

File S1: Sample code for linear mixed models

The linear mixed models employed were all variations on the following general model:

$$Y = X\beta + \sum_{j=1}^5 Z_j\gamma_j + \epsilon$$

where:

Y is an $n \times 1$ vector of responses.

X is a fixed effects design matrix which can accommodate sex and treatment (and the interaction thereof), the pre-treatment phenotype value, as well as an intercept.

β is a vector of fixed-effect parameters associated with X .

Z_j is an $n \times q_j$ random effect design matrix.

γ_j is the $q_j \times 1$ random effect vector associated with the j th random effect.

Our models of interest include up to five random effects: a batch effect (γ_1), parental strain effect (γ_2), a parental strain-by-treatment interaction effect (γ_3), a sex-by-strain effect (γ_4), and sex-by-strain-by-treatment interaction effect (γ_5). The associated random design matrices are constructed as follows:

- Each row of Z_1 has a single nonzero element, which is a 1 in the column corresponding to mouse's batch.
- Each row of Z_2 has two nonzero elements, which are 1's in the columns corresponding to the parental strains.
- Z_3 is constructed from Z_2 by switching the 1's to -1's for mice that are treated with placebo.
- Z_4 and Z_5 are constructed from Z_2 and Z_3 , respectively, by switching the signs of the two elements in each row corresponding to female mice.

We assume that the γ_j 's are mutually independent and $\gamma_j \sim N(0, \sigma_j^2 I_{q_j \times q_j})$. Further, the error term $\epsilon \sim N(0, \sigma_\epsilon^2 * I_{n \times n})$, independent of the random effects (n denotes the total sample size for the phenotype being studied).

All our models were fit with the SAS code below, where &depvar and &indvars are macro variables that contain the dependent and relevant independent variables, respectively, for the phenotype being modeled, and &numbatch and &numparent correspond to the number of batches and number of parental strains represented in the dataset.

```
proc mixed data=dataset;  
  model &depvar. = &indvars. / s;  
  random batch1-batch&numbatch. / type = TOEP(1);  
  random addint1-addint&numparent. / type = TOEP(1);  
  random addtmt1-addtmt&numparent. / type = TOEP(1);  
  random addsex1-addsex&numparent. / type = TOEP(1);  
  random addsextmt1-addsextmt&numparent. / type = TOEP(1);  
run;
```