**Appendix A: Adapting the alternating optimization algorithm**

To adapt the alternating optimization algorithm to competitive-confirmatory models, the negative intercept (the crossover point *c*) must be excluded from the constraint that all environmental weights sum to 1 in absolute values (i.e., cannot be enforced); this is because the crossover point must be free. While the original approach by Jolicoeur-Martineau et al. (2017) was guaranteed to converge to a local minimum, not enforcing a constraint on *c* means that the model can diverge if the starting point of the crossover is not close enough to its true value or if the true value is very close to -∞ or ∞. This can be prevented by fitting a G×E model with the regular formulation (equation 6), calculating the value of the cross-over point  and refitting the model with the formulation which includes the cross-over point as variable (equation 9) using *c* as starting point. If the crossover point still diverges toward -∞ or ∞, it generally indicates that the interaction effect is too small to estimate and is thus essentially nil (Widaman et al., 2012). Therefore, Belsky and Widaman (2018) suggest testing an interaction only when the magnitude of the F-ratio of the interaction is larger than 1. Fortunately, in models that include latent genetic and environmental scores, this issue occurs infrequently, because the inclusion of multiple genetic and environmental variables in the model tends to considerably increase the effect size of the interaction (Jolicoeur-Martineau et al., 2017).

**Appendix B: Special considerations and recommendations**

In addition to the small change in the alternating optimization algorithm, adapting the theory and testing of G×E to multiple genes and environments requires a few special considerations which need to be taken into account, as they influence how one should construct the competitive-confirmatory models and how the simulations will be set up.

Firstly, the transition from a binary genetic variant to an approximately continuous latent genetic score affects the interpretation of weak and strong competitive-confirmatory models. In cases of a single gene and environment, the interpretation is that individuals who possess no sensitivity gene variants (with a genetic score of 0) are completely non-susceptible to their environment in the strong models (*βe* = 0) and somewhat susceptible in the weak model (*βe* ≠ 0). However, as the number of included genetic variants increases, the probability of an individual possessing no sensitivity gene variants (genetic sensitivity score of 0) approaches zero.

|  |
| --- |
| Assuming that we have k independent binary genetic variants with different frequencies,  i.e. ***g****i* ~ Bernoulli(***θ****i*) for *i* = 1, … , *k*  We have |
|  |

The above means that, when including multiple genetic variants, extremely few (if any) individuals are expected to be completely non-susceptible to their environment. Consequently, weak models cannot be differentiated from strong models based on whether there are individuals that are completely non-susceptible. The only difference between weak and strong models, then, is that the slope of the environment-predicting-outcome regression line starts (with a genetic score of 0) at 0 for strong models and at *βe* for weak models. In practice, distinguishing between weak and strong models is difficult, especially when sample size is small. Thus, although we fit weak and strong models using the competitive-confirmatory approach, we do not consider the difference between weak and strong meaningful for interpretation nor classification purposes. Accordingly, our analyses of simulated data attempt only to classify the general pattern of interaction (i.e. whether it represents diathesis-stress, differential susceptibility, or vantage sensitivity) but not whether the pattern of interaction is weak or strong. Given that the RoS approach cannot naturally distinguish weak and strong models, not trying to determine whether an interaction is weak or strong using the competitive-confirmatory approach means that we can directly compare both approaches.

Secondly, the observable range of the environmental score is unknown a priori (before fitting the model) as the weights of the environmental variables have to be estimated first and the variables included in the environmental score often have different ranges. This not only makes interpretation of the environmental score difficult, but it also makes it difficult to properly select the fixed value of the cross-over point to be used in the vantage sensitivity and diathesis-stress models. To help with interpretation, we recommend rescaling all environmental variables beforehand using a method, such as POMP coding (Cohen, Cohen, Aiken, & West, 1999); this approach rescales all variables to lie in the range [0,100] where 0 is the minimum and 100 the maximum value. Certainly, this step can be ignored when all environmental variables already have the same range of values (e.g., when using the same questionnaire at different time points).

However, even if all environmental are scaled to the same range of observable values, a problem remains; the observed score range will be smaller than the observed range of the environmental variables (e.g. [0,100] when using POMP coding) unless individuals exist in the sample who carry only minimum values for all environmental measures, and conversely individuals with only maximum values for all environmental measures. This issue is encountered very often in small samples and when the environmental variables have unbounded distributions (e.g., normal distribution) or bounded but heavily skewed distributions. Nevertheless, in order to be able to construct the diathesis-stress and vantage sensitivity models, we need to fix the crossover point at, or near, the maximum and minimum observable environmental quality score, respectively.

To account for this issue, we recommend fixing the crossover point to the expected maximum or minimum of the environmental quality score, which is the environmental score that would be obtained when one has the highest or lowest possible values on all environmental variables. With POMP coding, this corresponds to simply setting the crossover point to 100 for diathesis-stress and to 0 for vantage sensitivity. We found that this approach markedly improved simulation results in small sample settings as opposed to using the observable minimum and maximum. We justify this approach with an example and through geometric intuition.

As an example, assuming that we have a few environmental variables in the range [0, 100] and that the true pattern of interaction is differential susceptibility with *c* = 25. Let say that, by chance, the sample observed environmental scores have a restricted range such as [10, 90] instead of the actual maximum possible range [0, 100]. If we set the crossover point of the vantage sensitivity models at the observed minimum (*c*low = 10) rather than the theoretically possible minimum (*c*low = 0), the probability of misclassification will increase. This can be explained by the fact that the closer we fix the cross-over point of the vantage sensitivity models to the real crossover of the differential susceptibility model, the more difficult it will be to differentiate the two models. Similarly, if the true pattern of interaction is diathesis-stress (*c*low = 100) and we set the crossover point of the diathesis-stress models at the observed minimum (*c*low = 90) rather than the theoretically possible maximum, the probability of misclassification will increase.

Figure 6 shows a geometric intuition to why it is preferable to fix the cross-over point of the vantage sensitivity and diathesis-stress models at values slightly outside the range of possible values than at values slightly inside the range of possible values. Thereby, using the expected maximum or minimum environmental score (i.e., the environmental score that would be obtained when one has the highest or lowest possible values on all environmental variables) is preferable to using the observed maximum or minimum. A more thorough mathematical explanation of this intuitive argument is available in Appendix C.

**FIGURE 6 HERE**

**Appendix C: Choice of crossover point in vantage sensitivity and diathesis-stress models**

To minimize the probability of misclassification, we want that 1) the true (unobserved) minimum (***e***min) and maximum (***e***max) of the environmental score are close enough to the fixed crossover point of the vantage sensitivity models (*c*low) and of the diathesis-stress models (*c*high) so that these models correctly represent vantage sensitivity and diathesis-stress respectively and 2) the vantage sensitivity and diathesis-stress models are as far as possible from the differential susceptibility models in terms of fit. Assuming that *ĉ* is the estimated crossover point from the differential susceptibility models, we can formulate this in the following way:

* Choose the fixed crossover point of the vantage sensitivity models (*c*low) such that
  1. the distance between *c*low and ***e***min is minimized
  2. the distance between *c*low and *ĉ* is maximized
* Choose the fixed crossover point of the diathesis-stress models (*c*high) such that
  1. the distance between *c*high and ***e***max is minimized
  2. the distance between *c*high and *ĉ* is maximized

This is represented visually in Figure 5. Choosing *c*low = ***e***min and *c*high = ***e***max would be ideal but we do not know ***e***min and ***e***max. However, we know the observable minimum and maximum of the environmental score in the sample (***ê***min and ***ê***max) and we know that the ***e***min ≤ ***ê***min and ***e***max ≥ ***ê***max. Assuming the distance between the observed and true minimum of the environmental score (***ê***min **-** ***e***min) is **ε**min and the distance between the observed and true maximum of the environmental score (***ê***max **-** ***e***max) is **ε**max. Then, any choice of *c*low such that *c*low < ***ê***min and *c*low > ***ê***min - 2**ε**min will be better, with respect to the two objectives above, than choosing *c*low = ***ê***min. Similarly, any choice of *c*high such that *c*high < ***ê***max and *c*high > ***ê***max + 2**ε**max will be better, with respect to the two objectives above, than choosing *c*high = ***ê***max. Overall, this means that to reduce the risk of misclassification when do not know the true minimum and maximum of the environmental score, it is preferable to fix the cross-over point of the vantage sensitivity and diathesis-stress models at values slightly outside the range of possible values than at values slightly inside the range of possible values.

Note that by choosing the theoretical minimum and maximum as the fixed value of the crossover point in the vantage sensitivity and diathesis-stress models respectively, we are not guaranteed that *c*low > ***ê***min **-** 2**ε**min and *c*high > ***ê***max + 2**ε**max. However, unless one’s data is extremely skewed or that certain combinations of values are impossible (e.g. if there are two environmental variables and we have that one is happiness and the other is sadness, then it is impossible to have high or low values in both variables), these assumptions are likely to apply. We encourage researchers to act with sound judgment and decide if these assumptions are reasonable or not in their own analysis; otherwise, simply using the observable minimum or maximum as the crossover point for the vantage sensitivity and diathesis-stress could be preferable.

**Appendix C: Multiple genes and environments scenarios when not testing for non-G×E models in competitive-confirmatory and using alpha level of .05 in RoS**

**FIGURE 7 HERE**