

Can NLME modeling correct for treatment-confounder feedback?

NLME modelling from a causal inference perspective when the dose-exposure-response relationship is confounded by the treatment regimen

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Motivation / Background

- In clinical development, we are often interested in answering “What... if...?” questions like: “What would the probability of response be under a new treatment regimen?”
- To answer such questions without running a new trial, we can integrate existing data and knowledge. Often, semi-mechanistic non-linear mixed effects (NLME) models are built for this purpose.
- However, when simulating under a new treatment regimen, we need to ensure that the aspects we learn from the data are valid for extrapolation. This includes taking the circumstances into account under which the data were generated.
- In particular, dose titrations for response optimization can confound the dose-exposure-response (D-E-R) relationship (Figure 1 and Figure 2). If unaccounted for, such treatment-confounder feedback can lead to biased extrapolations and wrong conclusions.

Objectives

- Illustrate why trials designed to investigate the effects of a treatment regimen with dose titrations for response optimization can confound the D-E-R relationship.
- Determine whether the D-E-R relationship is theoretically identifiable based on a simple but realistic causal diagram that describes a data-generating process for such a trial.
- Explore via simulations, given a theoretically identifiable D-E-R relationship, whether the D-E-R relationship is also practically identifiable based on limited available data.

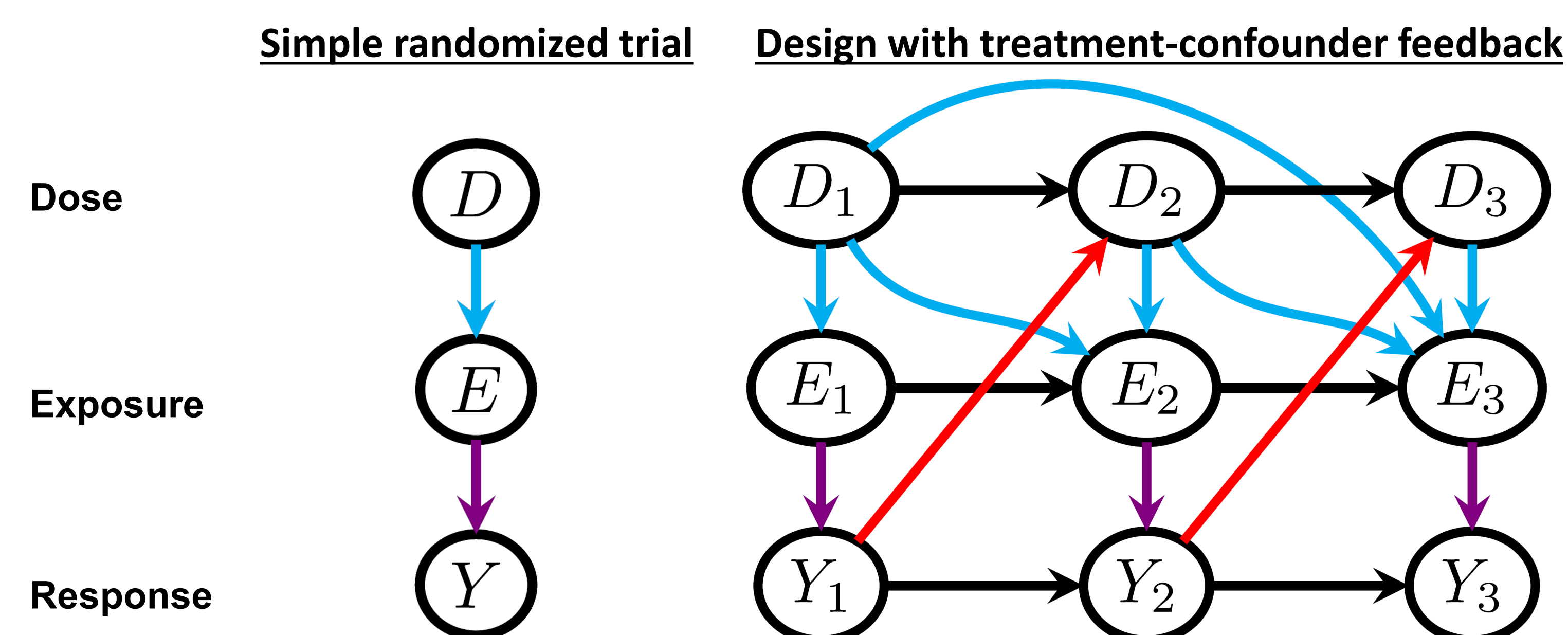


Figure 1: (left) DAG of the D-E-R relationship of a simple randomized trial, assuming that the effect of dose on response is fully mediated by exposure. (right) DAG of the D-E-R relationship with **treatment-confounder feedback**, again assuming that the effect of dose on response is fully mediated by exposure. Here, **early response takes a dual role: It is on the causal path from early dose to late response, but it also confounds the effect of late dose on late response.** (time is indicated by subscripts)

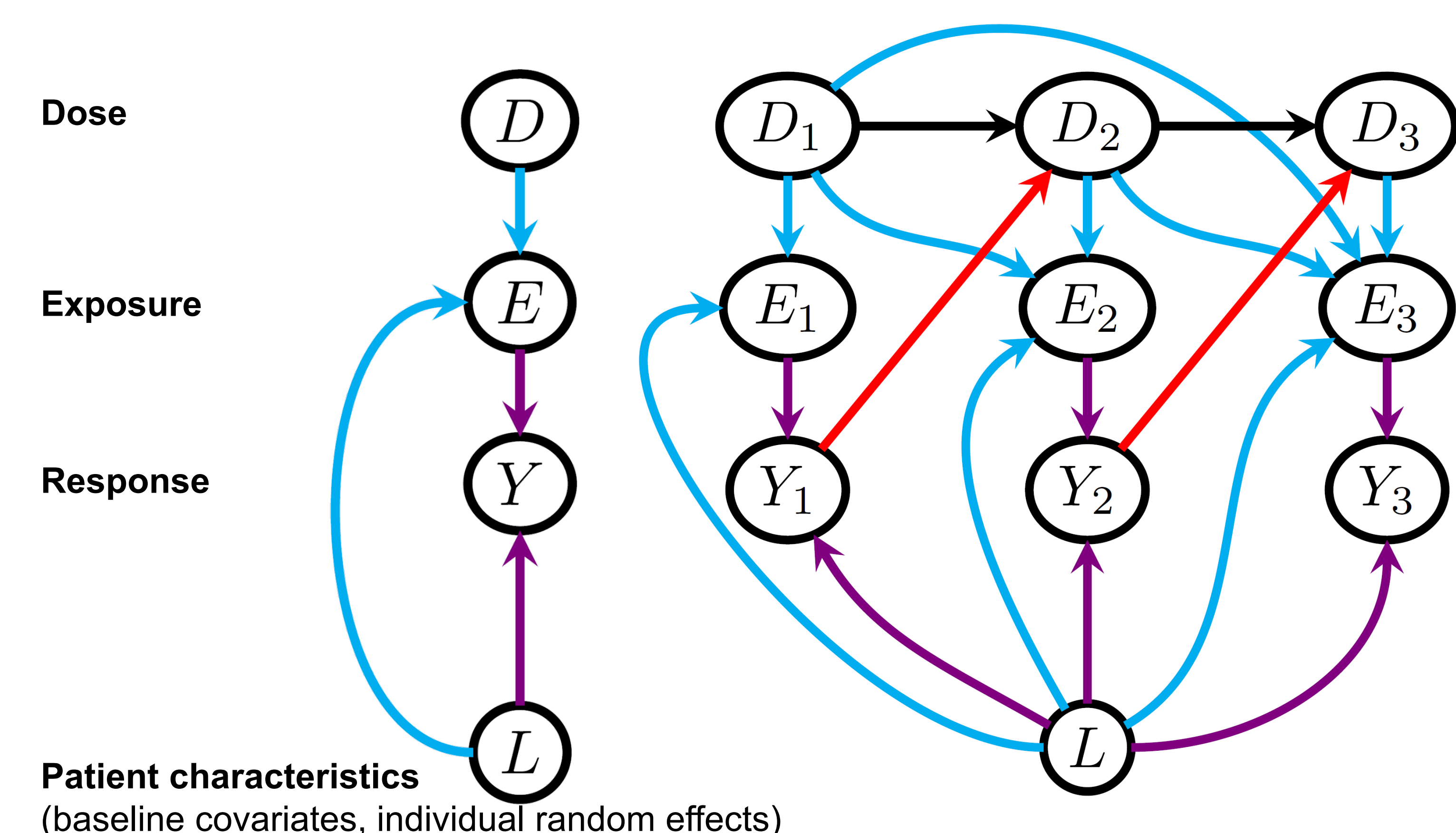


Figure 2: **The Pharmacometrics way to think** about a design with treatment-confounder feedback: Unique characteristics of each patient subgroup, L , such as baseline covariates and individual random effects, explain the association of consecutive exposure levels and consecutive response levels, respectively, given a dosing history.

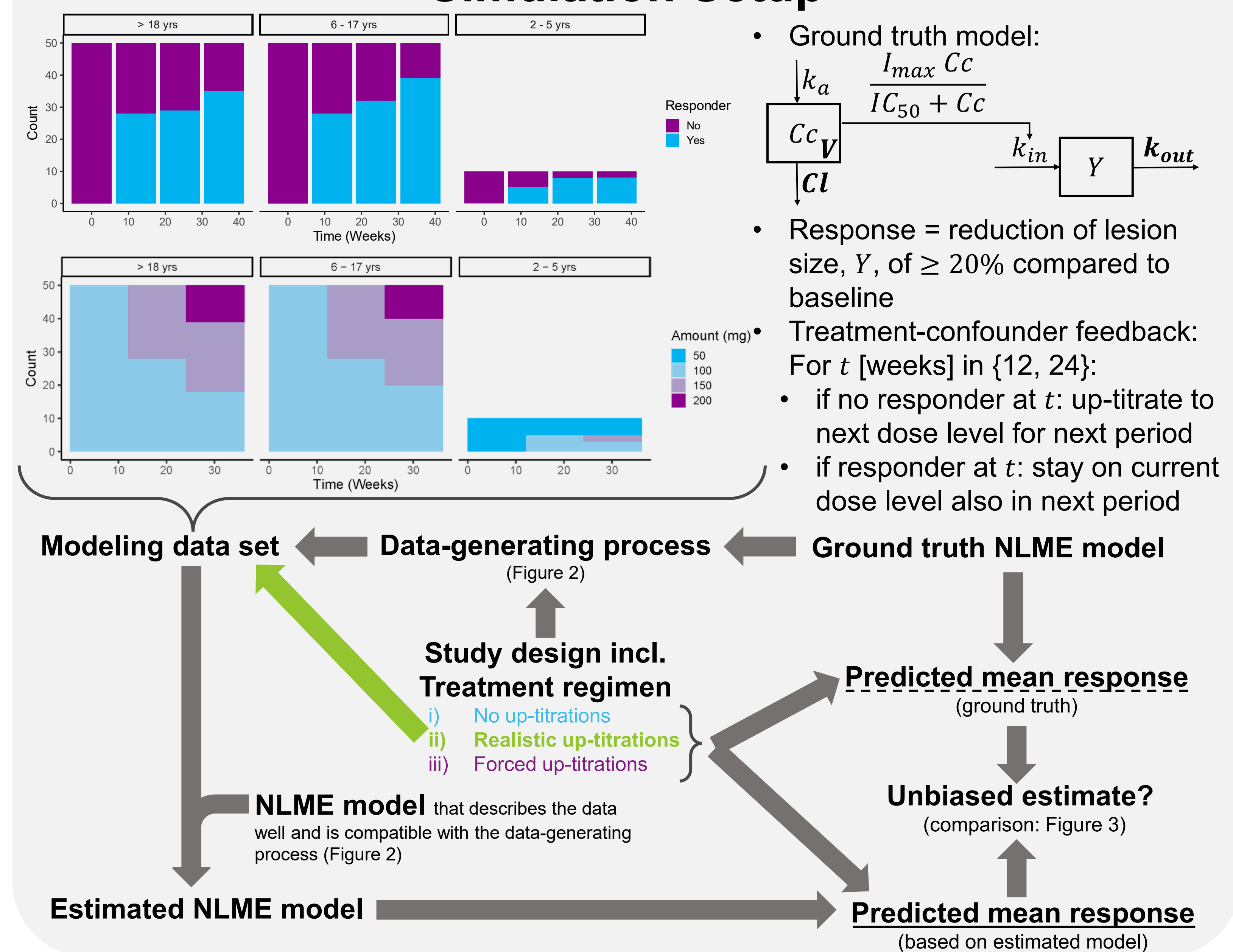
Summary & Conclusion

- Trials designed to investigate the effects of a treatment regimen with dose titrations for response optimization can confound the D-E-R relationship.
- NLME modeling can be used to correct for confounding in longitudinal experiments and enable unbiased simulations under alternative treatment regimen, but only under certain conditions. We are currently working on understanding these requirements fully, including requirements on study design.
- Understanding conditioning on random effects as a form of standardization bridges the Pharmacometrics and Causal Inference approaches.

The D-E-R relationship is theoretically identifiable

- Our estimand of interest is the proportion of responders at different time points under a possibly untested treatment regimen.
- To assess the **theoretical identifiability** of our estimand of interest, we assume the data-generating process captured in Figure 2 as well as common assumptions in the Causal Inference literature, namely consistency, positivity and no unmeasured confounders, and Pharmacometrics literature, namely an adequate popPKPD model.
- A common approach in the Causal Inference literature to correct for confounding is **standardization**, i.e. conditioning the response on the relevant covariate levels. This closes unwanted confounding paths, e.g. between early response and late exposure.
- The NLME modeling approach is to condition on individual random effects alongside the relevant patient baseline characteristics.**
- Thus, NLME modeling can be interpreted as an implementation of standardization.

Simulation Setup



NLME modeling can correct for confounding in practice – in certain settings

- In our exemplary setting of $n=110$, NLME modeling can correctly simulate the response under new treatment regimen (e.g. never or always up-titrate irrespective of earlier response) even when there is treatment-confounder feedback in the data (Figure 3).
- However, an NLME modeling approach does not always lead to unbiased estimates of the estimand of interest, e.g. we believe that biased estimates might be obtained when all data points in the modeling dataset are subject to treatment-confounder feedback. The intuition is that in this case, the distribution of random effects in the overall population cannot be estimated.

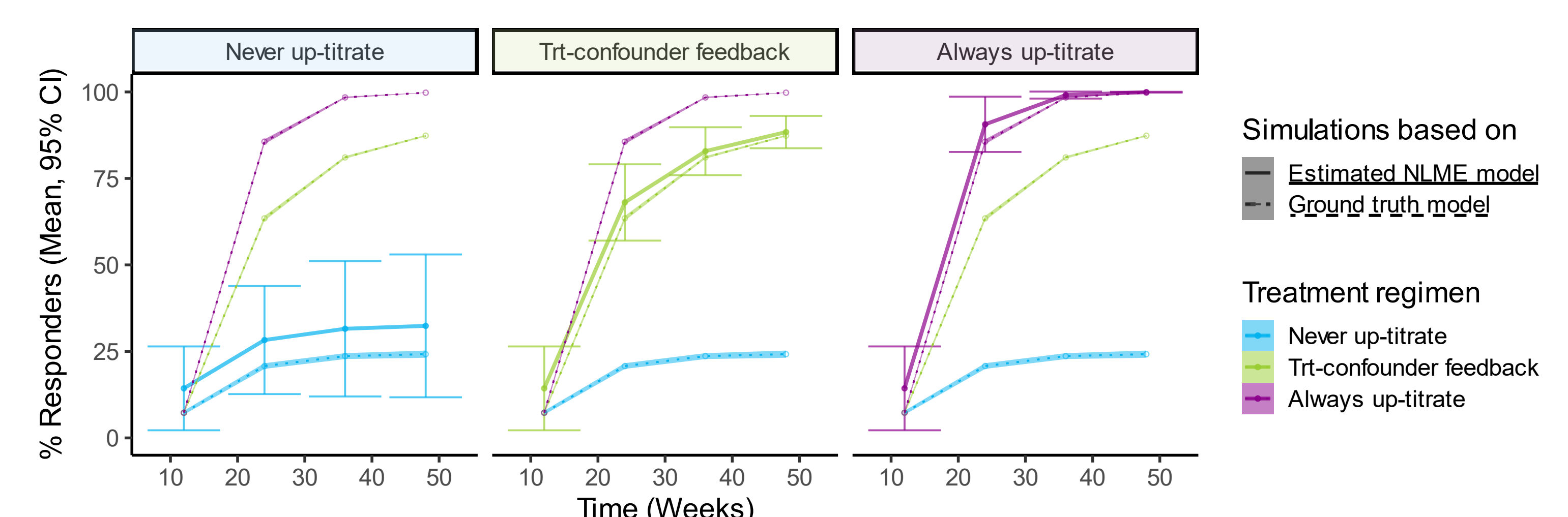


Figure 3: In this simulation setup, an NLME modeling approach can correctly predict the proportion of responders under different, possibly untested treatment regimen.

References

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