Using Graphical Models and Causal Thinking to Inform Pharmacometric Modeling

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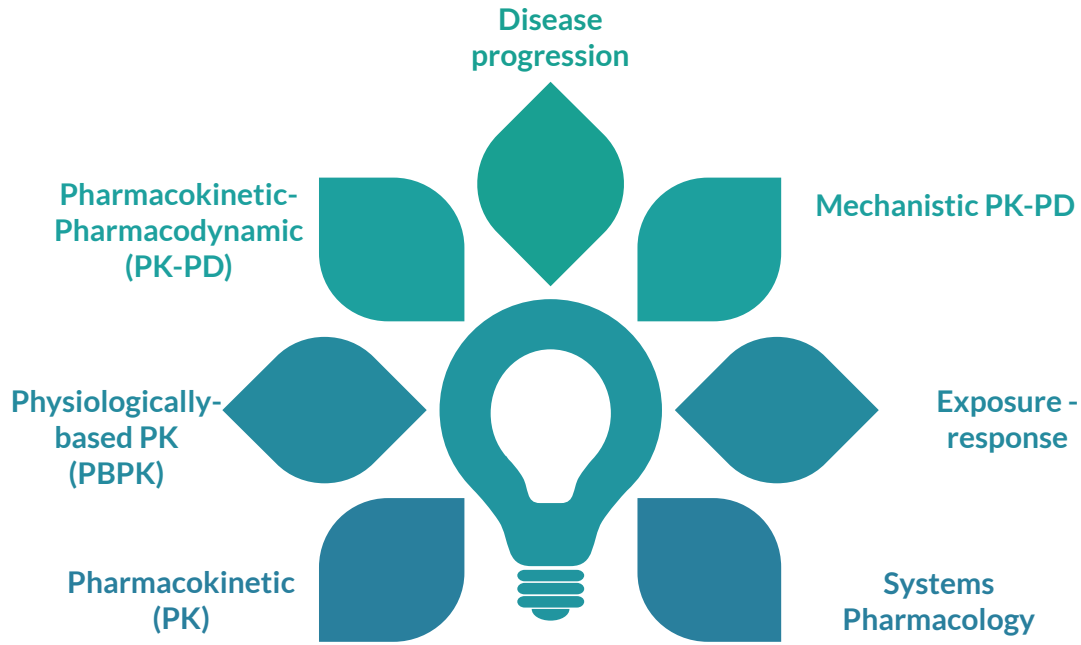
What is Pharmacometrics?

- The application of models to describe drug response and disease progression, incorporating aspects of biology and pharmacology.



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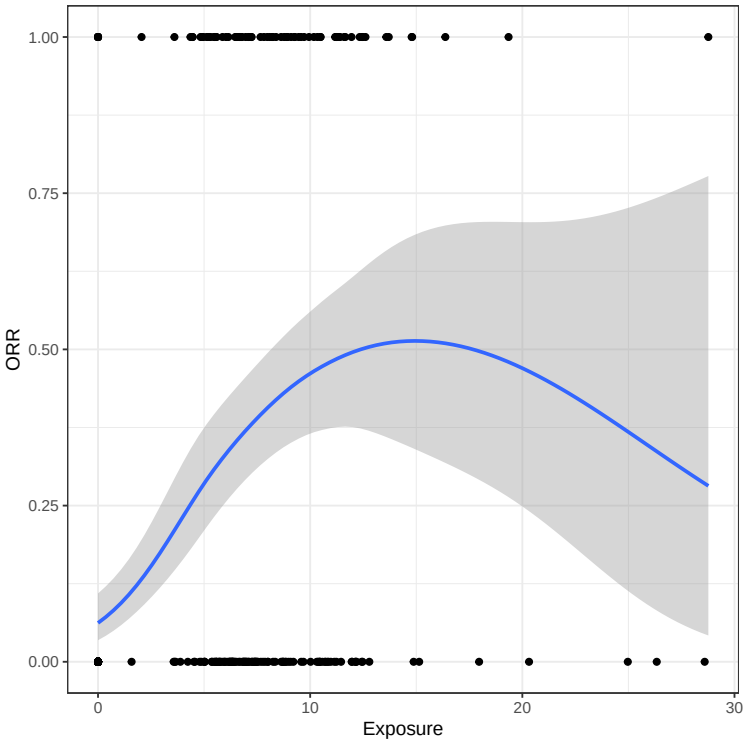
Often focused on informing selection of dose(s)

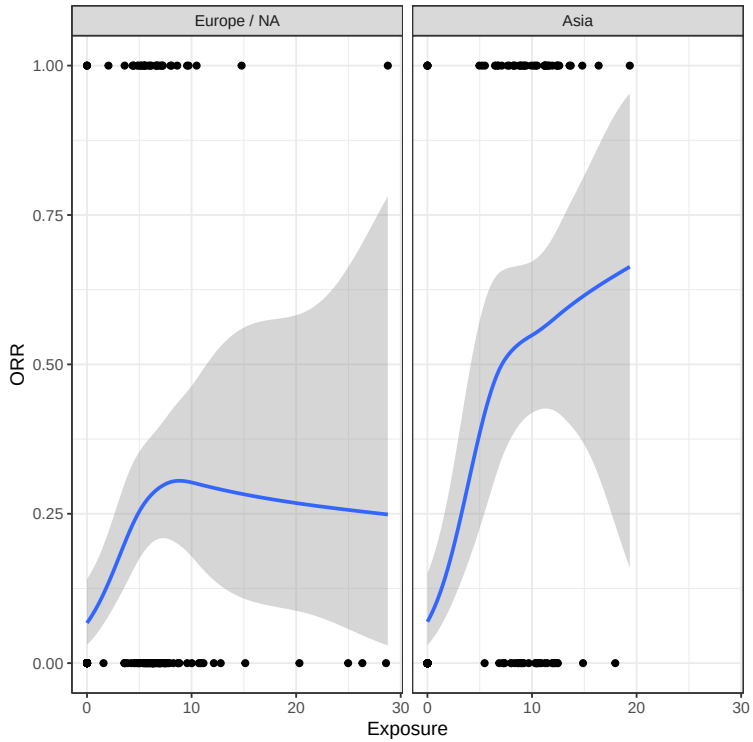
- Fundamental basis: Dose -> Exposure -> Response
- Exposure is often quantified as average concentration at steady-state
  - Empirical Bayes estimate of drug clearance: Population PK model + observed drug concentrations
  - PK models typically include covariates
- For some compounds (e.g. biologics), exposure is related to factors that also affect clinical outcomes (Dai et al., CPT, 2020)
- For some analyses, we pool data from multiple trials which may differ with respect to inclusion criteria (target population)
- The aim of this presentation is to bring a little more rigor to using pharmacometric exposure-response models for causal inference

Motivating example

- Hypothetical development of an mAb to treat a type of cancer
- Pooling data from three trials:
  - Phase 1: rising dose study with expansion cohort; multiple dose levels (0, 1, 3, 10 mg)
  - Phase 2 study: North America and Europe; placebo-controlled; 3 mg
  - Phase 2 study: Asia; placebo-controlled; placebo-controlled; 4 mg
- Outcome of interest: ORR ($Y \in \{0, 1\}$)
- Goal: Provide supporting information for recommended dose for registration

Marginal exposure-response relationships





Typical pharmacometric exposure-response modeling

- Focuses on a model for the response
  - Base model: functional relationship between exposure and response
  - Covariate model: adds covariate effects (main effects and, maybe, interactions)
- Covariate modeling strategies
  - Step-wise approaches
  - Full model (include all covariates of interest)
  - Hybrid approaches

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Rigor part one: Define the estimand

- Estimand: $E[Y^d] - E[Y^0]$
  - Y^d = (potential) outcome that would be observed at dose level $D = d$
- We can show that, under some conditions,

$$\begin{aligned} E[Y^d] &= E_X\left[E_{C|D,X}\left\{E\left(Y(c)|D,X\right)\right\}\right] \\ &= E_X\left[E_{C|D,X}\left\{E\left(Y|C=c,D,X\right)\right\}\right] \\ &= E_X\left[E_{C|D,X}\left\{E\left(Y|C=c,X\right)\right\}\right] \\ &= \int_x \int_c E(Y|c,x) f(c|d,x) f(x)\, dc\, dx \end{aligned}$$

where $Y(c)$ = (potential) outcome that would be observed at exposure level $C = c$

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Rigor part two: think about the causal associations

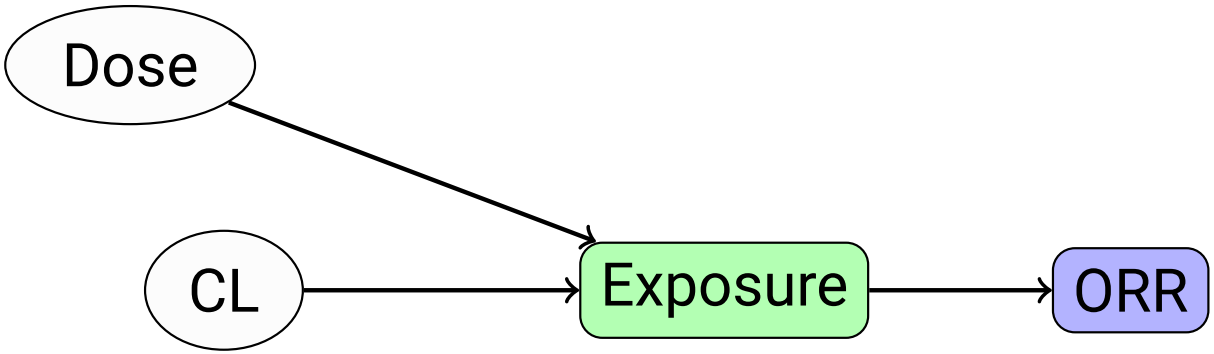
What are those conditions?

- Under the assumption of *conditional ignorability* ,
  - $E[Y(c)|D,X] = E[Y|C=c,D,X]$
- Under the assumption that $Y \perp D \mid C, X$,
  - $E[Y|C=c,D=d,X=x] = E[Y|C=c,X=x]$
- We can use directed acyclic graphs (DAGs) to help understand whether these assumptions are violated.

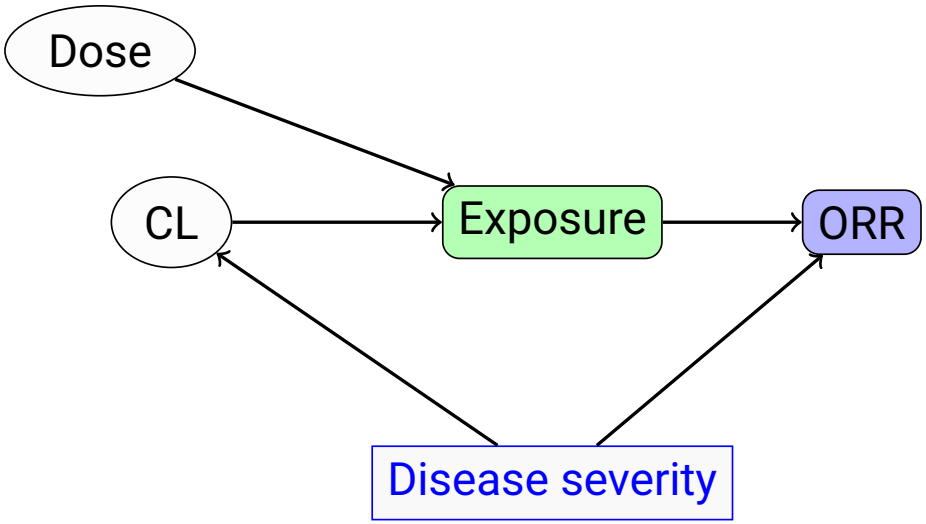
Brief intro to DAGs

- Building the graph
  - Start by representing treatment and outcome
  - For all variables on graph, identify common causes (including unmeasured ones)
  - Include selection variables
- Can use the graph to identify the adjustment set under which conditional ignorability holds
  - Adjustment set depends on the “exposure” of interest
- References:
  - Hernan MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.
  - On-line courses (Jason Roy; Miguel Hernan)
  - Judea Pearl’s books/articles

A DAG for our hypothetical example: start with the basics

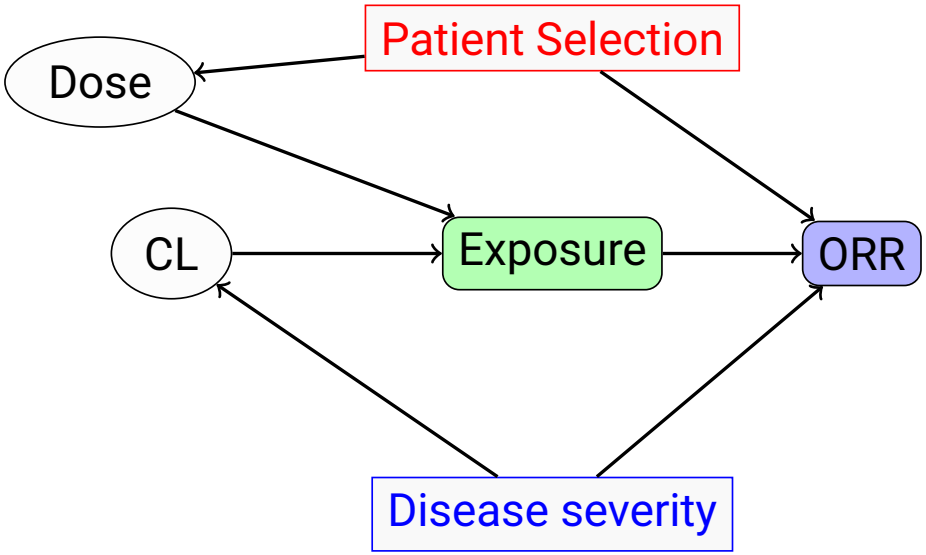


Consider common casues of exposure and outcome



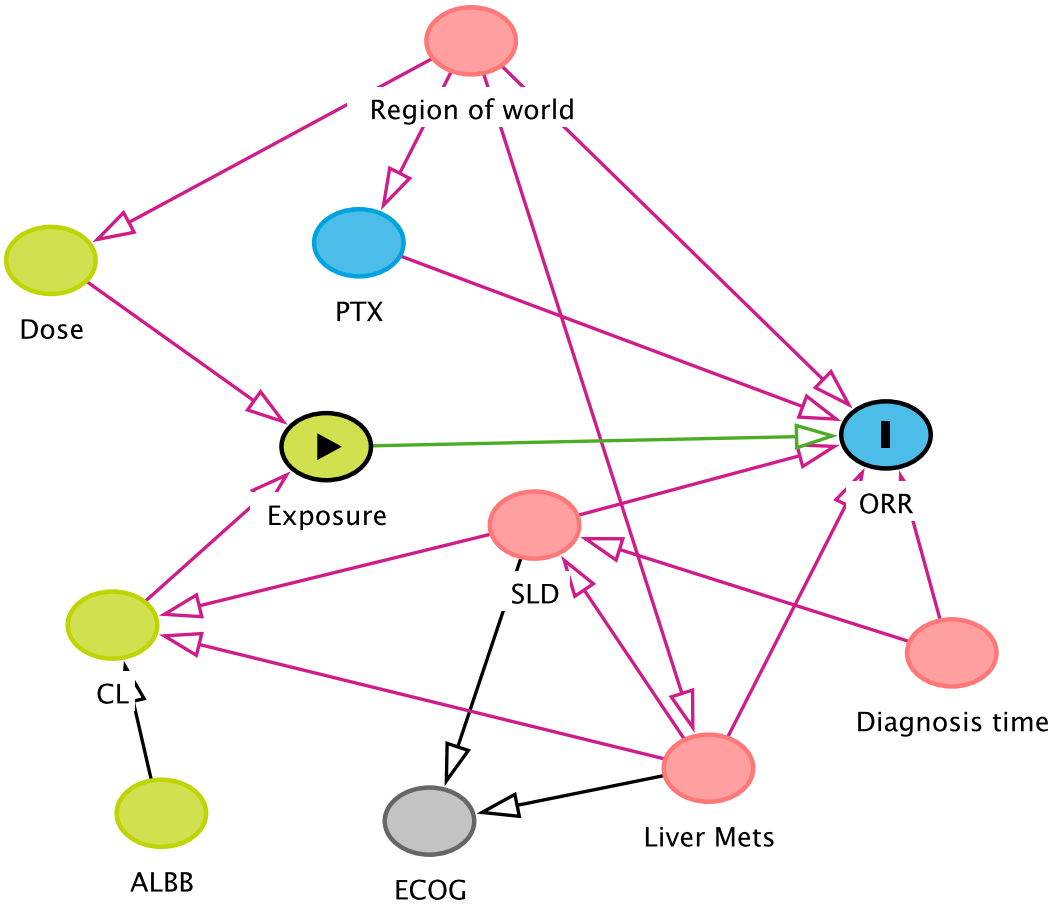
- Baseline tumor size
- ECOG status
- Time since diagnosis
- Albumin
- Liver metastases

Consider selection processes



- Baseline tumor size
- ECOG status
- Time since diagnosis
- Albumin
- Liver metastases
- Prior therapies
- Region of world

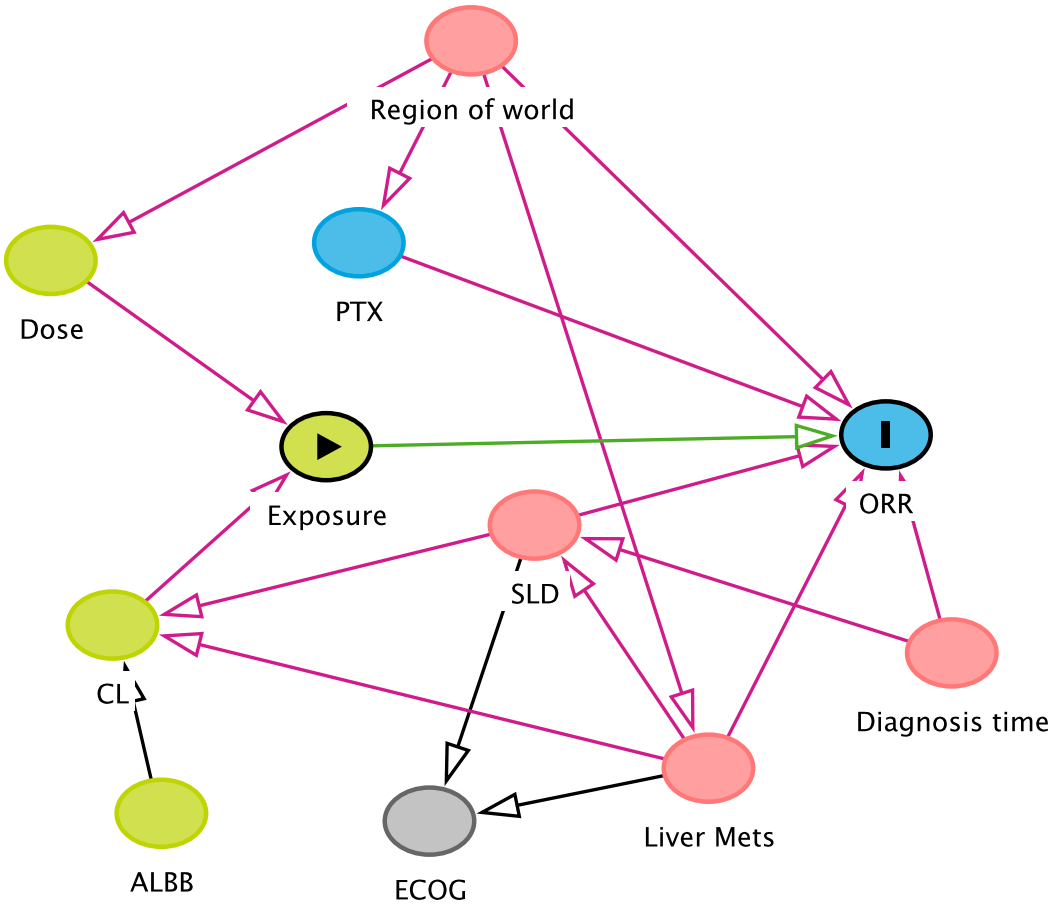
Leading to this ...



Adjustment Set:

- Liver metastases
- Baseline tumor size (SLD)
- Region of the world

What about other variables?



- Age
- ALT, AST, Bilirubin
- Sex

Compare the following modeling approaches

$$Y_i \sim \text{Bernoulli}(p_i)$$

$$\text{logit}(p_i) = \theta_{0i} + \frac{\text{Emax}_i \times c_i}{\text{EC50} + c_i}$$

$$\theta_{0i} = \theta_0 + \beta_{ME} X1_i \qquad \text{Emax}_i = \theta_1 + \beta_{IX} X2_i$$

Model	**Adjustment**	**Priors for β_{ME}, β_{IX}**
Unadjusted	None	NA
True	Adjustment set (ME)	N(0,5)
Regularized	Adjustment set (ME) Others (ME) All (Ix)	N(0,5) regularizing regularizing
Regularized (all)	All (ME) All (Ix)	regularizing regularizing
Unregularized	All (ME) All (IX)	N(0,5) N(0,5)

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Regularizing prior

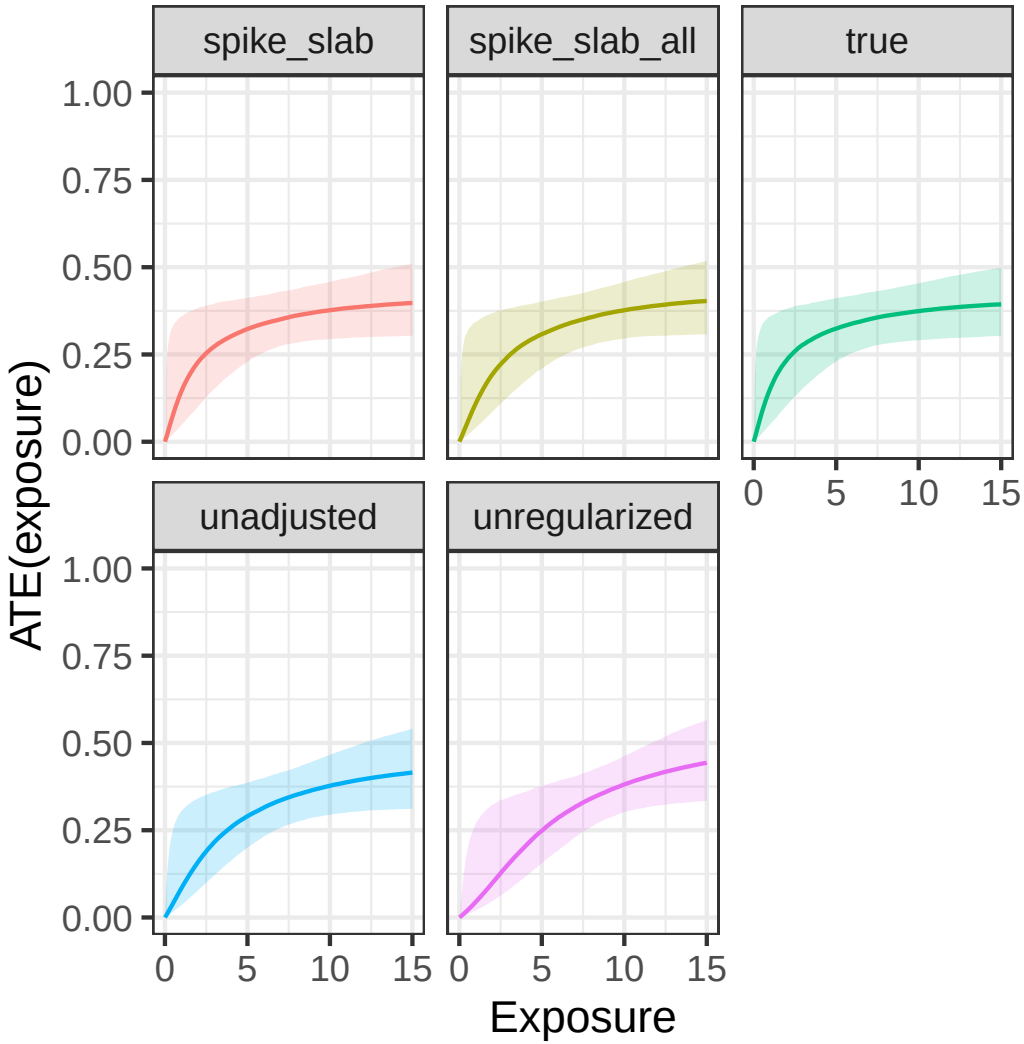
Two component normal mixture (spike and slab-ish)

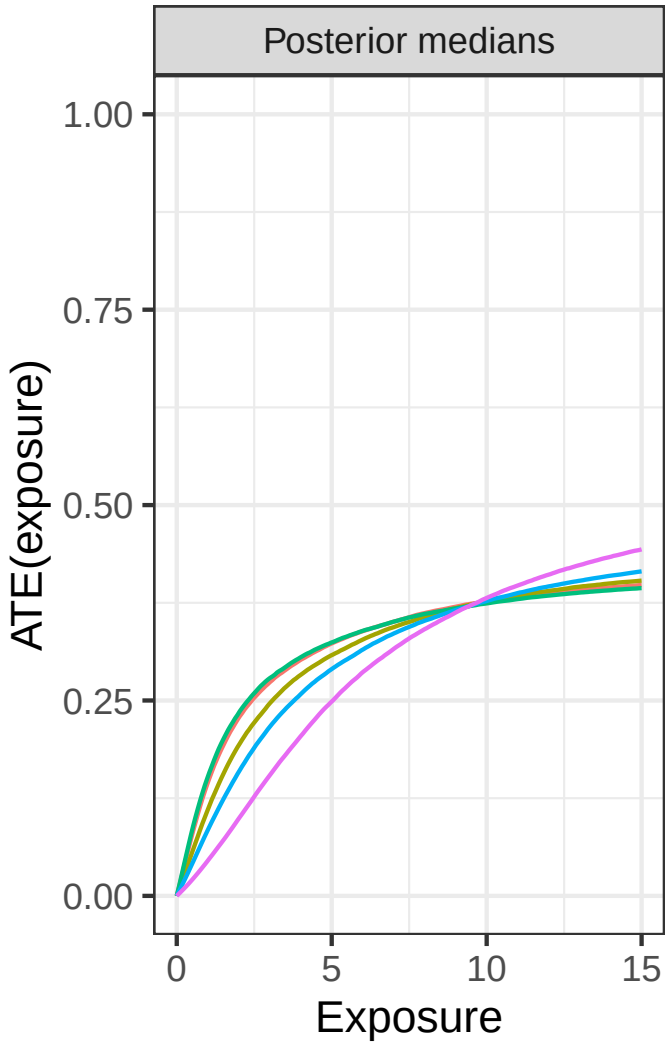
$$\beta_r|\gamma_r \sim \gamma_r N(0,\tau_1) + (1-\gamma_r)\, N(0,\tau_2), r = 1,\ldots,R$$
$$\gamma_r \sim \text{Beta}(a,b)$$

Taking τ_1 and τ_2 as fixed:

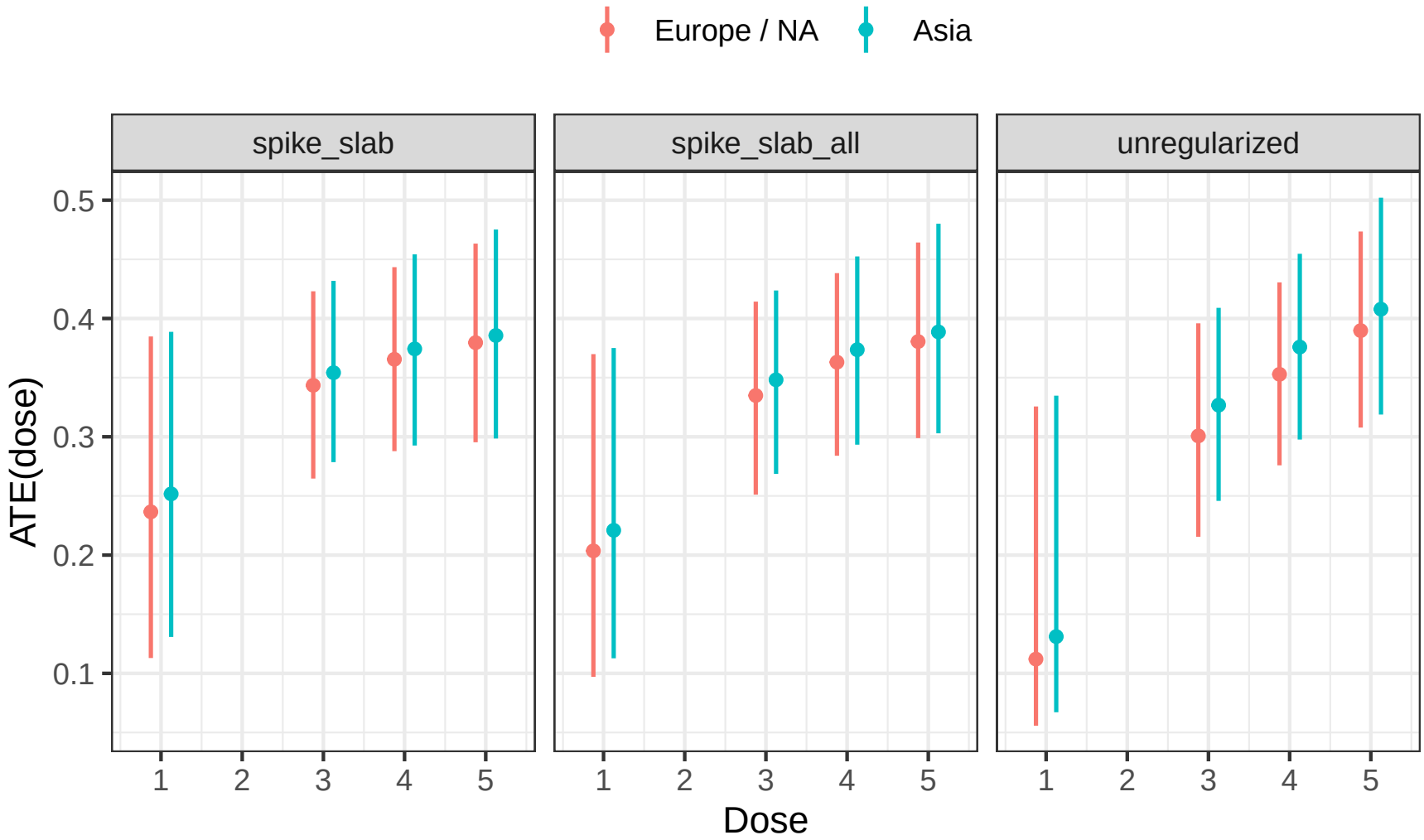
- $\tau_2 = 5$ (same as non-regularizing prior)
- $\tau_1 = 0.1$ (2 sd change < 0.05)

Average causal effect of exposure in overall population





Average causal effect of dose by region of the world



Take-away messages

- DAGs can be useful for planning (pharmacometric) analyses
  - Think about selection processes, particularly when pooling data from multiple trials
  - Consider common causes of drug exposure (clearance) and response
  - Recognize that we don’t know the true model
- Regularization may be useful (in combination with DAG-based adjustment sets) for estimating causal effects

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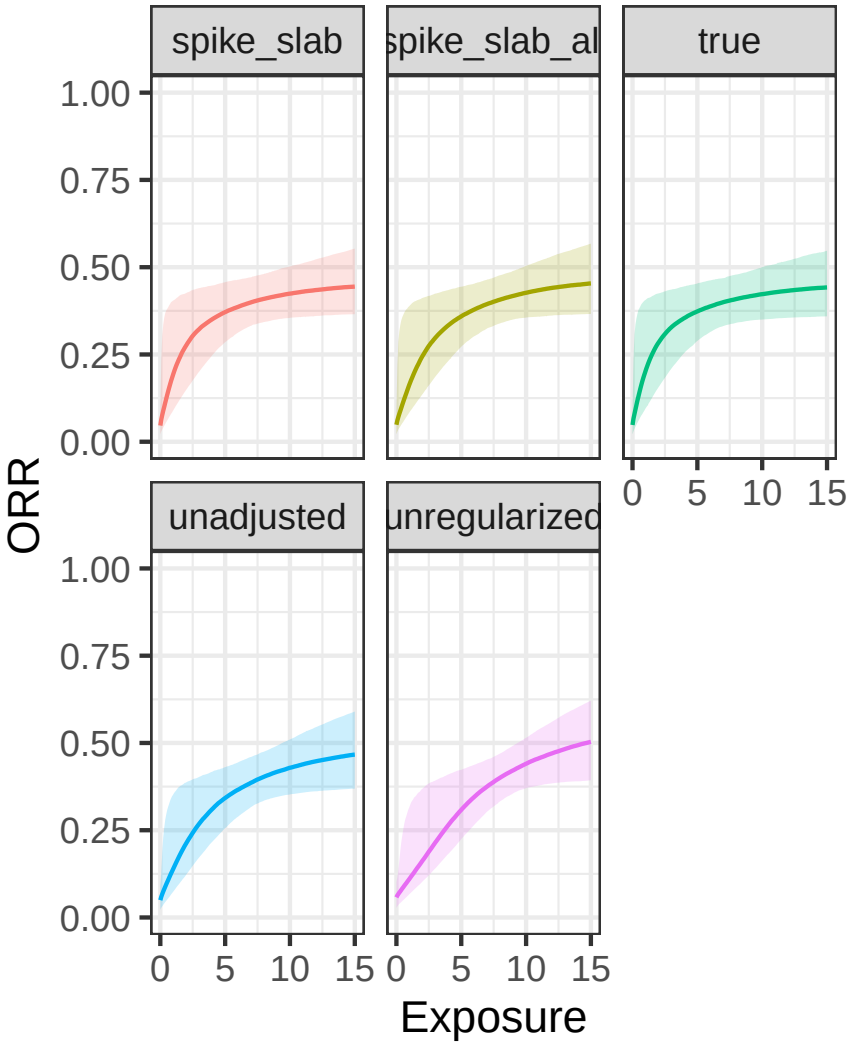
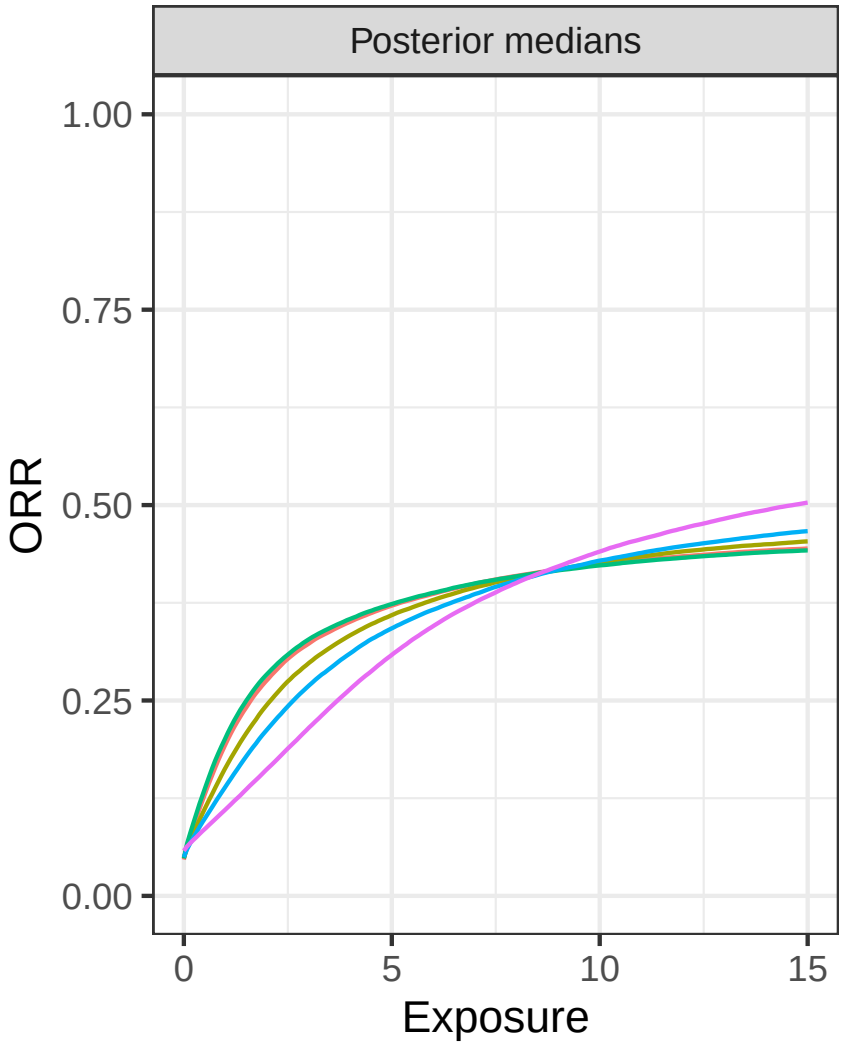
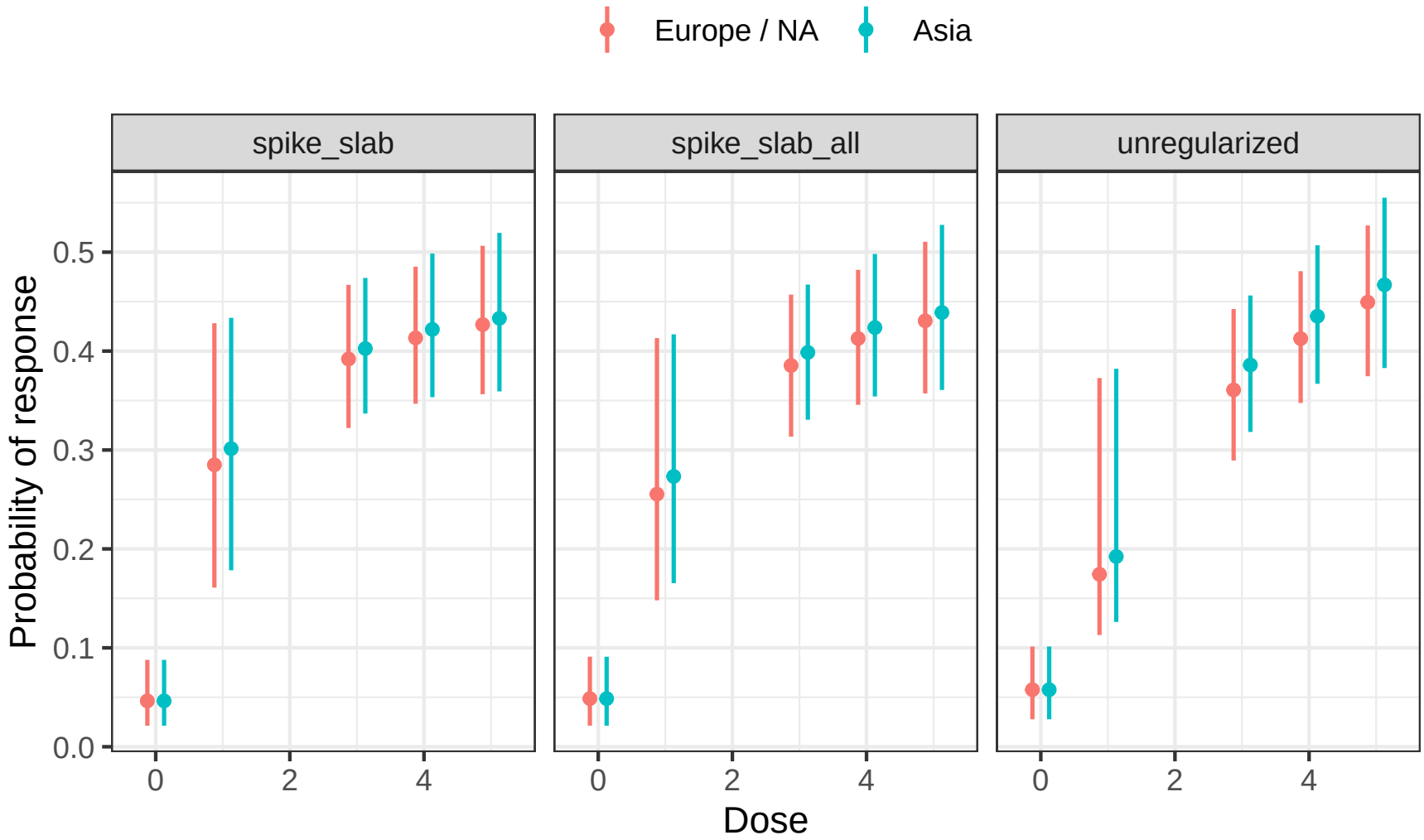
Back-up Slides

Average effect of exposure in overall population





Average effect of dose by region of the world