

Interaction and genotypes

SDC

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1 Intro

This is a brief account of (at least one side of) a discussion between BxC, AA, EJ and TS on 8 August 2016, trying to hammer out disagreements as precisely as possible

2 Statement of the controversy

The most general model described in the paper is a model where the GT (y) dependence on PAEE is described by a separate straight line for the three genotypes WT, HE and HO. The lines estimated under this model are shown in the paper as the left panel of figure 1, and the parametrization the three groups is (a being the measured PAEE):

$$\begin{aligned} y_{\text{WT}} &= \mu + a\beta_a \\ y_{\text{HE}} &= \mu + a\beta_a + \beta_{\text{HE}} + a\beta_{\text{HE}\times a} = (\mu + \beta_{\text{HE}}) + a(\beta_a + \beta_{\text{HE}\times a}) \\ y_{\text{HO}} &= \mu + a\beta_a + \beta_{\text{HO}} + a\beta_{\text{HO}\times a} = (\mu + \beta_{\text{HO}}) + a(\beta_a + \beta_{\text{HO}\times a}) \end{aligned}$$

This is also illustrated as the “Full base model” in figure 1 here.

This is an interaction model, stating that the dependence on PAEE is linear in all three genotypes but different between the three genotypes.

A model of no interaction would be one where the dependence of PAEE were the *same* for all three genotypes, corresponding to the null hypothesis of no interaction:

$$H_0 : \quad \beta_{\text{HE}\times a} = \beta_{\text{HO}\times a} = 0$$

and thus a 2-degree of freedom test. This is comparing the “Full base model” and the “Main effects PAEE model” in figure 1 (bottom right vs. top left).

What is described in the paper (and actually computed and used) is however the one degree of freedom test of the hypothesis:

$$H_0 : \quad \beta_{\text{HO}\times a} = 0$$

This corresponds to a reduction to a model where the dependence of the GT on PAEE has the *same* slope for WT and HO, but HE has a slope *different* from this.

My claim is that this is a biologically implausible model simply on the grounds that the HE is an intermediate group between the WT and HO. It is not reasonable to have the two outer groups have similar dependence on PAEE and the middle group a different one.

Another way of formulating this is that the model tested as null is a model that presupposes that the three genotypes are exchangeable (or at least the WT and HO are adjacent groups), that is *not* ordered as WT<HE<HO, Accepting this ordering will place restrictions on models that can be sensibly fitted, among other excluding the model described.

3 Possible modeling solutions

3.1 Recessive or dominant interaction

From a purely interaction point of view it would be possible to test the interaction in two steps, the first one being either the recessive (same PAEE effect in WT and HE) or

dominant (same PAEE effect in HE and HO):

$$\begin{aligned} \text{Recessive :} & \quad \beta_{\text{HE} \times a} = 0 \\ \text{Dominant :} & \quad \beta_{\text{HE} \times a} = \beta_{\text{HO} \times a} \end{aligned}$$

Then, *conditional* on either of these, it would be possible to do a one d.f. test of the interaction as:

$$\begin{aligned} H_0 | \text{Recessive :} & \quad \beta_{\text{HO} \times a} = 0 \\ H_0 | \text{Dominant :} & \quad \beta_{\text{HE} \times a} = \beta_{\text{HO} \times a} = 0 \end{aligned}$$

But essentially it would be a two step procedure — two successive tests each with 1 d.f., and in both cases the last test being the one of interest.

3.2 Expansion of the non-PAEE model

An alternative line of arguing would be to note that in the original paper there were but a tiny difference in GT between WT and HE, suggesting a recessive model for the trait.

Hence the logical thing would be to use an expansion of the recessive model and assume:

$$\begin{aligned} y_{\text{WT}} &= \mu + a\beta_a \\ y_{\text{HE}} &= \mu + a\beta_a \\ y_{\text{HO}} &= \mu + a\beta_a + \beta_{\text{HO}} + a * \beta_{\text{HO} \times a} \\ &= (\mu + \beta_{\text{HO}}) + a(\beta_a + \beta_{\text{HO} \times a}) \end{aligned} \tag{1}$$

Under the (admittedly testable) assumption of identical behaviour of GT in the (neighboring!) groups WT and HE, it is now possible to make a one d.f. test of interaction; the null hypothesis being that the PAEE dependence in the HO is the same as the (*assumed* common) dependence on PAEE in the (WT & HE) group:

$$H_0 : \quad \beta_{\text{HO} \times a} = 0$$

The formal looks of this test is as above, but the difference is that it is now a test comparing two other models, *both* of which are biologically plausible.

Of course it might be debated at length whether the base model as outlined in (1) should be used, or whether the base model should allow for a constant difference between WT and HE, that is a term β_{HE} for the constant difference between HE and WT. Either way, the two models compared would both be biologically sensible.

In summary, the controversy is whether we assess the interaction by comparing the two models in the leftmost column (as proposed in the manuscript), or the two models in the middle or rightmost columns as illustrated in figure 1. Only the latter two obey the ordering of the genotypes.

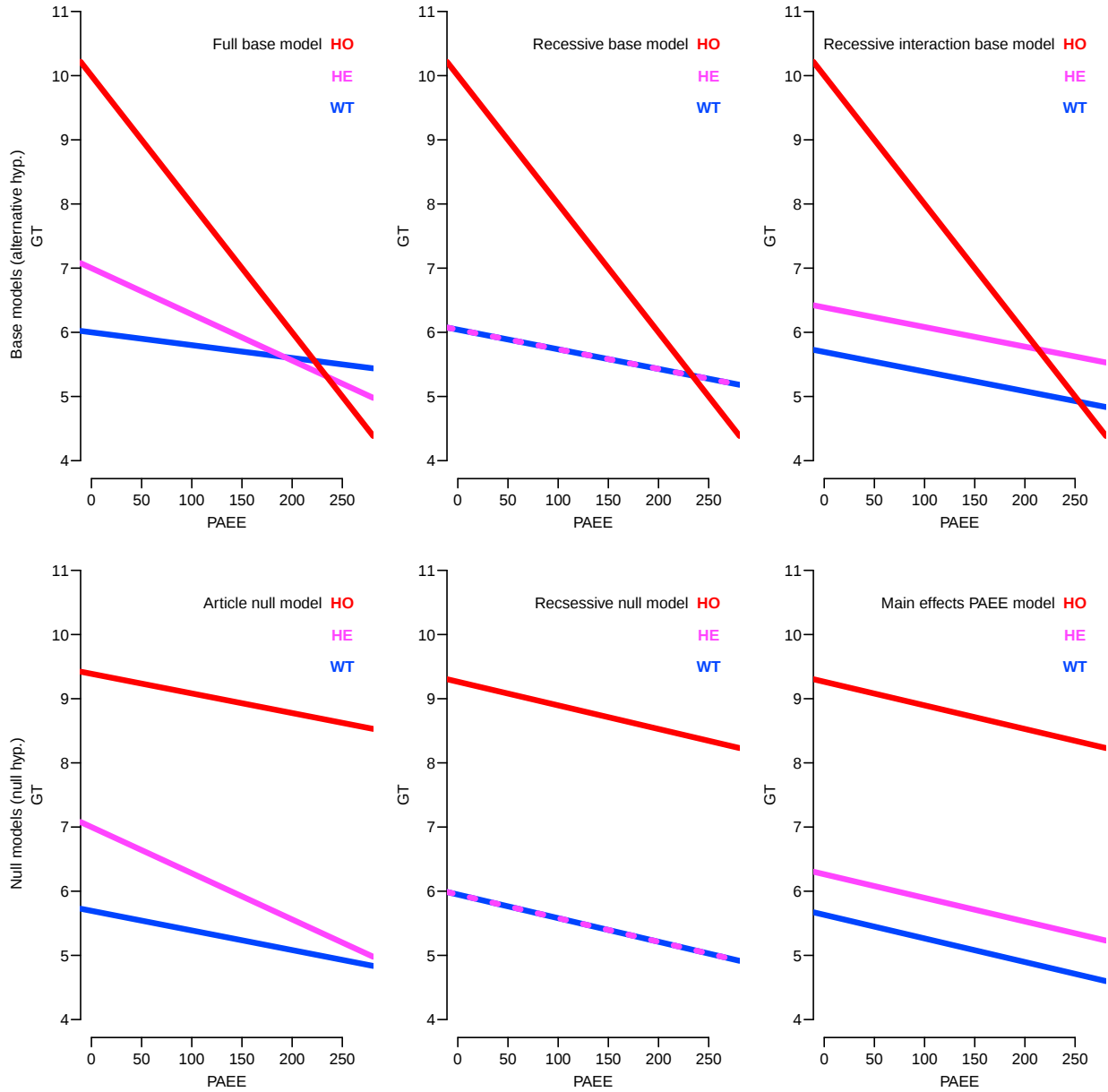


Figure 1: *Illustration of the model comparisons for test of interaction focused on the HO group with 1 d.f.*

The leftmost two models are those described in the paper. The bottom left is the model claimed to be biologically meaningless.

The middle two models are based on an assumed recessive model, there is no difference between WT and HE, neither in the interaction or the main effects model (Recessive null model).

The rightmost two models only assume a recessive structure for the interaction, not for the general level.

The formal 2 d.f. test for interaction is the test comparing the top left with the bottom right model; which can be broken down in the 1 d.f. test of the top left versus the top right (test of the recessive structure of the interaction) and the 1 d.f. test of no interaction given recessive interaction.

Here is the code generating the example plots:

```
> clr <- c("blue","purple","red")
> clr <- c("#0044FF","FF44FF","FF0000")
> awt <- 6.0
> ahe <- 7.0
> aho <- 10
> bwt <- -0.5/250
> bhe <- -1.8/250
> bho <- -5/250
> wt <- c(80,15,5)
> par( mfc=c(2,3), mar=c(3,3,1,1), oma=c(0,1,0,0), mgp=c(3,1,0)/1.6, las=1, bty="n" )
> plot( NA, xlim=c(0,270), ylim=c(4,11),
+       xlab="PAEE", ylab="GT" )
> abline( awt, bwt, lwd=4, col=clr[1] )
> abline( ahe, bhe, lwd=4, col=clr[2] )
> abline( aho, bho, lwd=4, col=clr[3] )
> text( 230, 10.5, "Full base model", adj=1 )
> text( rep(250,3), 9.5+0:2/2, c("WT","HE","HO"), font=2, col=clr)
> plot( NA, xlim=c(0,270), ylim=c(4,11),
+       xlab="PAEE", ylab="GT" )
> bbb <- (bwt*wt[1]+bho*wt[3])/sum(wt[-2])
> abline( awt+100*bbb, bbb, lwd=4, col=clr[1] )
> abline( ahe, bhe, lwd=4, col=clr[2] )
> abline( aho+200*bbb, bbb, lwd=4, col=clr[3] )
> text( 230, 10.5, "Article null model", adj=1 )
> text( rep(250,3), 9.5+0:2/2, c("WT","HE","HO"), font=2, col=clr)
> plot( NA, xlim=c(0,270), ylim=c(4,11),
+       xlab="PAEE", ylab="GT" )
> bbb <- (bwt*wt[1]+bho*wt[3])/sum(wt[-2])
> abline( (awt+ahe)/2+150*bbb, bbb, lwd=4, col=clr[1] )
> abline( (awt+ahe)/2+150*bbb, bbb, lwd=4, col=clr[2], lty="22" )
> abline( aho, bho, lwd=4, col=clr[3] )
> text( 230, 10.5, "Recessive base model", adj=1 )
> text( rep(250,3), 9.5+0:2/2, c("WT","HE","HO"), font=2, col=clr)
> plot( NA, xlim=c(0,270), ylim=c(4,11),
+       xlab="PAEE", ylab="GT" )
> bbb <- (bwt*wt[1]+bhe*wt[2]+bho*wt[3])/sum(wt)
> abline( (awt+ahe)/2+150*bbb, bbb, lwd=4, col=clr[1] )
> abline( (awt+ahe)/2+150*bbb, bbb, lwd=4, col=clr[2], lty="22" )
> abline( aho+200*bbb, bbb, lwd=4, col=clr[3] )
> text( 230, 10.5, "Recessive null model", adj=1 )
> text( rep(250,3), 9.5+0:2/2, c("WT","HE","HO"), font=2, col=clr)
> plot( NA, xlim=c(0,270), ylim=c(4,11),
+       xlab="PAEE", ylab="GT" )
> bbb <- (bwt*wt[1]+bho*wt[3])/sum(wt[-2])
> abline( awt+100*bbb, bbb, lwd=4, col=clr[1] )
> abline( ahe+200*bbb, bbb, lwd=4, col=clr[2] )
> abline( aho, bho, lwd=4, col=clr[3] )
> text( 230, 10.5, "Recessive interaction base model", adj=1 )
> text( rep(250,3), 9.5+0:2/2, c("WT","HE","HO"), font=2, col=clr)
> plot( NA, xlim=c(0,270), ylim=c(4,11),
+       xlab="PAEE", ylab="GT" )
> bbb <- (bwt*wt[1]+bhe*wt[2]+bho*wt[3])/sum(wt)
> abline( awt+100*bbb, bbb, lwd=4, col=clr[1] )
> abline( ahe+200*bbb, bbb, lwd=4, col=clr[2] )
> abline( aho+200*bbb, bbb, lwd=4, col=clr[3] )
> text( 230, 10.5, "Main effects PAEE model", adj=1 )
> text( rep(250,3), 9.5+0:2/2, c("WT","HE","HO"), font=2, col=clr)
> mtext("Base models (alternative hyp.)",side=2,outer=T,at=0.75,las=0,cex=0.66)
> mtext("Null models (null hyp.)",side=2,outer=T,at=0.25,las=0,cex=0.66)
```