

A POTENTIAL COST OF BLOCK-DIAGONAL Ω : BIASED DOSE-RESPONSE ESTIMATES IN THE PRESENCE OF EXPOSURE-RESPONSE CONFOUNDING

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INTRODUCTION

- **A common (implicit) assumption...**: In pharmacometrics, it is often (implicitly) assumed that the exposure-response relationship in a dose-randomized study is unconfounded, at least after adjusting for measured covariates and when the dose is not influenced by prognostic factors of response.
- **... might not always be plausible**: A growing body of examples in the literature illustrates that this exposure-response unconfoundedness assumption might not be plausible in all practically relevant settings. [1,2,3]
- **Specifically in popPKPD modelling**: In population modelling, between-patient variability in exposure and response is explained via individual PK and PD parameters. [4] A confounder of the exposure-response relationship may therefore exert its effects via at least one individual PK and at least one individual PD parameter. This induces a correlation between these parameters (Fig. 1).
- Can ignoring this correlation induce bias in the estimated exposure-response relationship, and by extension the inferred dose-response relationship?

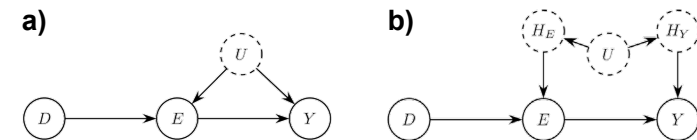


Figure 1: Directed acyclic graph (DAG) of a confounded exposure-response relationship. b) is a special case of a) in which this confounding is via a correlation in individual PK and PD parameters. D: dose, E: PK exposure, Y: PD response, U: (unmeasured) confounder, H: individual parameters

RESULTS

- **In the described setting of a time-invariant confounder, enforcing that Ω has separate blocks for the PK and PD model parameters ("block-diagonal") misrepresents the data-generating process.** Therefore, [6] modelling approaches implementing a block-diagonal Ω are expected to yield biased estimates of the causal dose-response.
- For models that incorrectly enforced a block-diagonal Ω (joint popPKPD and PPP&D with a block-diagonal Ω , as well as IPP),
 - empirical sampling distributions were not centred around the truth (Fig. 2).
 - with increasing confounding strength, an increasing fraction of the mean squared-error (MSE) was due to bias (Fig. 3).
- For the correctly specified models (joint popPKPD and PPP&D with full Ω),
 - empirical sampling distributions were centred around the truth (Fig. 2).
 - only a small fraction (< 5%) of the mean squared-error (MSE) was due to bias at the tested doses (Fig. 3).
 - Of course, this does not directly imply unbiased extrapolation (here illustrated via shrunk $\bar{E}0$).

Towards diagnosing this type of confounding:

- The off-diagonal elements of Ω can contain information about the possible presence and approximate strength of the investigated type of confounding (Fig. 4).
- However, with increasing confounding strengths, the extend of confounding was increasingly underestimated, despite the models still being correctly specified (Fig. 4).
 - This was attributed to the fact that the true Ω was approaching a boundary (near-singular Ω), which can render the estimation ill-conditioned in these settings.
- Important caveat: In this poster, we assumed a specific parametric form of exposure-response confounding. However, in general, confounding can also be of a different form.

OBJECTIVES

Investigate whether incorporating a full (unstructured) Ω in a popPKPD modelling approach can

- help diagnose the presence of a confounder, and
- partially mitigate bias in the model-based estimation of the average causal dose-response relationship when the exposure-response relationship is confounded by an unmeasured time-invariant covariate.

METHODS

- Simulation re-estimation study (empirical sampling distribution approximated by R=1000 repetitions) with
 - popPK: one-compartmental IV bolus, linear elimination; popPD: Emax
 - True variance-covariance matrix:

$$\Omega^* = \begin{pmatrix} (\sigma_{C_L}^*)^2 & 0 & 0 & 0 & \rho^* \sigma_{C_L}^* \sigma_{E_{max}}^* \\ 0 & (\sigma_V^*)^2 & 0 & 0 & 0 \\ 0 & 0 & (\sigma_{E_0}^*)^2 & 0 & 0 \\ 0 & 0 & 0 & (\sigma_{EC_{50}}^*)^2 & 0 \\ \rho^* \sigma_{C_L}^* \sigma_{E_{max}}^* & 0 & 0 & 0 & (\sigma_{E_{max}}^*)^2 \end{pmatrix}$$
 - 1:1 randomization to 100mg or 400mg (n=200)
 - Dense PK and PD profiles in all patients
 - Correctly specified structural and residual error models
 - Random effects models [5]: Joint popPKPD or population PK parameters and data (PPP&D) approach with either a full or block-diagonal Ω , as well as individual PK parameters (IPP)
- Estimand: Mean causal effects of selected doses on response at a pre-defined time point, $E[Y_{12h}^{D=d}]$ where $d[mg] \in \{0, 25, 50, 100, 200, 400, 800\}$

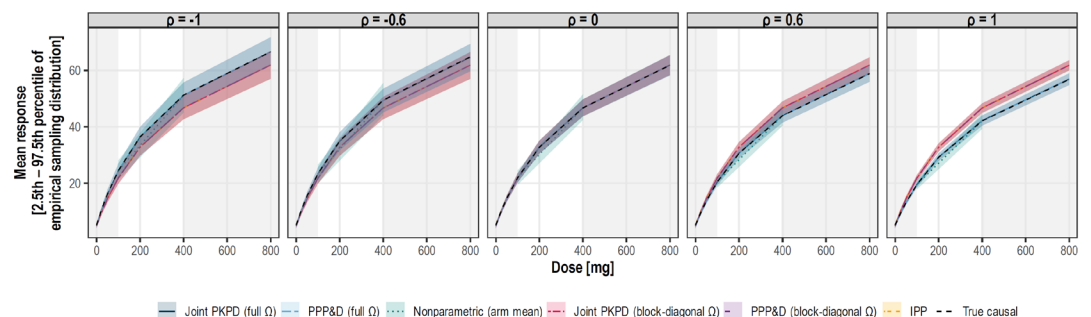


Figure 2: Empirical sampling distributions of inferred mean dose-response relationships.

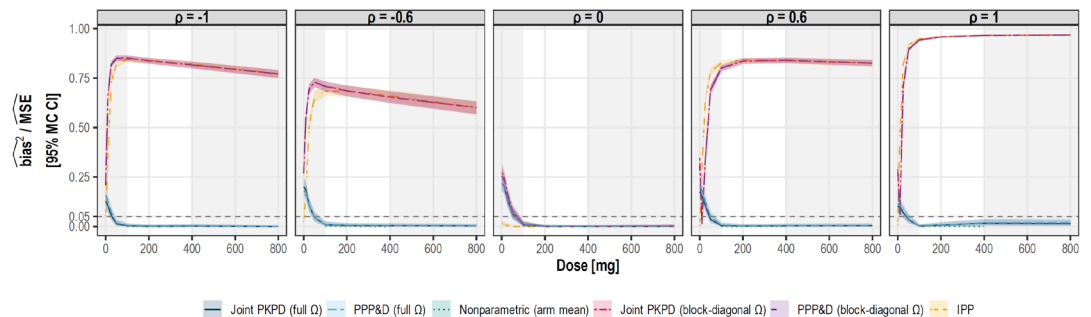


Figure 3: Fraction of mean squared-error (MSE) which is due to bias.

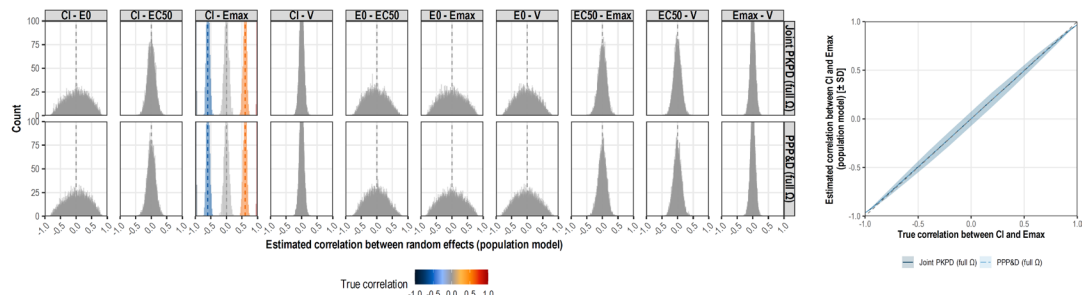


Figure 4: Empirical sampling distributions of correlations between population parameters.

CONCLUSIONS

- Exposure-response associations can be confounded even in dose-randomized studies. We illustrated that allowing the Ω of a popPKPD model to be unstructured (full) can serve two purposes:
 - i) as a **diagnostic**, by revealing **potential non-negligible PK-PD random effects dependencies suggestive of unmeasured confounding**, and
 - ii) as a **partial mitigation strategy at least for certain types of confounding of the exposure-response relationship**.
- We recommend to routinely incorporate a full Ω in popPKPD modelling approaches where feasible, at least as a sensitivity analysis. Furthermore, benchmarking PKPD model-based causal estimates against complementary causal methods (e.g., instrumental-variable and nonparametric g-formula approaches [6]) can provide valuable insights on the potential presence of confounders.

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