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INVITED ARTICLE: AKAIKE MEMORIAL LECTURE

Rejoinder

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I would like to thank Dr. Peng and Dr. Yoshida for their efforts in reading and commenting on my original presentation given in the Japanese Statistical Society Meeting in Kanazawa in September of 2016 and for their written comments presented here. My reply is organized in three parts to address three major points of their discussions.

Dr. Peng raised two issues about CME analysis for designed experiments. Both are interesting and stimulating. The first example is based on an 8-run resolution III design with seven factors. This is a highly fractionated experiment with many aliasing relationships. His analysis led to two models 1.2 and 1.5 which are equally credible (given the available data) but contain different CMEs: $(D|B+)$ and $(A|B+)$, respectively. The short answer is that the experiment is too small and does not contain sufficient information to facilitate the discrimination between two competing choices of models. Generally speaking, the proposed CME analysis works effectively when the number of aliased pairs between main effects and 2fi's or between pairs of 2fi's is small. When this condition does not hold, which typically happens with resolution III designs or highly fractionated resolution IV designs, the CME analysis alone does not work. It is not the fault of the method. When the experiment does not contain enough information, one cannot squeeze too much out of it. In some sense, CME has done miracle by squeezing more information from the data than historically allowed for. The only recourse is to collect more data to better discriminate between competing models. Here is a realistic two-stage approach. Suppose a highly fractionated experiment is

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employed in stage one, and a careful analysis leads to two (or more) competing models with CME effects that need to be "separated." A more efficient approach than fold-over technique is to use, for stage two, an optimal design approach that chooses additional design points to best discriminate between these CME effects. For details on the optimal design approach, see Section 5.4.2 of Wu and Hamada (2009).

Turning to the second example. It is interesting and logically the next step to try to apply CME analysis to designs with complex aliasing. Because in such designs some pairs of effects are not orthogonal (nor fully aliased), the CME analysis is not applicable because it requires that all models be orthogonal. However, for pairs of orthogonal effects, it is still applicable. This can be seen by comparing models 2.5 and 2.3: the coefficient .9163 of the CME effect $(F|G-)$ in model 2.5 is equal to the difference $(.4576 - (-.4588))$ between the coefficient of F and of FG in model 2.3. This relationship follows Rule 1 of Su and Wu (2017), which is reproduced below. For two orthogonal effects A and B (as in regular two-level designs), the following two identities hold: $(A|B+) = A + AB$, $(A|B-) = A - AB$. Even though this example uses a 12-run Plackett–Burman design, which is not regular, the two effects F and FG are orthogonal. Therefore, the above algebraic relationships should hold. Next we consider models 2.6 and 2.4 as in Peng's discussion. Because the main effect D in model 2.4 is not orthogonal to the interaction FG, such an algebraic relationship does not hold. However, because the effect D is much smaller than the effects F and FG in model 2.4, the relationship is approximately true. This can be seen by comparing .8791 (coefficient of $(F|G-)$) and the difference $.8769(= .4576 - (-.4193))$ between the coefficients of F and of FG in model 2.4. Peng raised a general question: whether the CME analysis can be used for designs with nonorthogonal effects? Strictly speaking, the answer is no but approximately is yes under the assumption that the orthogonal effects dominate the model as in model 2.4. However, I will not endorse the indiscriminate use of CME for general nonregular designs because it can be misused. The example given above for models 2.6 and 2.4 is probably an exception. Because the aliasing relationships for nonregular designs as discussed in Section 3 can be complicated, CME can only be used as a first step to identify tentative models containing CME effects. Facing with the paucity of information in the data, one can invoke something similar to stage two of the two-stage approach described previously in adding new design points for better discrimination between effects under consideration.

Now let me turn to the comments by Dr. Yoshida. The computational chemistry example he gave is really interesting. In some sense, it is even more interesting and challenging than the genomics example alluded to in Section 2.2 and discussed fully in Mak and Wu (2017). In predicting the functional properties of a compound in terms of its molecular structure, it happens commonly that several (two or more) chemical fragments *jointly* affect the functional properties. As pointed out by Yoshida, instead of using the traditional two-factor or higher-order interactions to describe or capture these joint effects, CME's (and extensions to higher order) can be better predictors. Formally, the CME $(A|B+)$ can be interpreted as the effect of fragment A conditional on whether or not the current compound contains fragment B. The selection of $(A|B+)$ or $(A|B-)$ then reveals meaningful insight on the underlying structural chemistry problem: fragment B acts as an activator (or silencer) of fragment A. While the use of multiple testing and false-discovery rates (e.g., the q-values studied in Storey

(2003)) is a well-established technique, it becomes cumbersome and less powerful when many tests need to be performed, especially if the number of considered fragments is much higher than 102. In this regard, we think the method in Mak and Wu (2017) offers a more effective strategy for selecting CME's, because such a method allows for a "one-shot" selection of *all* considered conditional effects via the minimization of a bi-level penalized criterion. Computationally, this method employs two fundamental principles—CME coupling and reduction—which help navigate the selection algorithm using the underlying grouped structure of CME's. These two principles are instrumental for developing a practical and efficient CME selection method, one which can effectively handle a much larger number of chemical fragments compared to multiple testing. As Yoshida pointed out, the selection of higher-order CME's can indeed be a computational challenge, but one which yields important applications in a wide variety of fields; we look forward to exploring such an extension in a future work.

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