full design matrix is omitted here due to space limitations.

## Genotype Model

Finally, the genotype model described by Cordell (2009, Supplementary Box S1), is defined by

$$\begin{bmatrix} u_{AABB} \\ u_{AaBB} \\ u_{aaBB} \\ u_{AABb} \\ u_{AaBb} \\ u_{aaBb} \\ u_{AAAb} \\ u_{AAbb} \\ u_{Aabb} \\ u_{aabb} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 1 & 0 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 & 0 & 0 & 1 & 0 \\ 1 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} \alpha \\ \gamma_1 \\ \gamma_2 \\ \beta_1 \\ \beta_2 \\ i_{11} \\ i_{12} \\ i_{21} \\ i_{22} \end{bmatrix}$$

As with the other models, the interaction parameters for the genotype model correspond to cross-products of a single-locus model.

$$\begin{bmatrix} u_{AA} \\ u_{Aa} \\ u_{aa} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 1 & 1 & 0 \\ 1 & 0 & 1 \end{bmatrix} \begin{bmatrix} \alpha \\ \gamma_1 \\ \gamma_2 \end{bmatrix}$$

## S2 NOIA Model Variance Components

The orthogonal parameters of the NOIA Statistical model (Alvarez-Castro & Carlborg, 2007) correspond to the orthogonal variance components for partitioning the total variance explained by the two loci  $V_g$  (Equations 4, 6). This enables direct conversion between the GLM model parameters and variance components. The relationship between the two models is detailed below.

$$V_{A_a} = \alpha_a^2 [p_{A_a}(1 - p_{A_a}) + 4p_{aa}(1 - p_{A_a}) - 4p_{aa}^2]$$

$$V_{D_a} = \delta_a^2 \left[ \frac{4p_{AA}p_{A_a}p_{aa}}{p_{A_a}(1 - p_{A_a}) + 4p_{aa}(1 - p_{A_a}) - 4p_{aa}^2} \right]$$

$$V_{A_b} = \alpha_b^2 [p_{B_b}(1 - p_{B_b}) + 4p_{bb}(1 - p_{B_b}) - 4p_{bb}^2]$$

$$V_{D_b} = \delta_b^2 \left[ \frac{4p_{BB}p_{B_b}p_{bb}}{p_{B_b}(1 - p_{B_b}) + 4p_{bb}(1 - p_{B_b}) - 4p_{bb}^2} \right]$$

$$V_{AA} = (\alpha\alpha)_{ab}^2 [p_{A_a}(1 - p_{A_a}) + 4p_{aa}(1 - p_{A_a}) - 4p_{aa}^2] [p_{B_b}(1 - p_{B_b}) + 4p_{bb}(1 - p_{B_b}) - 4p_{bb}^2]$$

$$V_{DA} = (\delta\alpha)_{ab}^2 \left[ \frac{4p_{AA}p_{A_a}p_{aa}}{p_{A_a}(1 - p_{A_a}) + 4p_{aa}(1 - p_{A_a}) - 4p_{aa}^2} \right] [p_{B_b}(1 - p_{B_b}) + 4p_{bb}(1 - p_{B_b}) - 4p_{bb}^2]$$

$$V_{AD} = (\alpha\delta)_{ab}^2 [p_{A_a}(1 - p_{A_a}) + 4p_{aa}(1 - p_{A_a}) - 4p_{aa}^2] \left[ \frac{4p_{BB}p_{B_b}p_{bb}}{p_{B_b}(1 - p_{B_b}) + 4p_{bb}(1 - p_{B_b}) - 4p_{bb}^2} \right]$$

$$V_{DD} = (\delta\delta)_{ab}^2 \left[ \frac{4p_{AA}p_{A_a}p_{aa}}{p_{A_a}(1 - p_{A_a}) + 4p_{aa}(1 - p_{A_a}) - 4p_{aa}^2} \right] \left[ \frac{4p_{BB}p_{B_b}p_{bb}}{p_{B_b}(1 - p_{B_b}) + 4p_{bb}(1 - p_{B_b}) - 4p_{bb}^2} \right]$$

## References

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