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.
What is Pharmacometrics?

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
What is Pharmacometrics?

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
What is Pharmacometrics?

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,

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

where \( Y(c) \) = (potential) outcome that would be observed at exposure level \( C = c \)
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:
  - On-line courses (Jason Roy; Miguel Hernan)
  - Judea Pearl’s books/articles

What is Pharmacometrics?
A DAG for our hypothetical example: start with the basics
Consider common causes of exposure and outcome

- Baseline tumor size
- ECOG status
- Time since diagnosis
- Albumin
- Liver metastases
What is Pharmacometrics?

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 is Pharmacometrics?

What about other variables?

- Age
- ALT, AST, Bilirubin
- Sex

Diagram:
- Dose
- PTX
- Region of world
- Exposure
- SLD
- CL
- ALBB
- ECOG
- Liver Mets
- Diagnosis time
- ORR
What is Pharmacometrics?

Compare the following modeling approaches

\[ Y_i \sim \text{Bernoulli}(p_i) \]

\[ \text{logit}(p_i) = \theta_{0i} + \frac{E_{\text{max}}_i \times c_i}{\text{EC50} + c_i} \]

\[ \theta_{0i} = \theta_0 + \beta_{ME}X_{1i} \quad E_{\text{max}}_i = \theta_1 + \beta_{IX}X_{2i} \]

<table>
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<th>Adjustment</th>
<th>Priors for ( \beta_{ME}, \beta_{IX} )</th>
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<td>All (Ix)</td>
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<tr>
<td>Regularized</td>
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<td>Unregularized</td>
<td>All (ME)</td>
<td>N(0,5)</td>
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<tr>
<td></td>
<td>All (IX)</td>
<td>N(0,5)</td>
</tr>
</tbody>
</table>
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 $\tau_1$ and $\tau_2$ as fixed:

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

Average causal effect of exposure in overall population

- spike_slab
- spike_slab_all
- true

Posterior medians

Exposure

ATE(exposure)
What is Pharmacometrics?

Average causal effect of dose by region of the world

- Europe / NA
- Asia

![Graph showing average causal effect of dose by region](image_url)

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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

Conclusions
Average effect of dose by region of the world

Europe / NA

Asia

Dose

Probability of response

spike_slab

spike_slab_all

unregularized

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