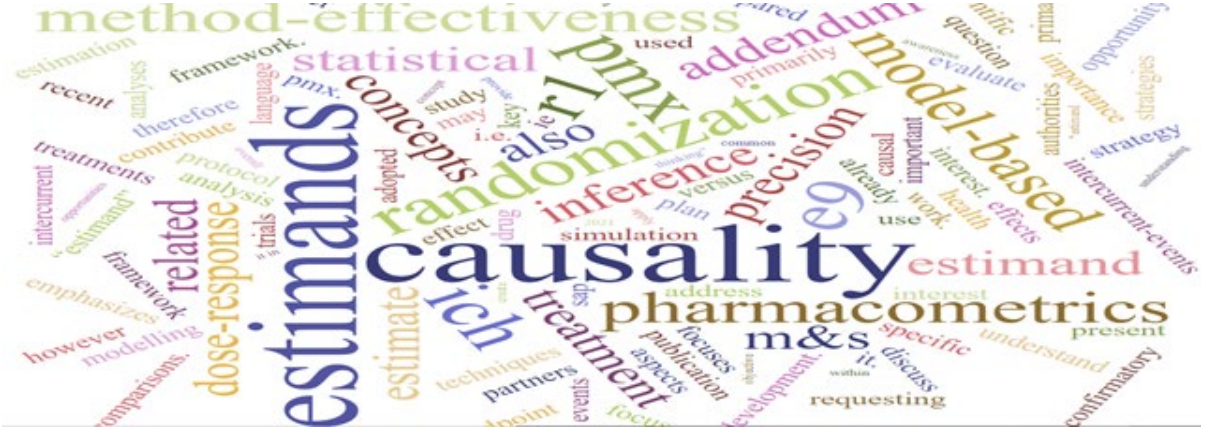
Pharmacometrics (PMX)



Pharmacometric modeling and simulation and causal inference

Christian Bartels, Neva Coello, Thomas Dumortier, Oliver Sander, and Camille Vong, Didier Renard

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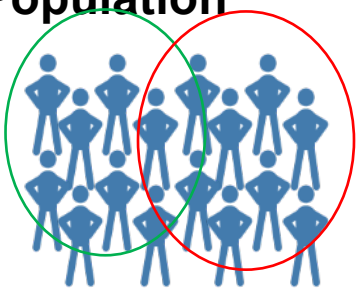
Context: drug development, causal inference and PMX modeling and simulation

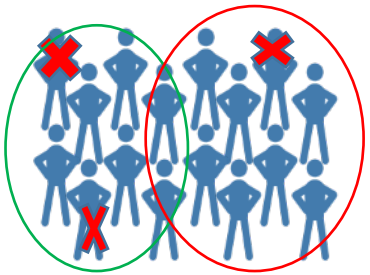
- Clinical research aims at informing treatment decisions: what change in outcome should we expect, if we administer this drug? These are causal questions.
- Clinical research relies on randomized experiments to answer such causal questions
- Sometimes, the (causal) clinical question of interest cannot be answered relying on randomization alone, and randomization must be complemented by (causal) assumptions and analysis methods
  - This is recognized by the Estimand framework, with the estimand defining the (causal) question of interest, intercurrent events interfering with the observation of a randomized treatment outcome, and the framework proposing strategies to handle the intercurrent events
- PMX M&S is well suited for causal inference on clinical trials with established ways to correct for confounding taking advantage of longitudinal exposure-response data
- Here:
  - Familiarize ourselves with directed acyclic graphs (DAGs) and language of causal inference
  - Start to discuss how to use modeling and simulation, in general, and pharmacometric modeling, in particular, to answer causal questions?

Randomization allows to estimate causal treatment effects. Intercurrent events may interfere and causality could be lost

Randomized Population



Subjects with intercurrent events



With Randomization & no missingness – Patients that receive a randomized treatment option are representative for the entire study population → CAUSALITY WITHOUT ADDITIONAL ASSUMPTIONS!!

Patients receiving treatment of interest and having observed outcomes may not be anymore representative for the entire study population → there may be confounding

Counterfactual outcomes – a way to write down what we want to estimate

Define the counterfactuals of what would happen if taking the drug or not, $Y(1)$ and $Y(0)$

Express the causal treatment effect based on the counterfactuals, e.g., as expectations

$$E(Y(1)) - E(Y(0))$$

or as probability distribution

$$p_{d=1}(Y(1))$$

Can we estimate the counterfactual treatment effect from the observed dosing D and outcome Y

$$p_d(Y) = p(Y|D = d) \text{ ?}$$

Or can we do something else?

Patient	D	Y	Y(0)	Y(1)
A	1	0	?	0
B	1	1	?	1
C	1	0	?	0
D	0	1	1	?
E	0	0	0	?
F	0	0	0	?

Observed

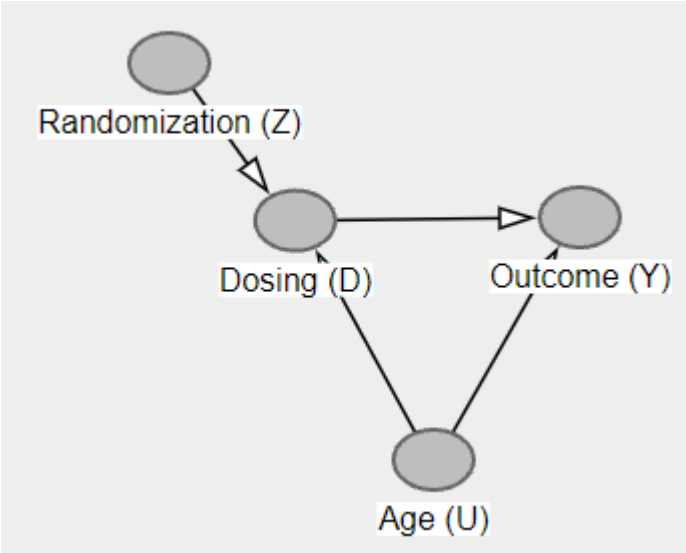
Counter-factual

Directed acyclic graph (DAG) to express assumptions

Simplistic **randomized single dose trial with age affecting adherence (dosing) and the clinical outcome**:

- Patients get assigned to different doses of the treatment or placebo
- They receive the pill to be taken at home
- At home, a few of the patients may not comply, e.g., in particular younger patients
- In addition, younger patients tend to have better outcomes

Definition of confounding: A third variable influencing both the dependent variable and independent variable(s) and that distorts their relationship



DAGs illustrate conditional dependencies and independencies. E.g.,
$p(Y, U, D, Z) = p(Y|U, D)p(D|U, Z)p(U)p(Z)$
We have confounding between the dosing and outcome by age
Good definitions, see Rogers et al. (2022)

Strategies to obtain causal estimates of treatment effects – randomized experiment or standardization

Treatment policy estimand

What is the effect of assigning treatment – regardless of whether doses were actually taken as scheduled or not?

We are interested in

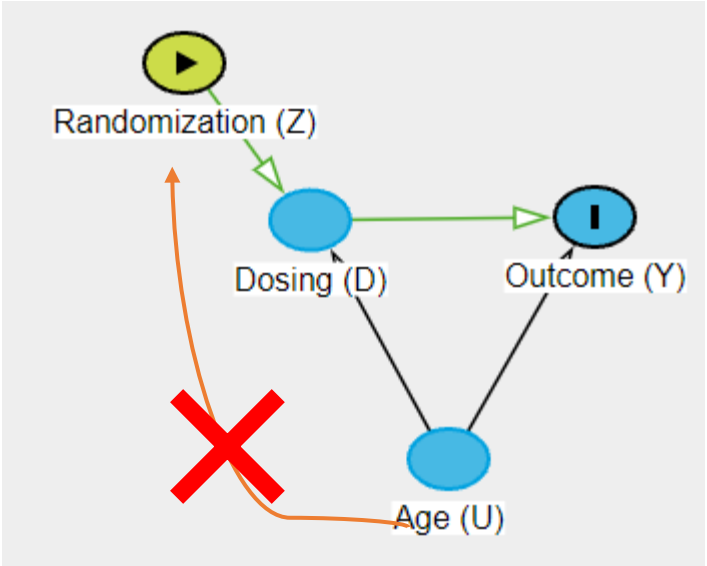
- The effect of the randomized treatment assignment (Z)
- On the outcome (Y)

There is no confounding between the intervention and the outcome. Age does not influence the randomization.

Summarizing the outcome given the intervention, here the randomization, $p(Y|Z = z)$, gives a causal estimate of the treatment effect $p_z(Y)$

Resource: *DAGitty (Textor et al., 2016)*

- Draw causal DAGs
- Identify confounders



Intervention as green triangle (>), observed outcome as blue I

Hypothetical estimand

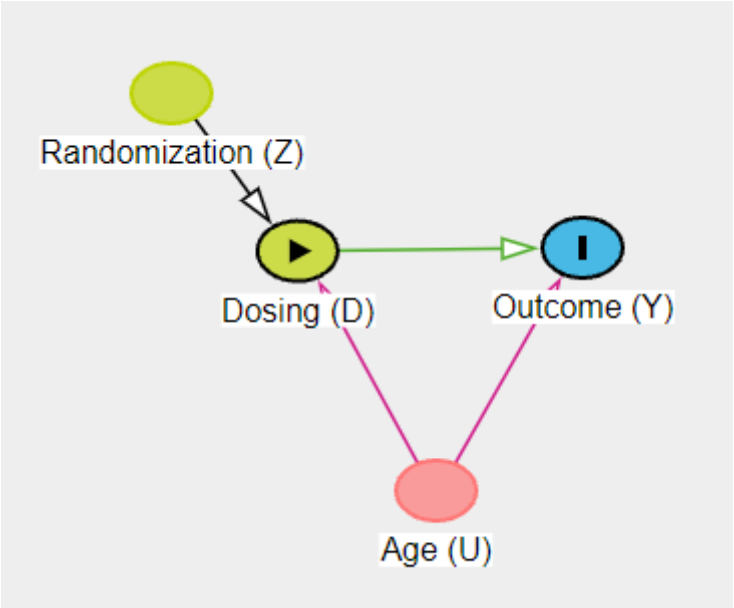
What is the effect of the treatment – if it were taken according to the prescribed/idealized schedule?

We are interested in

- The effect of dosing
- On the outcome.
- Regardless of the randomized treatment allocation

There is confounding of the intervention and the outcome by age

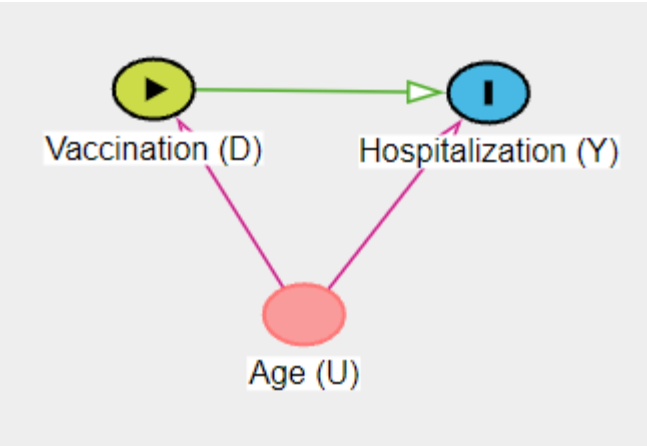
Summarizing the outcome given the intervention, $p(Y|D = d)$, does not give a causal estimate of the treatment effect $p_d(Y)$



Intervention as green triangle (>), observed outcome as blue I. Confounding with red nodes and arrows. Age as a confounder, e.g., younger patients are less compliant but have better outcomes

A simpler example for illustration: Efficacy of COVID vaccination

- We have vaccination as the intervention and are interested in hospitalization as the outcome
- Age is a **confounder** influencing both the dependent variable and independent variable and that distorts their relationship
- Thus again, summarizing the outcome given the intervention, $p(Y|D = d)$, **does not give a causal estimate** of the treatment effect $p_d(Y)$



Intervention as green triangle (>), observed outcome as blue I.
Confounding with red nodes and arrows.

COVID-19 example

Stratifying by age is necessary to avoid underestimating vaccine efficacy [1]

To get unbiased estimate

1. Estimate for each age group
2. Average across age groups

This approach is referred to as standardization and is related to the g-formula

Age Group	Percent vaxxed	Severe Cases per 100k people		Efficacy $1 - \frac{\text{vax}}{\text{no vax}}$
		No vax	Vax	
All Ages	78%	16	5.3	**68%**
12-15	30%	0.30	<0.01*	**>97%***
16-19	74%	1.6	<0.01*	**>99%***
20-29	76%	1.5	<0.01*	**>99%***
30-39	81%	6.2	0.20	**97%**
40-49	84%	17	1.0	**94%**
50-59	88%	40	2.9	**93%**
60-69	90%	77	8.7	**89%**
70-79	95%	190	20	**89%**
80-89	93%	250	48	**81%**
90+	91%	510	39	**92%**

* Andy's guess for upper level of quantification

1. https://www.covid-datascience.com/post/israeli-data-how-can-efficacy-vs-severe-disease-be-strong-when-60-of-hospitalized-are-vaccinated
Israel data with Pfizer Vaccine, August 2021

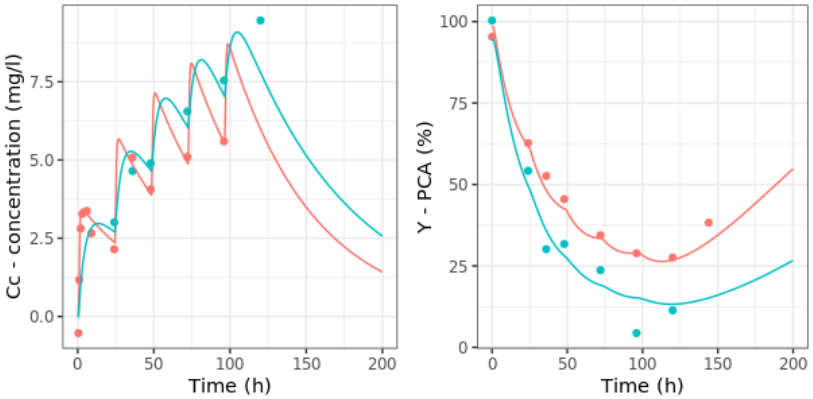
Modeling and simulation to calculate causal estimates

Excursion: pharmacometrics modeling and simulation

- Fit semi-mechanistic **model** to describe the pharmacokinetic-pharmacodynamic data and its variability
- **Simulate** outcomes of interest, e.g., for hypothetical estimands such as full adherence

Often:

- Longitudinal models
- Dose-exposure-response
- Described via differential equations
- Mixed-effects models to describe between subject variability



$$\frac{dA_1}{dt} = -ka \cdot A_1$$

$$\frac{dA_2}{dt} = ka \cdot A_1 - k \cdot A_2$$

$$C(t) = \frac{A_2}{V}$$

$$\frac{dR}{dt} = k_{in} \cdot (1 - \frac{E_{max} \cdot C(t)}{C(t) + EC_{50}}) - k_{out} \cdot R(t)$$

Illustration of data described by a pharmacokinetic-pharmacodynamic non-linear mixed effect model. Left, pharmacokinetics; right, pharmacodynamics. Bottom, differential equations used to describe the data.

G-formula and modeling and simulation

(see also Section 13.3 of Hernán & Robins, 2020; Rogers et al., 2022)

Approach used for vaccination example is known as standardization or g-formula

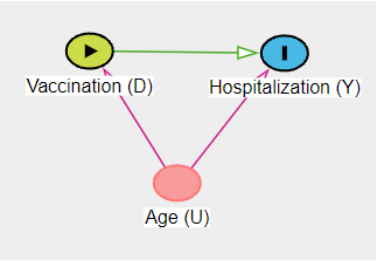
A causal estimate is obtained by "conditioning on" or "blocking" the confounder. Obtain estimates of the treatment effect given the confounder $p(Y|D = d, U = u)$ and average over the distribution of the confounder in the study population $p(U = u)$

$$p_d(Y) = \sum_u p(Y|D = d, U = u)p(U = u)$$

Population average over the distribution of the confounder in the study population can be replaced by an average over the n subjects, i, in the study with their individual values of the covariates, u_i

$$p_d(Y) = \frac{1}{n}\sum_i p(Y|D = d, U = u_i)$$

We arrive at a modeling and simulation approach as outlined in more detail on the next slide

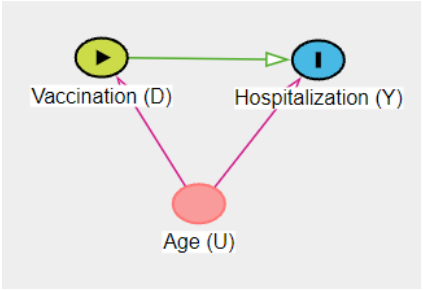


Alternatives to obtain causal estimates exist and are not further discussed here (key words: inverse probability weighting, propensity scores, g-estimation)

Modeling and simulation to estimate a causal effects in the presence of observed confounders

Modeling and simulation approach:

(1) Establish **model** $p_\theta(Y|\, D, U)$ **based on observed data**.



(2) Based on the model and for each patient i and intervention d, **simulate** $j = 1 \ldots m$ "counterfactual" outcomes

$$y_{d,i,j} \sim p_\theta(. \mid D = d, U = u_i)$$

(3) Summarize simulated counterfactual outcomes (population average)

$$E\big(Y(d)\big) = \frac{1}{nm}\sum_{i,j} y_{d,i,j}$$

E.g., probability of hospitalization if being vaccinated: $E\big(Y(1)\big) = \frac{1}{nm}\sum_{i,j} y_{1,i,j}$

or protection from hospitalization by vaccination: $E\big(Y(1)\big)/E\big(Y(0)\big) = \frac{1}{nm}\sum_{i,j} y_{1,i,j} / \frac{1}{nm}\sum_{i,j} y_{0,i,j}$

Modeling and simulation is a generic approach for causal inference

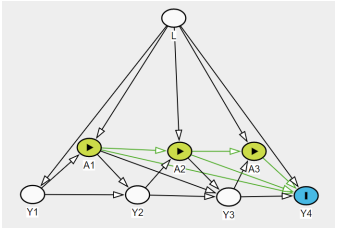
The generic modeling and simulation approach consists of

1. Build model based on observed data
2. Simulate outcomes of interest
3. Summarize simulation results

To account for observed confounding

- Use DAGs (and *DAGitty)* to identify confounders that need to be adjusted for to obtain estimates of causal effects
- Include confounders into the model, e.g., include age dependence on the effect of vaccination on the outcome of hospitalization
- Use model diagnostics to ensure that the effect of the confounder is appropriately captured by the model, e.g., VPC of hospitalization versus age depending on vaccination status

Pharmacometrics (PMX) beyond modeling and simulation: ER, NLME, PKPD, ...?



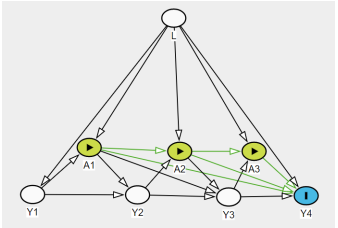
Pharmacometrics beyond modeling and simulation: exposure-response (ER), nonlinear mixed effects models (NLME), PKPD models, ...

Some of the approaches established in PMX may be advantageous for causal inference and help to correct for confounding

However, the corresponding DAGs are complex and need more work. We will have to bring together

- Pharmacometric modeling and simulation
- Estimand framework
- Causal inference

Pharmacometric topics anticipated to be particularly relevant for causal inference



- Dose-exposure-response analyses vs "*front-door adjustment*"
- Modeling longitudinal trials and *"g-computation"* based on "*sequential conditional exchangeability*"
- Dosing records and randomization vs "*instrumental variable*" approach and "*treatment homogeneity assumptions*"
- Condition on random effects in non-linear mixed effects models to correct for confounding vs "*latent variables*" in "*Bayesian dynamic networks*"
- ...

I expect to see several publications per topic within the next few years

Conclusions: To answer causal questions different approaches may have to be combined

1. Use Randomization as the primary tool to have homogeneous groups for comparison that can represent the entire study population → avoids confounding
2. In the presence of confounding, that may be introduced by intercurrent events, additional assumptions and methods are needed to come up with a causal estimation of the treatment → estimand framework, causal inference, pharmacometrics
3. Assumptions may be represented as and discussed with DAGs
4. Modeling and simulation is a generic approach to obtain causal estimates
5. Beyond modeling and simulation, PMX M&S seems well suited for causal inference on clinical trials with advanced techniques to correct for confounding taking advantage of longitudinal exposure-response data

We should start to make this more often more explicit!

Acknowledgement

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Thank you

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