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# The Confound Continuum: A 2D confounder assessment for AI in precision medicine

## Content

### Introduction

Confounding presents a major challenge in neuroimaging machine learning applications. Confounders can influence both, brain-derived features and phenotypical targets1. Removing their signal from the data changes the feature-target relationship which ultimately affects the model interpretation. Additionally, confounders are not always straightforward to identify. To target this, we introduce the idea of a 2D Confound Continuum (CC). Its ordinate evaluates the strength of the statistical relationship between a confound and the feature(s)/target, thereby helping to better understand its signal contributions to the data (statistical CC). Its abscissa defines the strength of the conceptual or biological relationship and hence the effects of removal on the model interpretation (conceptual CC). Sorting potential confounders within the CC can help to better understand their role and impact on building predictive models.

### Methods

To illustrate the use-case dependent CC, we exemplarily predicted the robust, reliable and clinically relevant target hand grip strength (HGS)2 from grey matter volume (GMV, cortical3: 1000 ROIs, subcortical4: S4 3T, cerebellar5: SUIT) with N=30254 subjects from the UK Biobank. We used LinearSVR6,7 (heuristic C8, L2 loss) with confounds being either sex, age, sex and age together, scan-site, time of day (scan-time) or no confounds. Additionally, we used the confounds as features alone or together with GMV to investigate the contribution of the two signal sources. We also validated the CC with further linear and non-linear learning algorithms as well as functional connectivity and cortical thickness as features.

### Results

"Sex" was mechanistically strongly related to both HGS (Fig. 1A) and GMV (What is brain information without sex information?). The statistical association of sex with both HGS and GMV (Fig. 1B, C) confirmed its (linear) signal contributions to the data. Consequently, it was valid to be removed, but the strong conceptual relationship indicates major consequences for model interpretation and positioned "sex" at the problematic right upper corner of the 2D CC (Fig. 1D). Removing "sex" expectedly led to a drop in predictive performance from R2=.41 to R2=.02 and to R2=-.02 for "sex&age" (Fig. 1E). Accordingly, brain features did not add signal to "sex" or "sex&age" alone as features (Fig. 1F). Neither scan-site nor scan-time were problematic in the sense of the CC: Scan-time was not statistically related to the data (Fig. 1B, C) and scan-site showed a low statistical relationship with HGS (Fig. 1B) but was not conceptually related.

### Conclusion

The CC is an orthogonal 2D covariate assessment to support confound removal decisions particularly in large cohorts with a large sensitivity to confounding effects9. Both removing or not removing certain confounds is inherently valid. The interpretation of ensuing results however must differ. Here, one can either conclude that prediction of HGS from GMV is possible (however not that HGS information is encoded in GMV!), or the opposite, that GMV does not carry information about HGS in addition to sex and age. The latter result can provide a deeper insight in "pure" brain-behaviour relationships and hence can strengthen our conceptual understanding.

## Keywords

Machine Learning, Confounds, Big Data, Neuroimaging

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