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A new PKPD modelling approach allowing a granular Exposure-Response analysis

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Exposure Response (ER) analysis = PKPD Modelling

- ER analyses are often instrumental in
  - deciding dosing strategy (dose, frequency)
  - planning or performing dose individualisation based on
    - covariate (a priori)
    - response (a posteriori)
    - drug concentration (a posteriori; ”TDM”)
  - extrapolation
  - …

Two standard ER assumptions

”Concentration has a causal effect on response”

”Changes in response are independent of the reasons for change in concentration”

No justification is typically given for why these assumptions would hold

No available systematic strategy for such assessments?

Here, we introduce the ”**Partitioned effect” model**, which can form the basis for such a strategy

Exposure – response (PKPD) models

$$C = \frac{R_{inf}}{CL}$$

$$Effect = \frac{E_{max} * C}{C_{50} + C}$$

Separating concentration components

$$C_{dose} = \frac{R_{inf}}{\theta_{CL}}$$

$$C_{cov} = \frac{R_{inf}}{\theta_{CL} e^{\theta_{cov}(COV - \overline{COV})}}$$

$$C = \frac{R_{inf}}{\theta_{CL} e^{\theta_{cov}(COV - \overline{COV}) + \eta_{CL}}}$$

Partitioned Effect (PE) model

Partitioning of:

$$Effect = \frac{E_{max,dose} * C_{dose}}{C_{50,dose} + C_{dose}} +$$ dose

$$\left[\frac{E_{max,cov} * C_{cov}}{C_{50,cov} + C_{cov}} - \frac{E_{max,cov} * C_{dose}}{C_{50,cov} + C_{dose}}\right] +$$ covariate

$$\left[\frac{E_{max,re} * C}{C_{50,re} + C} - \frac{E_{max,re} * C_{cov}}{C_{50,re} + C_{cov}}\right]$$ random effects

re = random effects

Instrumental variable

An instrumental variable can be used to estimate causal effects in observational data given that it fulfills three conditions:

i. Relevance assumption: it has a causal effect on exposure
ii. Exclusion restriction: it is related to the response only through exposure
iii. Exchangeability assumption: it doesn't share common causes with response

For ER analysis, randomised dose can act as an instrumental variable

Design for 6 simulation scenarios

Constant rate infusion at steady state

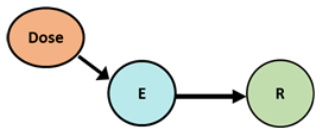
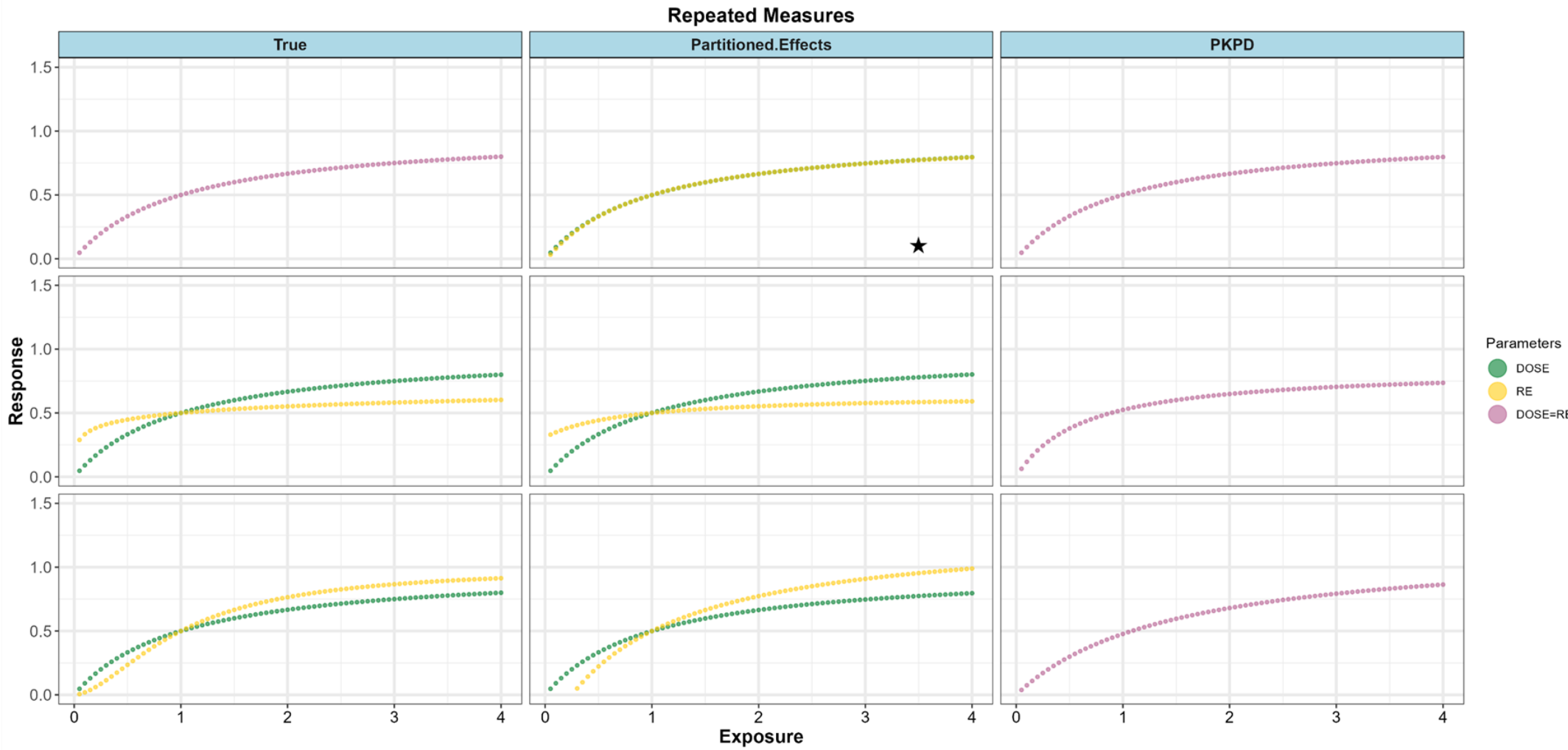
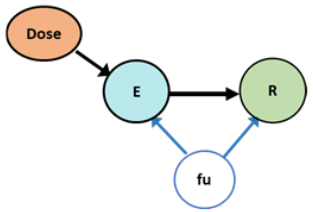
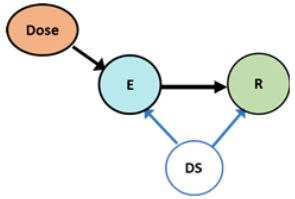
- Randomized R_{inf}: 1 or 2 units/time
- $N_{subjects}$ = 100 /arm
- 2 PK and 2 PD obs/subj
- $N_{replicate\ trials}$=500

Parameter values:

$$CL = \theta_{CL} e^{\eta_{CL}} \; ; C_{50} = \theta_{C50} e^{\eta_{C50}} \; ; E_{max} = \theta_{Emax}$$

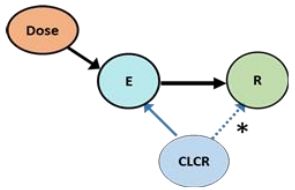
$$\theta_{CL} = 1; \theta_{C50} = 1; \theta_{Emax} = 1$$

$$\omega^2_{CL} = 0.09; \omega^2_{C50} = 0.09, \sigma^2 = 0.01$$

Designs/Model	Repeated Measures
Base Case 	
Protein Binding 	
Disease Severity 	

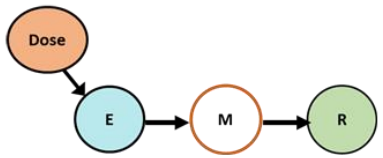
Designs/Model

Renal Function

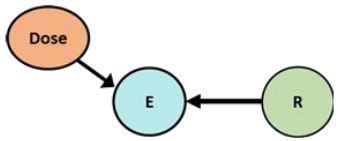


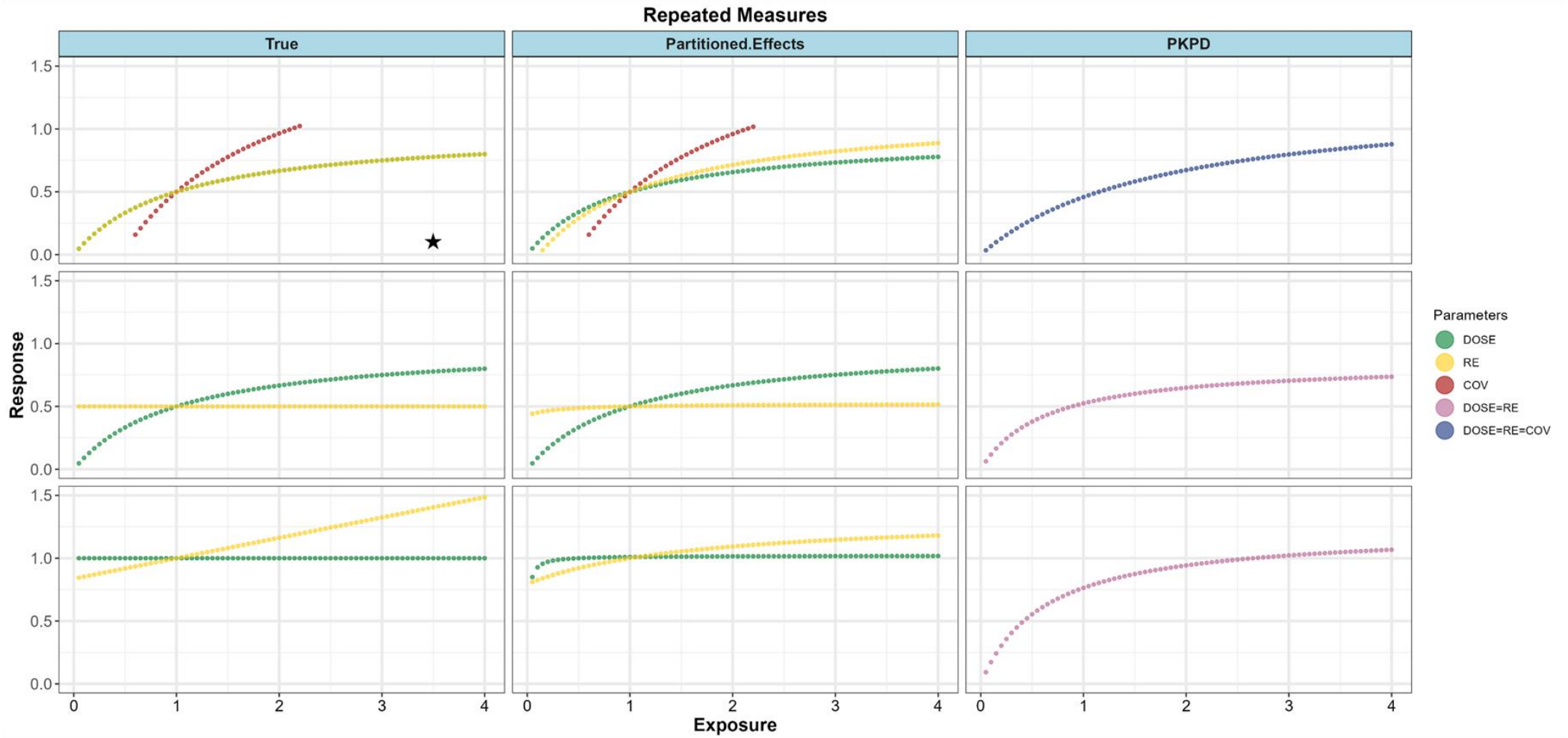
*Simulated but not modelled

Active Metabolite



Reverse Causality





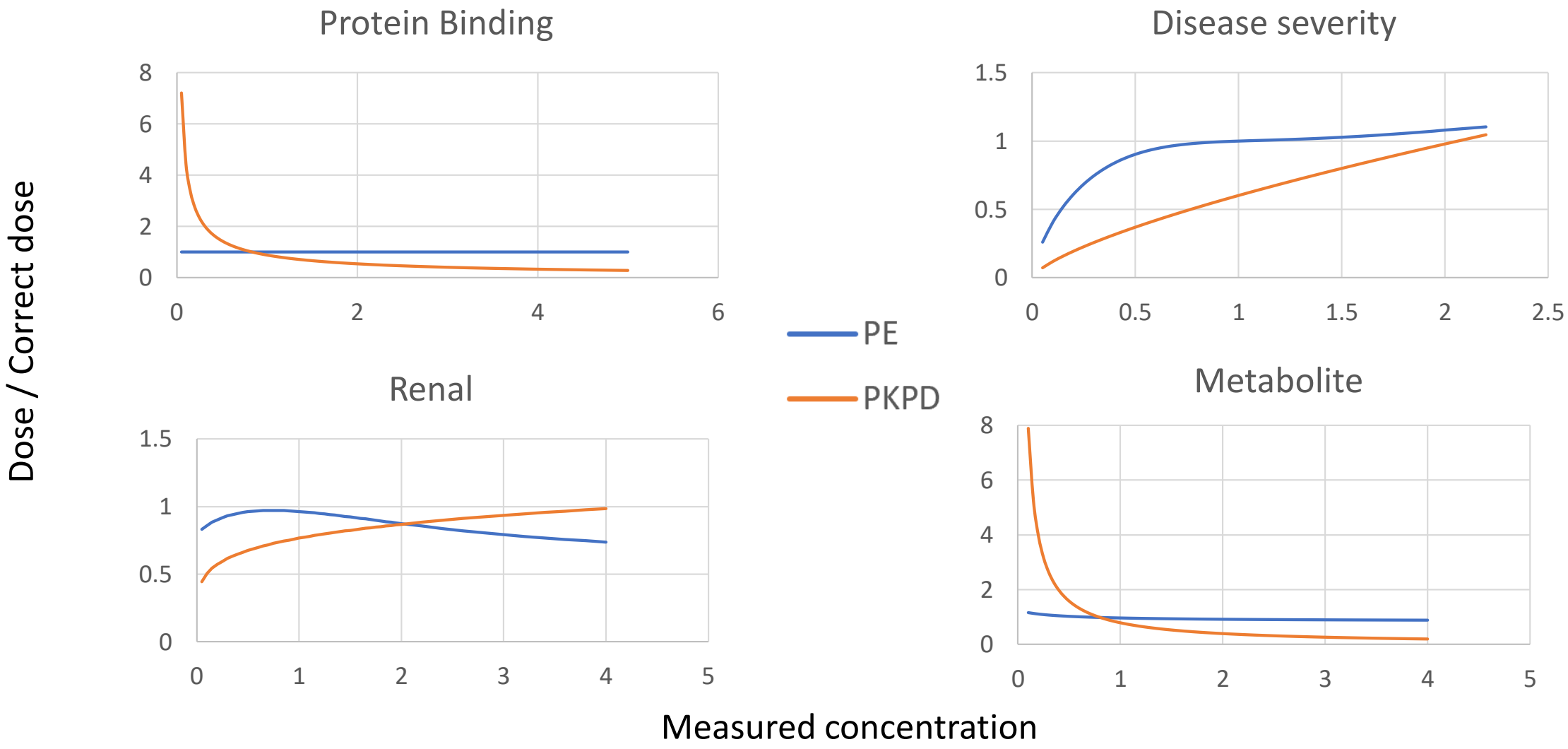
Preliminary conclusions

$E_{max,dose}, C_{50,dose}$ **This is our best estimate of the causal ER relation.**

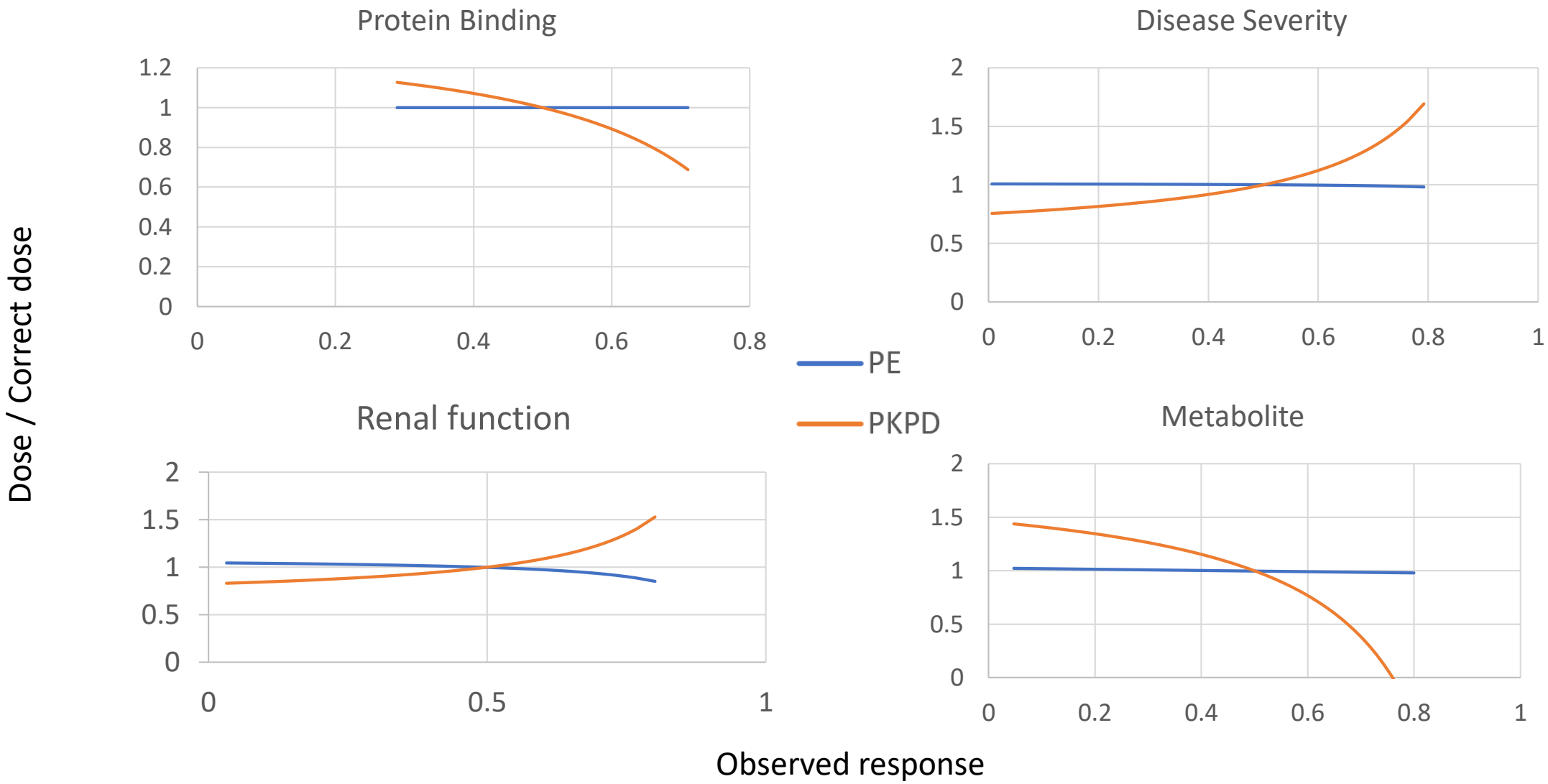
$E_{max,cov}, C_{50,cov}$ **If different from the above, add PK covariates to the PD model**

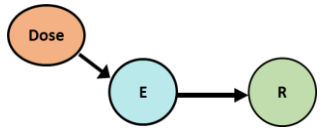
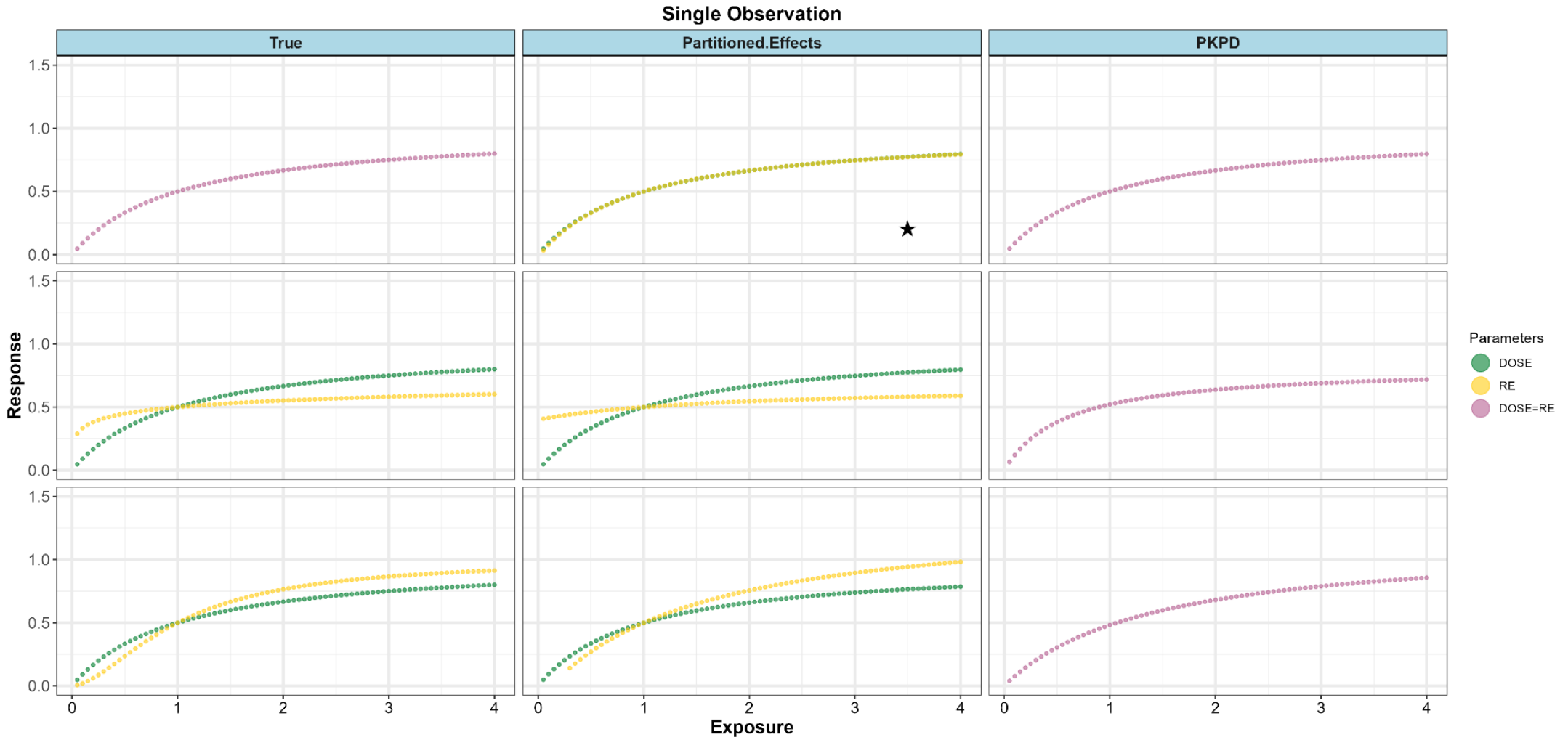
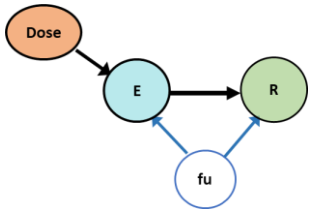
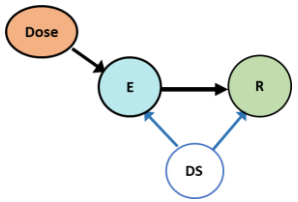
$E_{max,re}, C_{50,re}$ **These parameters should guide TDM. Check precision and agreement with causal relation**

Concentration-based individualisation (TDM)



Response-based individualisation



Designs/Model	Single Observation
Base Case 	
Protein Binding 	
Disease Severity 	

Final comments

- **Assumptions of ER causality and independence** of origin of concentration variability are often **testable based on data**. The **Partitioned Effect model** is a way to do this.
- Individualization strategies are sensitive to violations of causality and independence assumptions
- Sensitivity of other drug development decisions to assumption violations have not been explored
- For a survey of recently published ER analyses, see poster 11474

Acknowledgments

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Population approach research groups at the Dept of Pharmacy

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Thank you!

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Partitioning of:

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dose

$$\left[\frac{E_{max,re} * C}{C_{50,re} + C} - \frac{E_{max,re} * C_{dose}}{C_{50,re} + C_{dose}}\right]$$

random effects

re = random effects