Causal Inference with Continuous Multiple Time Point Exposures

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Talk at the ViCBiostat Seminar, Melbourne

24 October 2024

Motivation – Continuous Exposures

Data:

- CHAPAS-3 trial (📚 Mulenga et al., *Lancet Infectious Diseases*, 2016): children, $\leq$13 years, from Zambia/Uganda
- Every child received
  - i) lamivudine (first drug, not randomized)
  - ii) nevirapine or efavirenz (second drug, not randomized)
  - iii) stavudine, zidovudine, or abacavir (third drug, randomly assigned, 1:1:1)

Pharmacological Substudy:

- *Note:* different patients who take the same drug dose, may still have different drug *concentrations* in their blood, for example because of their individual metabolism
- 📚 Bienczak et al. (*AIDS*, 2017) evaluated concentrations of efavirenz
  $\rightarrow$ higher probability of "viral failures" with lower concentrations ("association")

Motivation – Continuous Exposures (II)

Actual question: at which concentration levels is the drug safe and effective? This is a causal question:

> Probability of failure at t weeks of follow-up, if (possibly contrary to the fact) *every* patient had achieved to have a concentration of x mg/L throughout follow-up.

More generally: how does the probability of failure at time t vary as function of different possible concentration trajectories?

Proposal:[1] the lowest concentration which guarantees that the counterfactual outcome probability is below x% is the recommended lower target concentration limit.

[1] Schomaker et al., *Pharmacoepidemiology and Drug Safety*, 2024

Motivation – Continuous Exposures (III)

- Randomized studies not possible:
  1. only drug dose can be practically assigned, but not the concentration!
  2. concentration is *continuous* which would lead to many groups: $0, 0.5, 1, 1.5, \ldots$ mg/L
- Thus: use longitudinal observational data (from the trial)
  - Note: regression often not valid
    (e.g: time-dependent confounders with treatment confounder feedback)
  - Note: *Positivity assumption may often not be satisfied with continuous interventions*!
  - Possible options to answer motivating question:
    Option 1: Change question: "modified treatment policies" (📖 Diaz et al., *JASA*, 2021)
    Option 2: G-methods $\rightarrow$ simple application (i.e., intervene for many trajectories) today
    Option 3: Find a compromise between interpretability and identifiability today
    Also: for 1 time point, great DR approach developed (📖 Kennedy, JRSS B, 2017)

Notation

- Follow-up time: $t = 0, 1, \ldots, T$
- Outcome: Y_t
- Intervention: A_t
- Confounder, Covariate: L_t
- History: e.g. $\bar{A}_t = (A_0, \ldots, A_t)$
- History up to *before* A_t: H_t
- **Counterfactual:** e.g. $Y_t^{\bar{a}_t}$

Estimand & Estimation with Sequential G-computation

Estimand: Causal Dose-Response Curve

$$m_t : \bar{a}_t \mapsto E(Y_t^{\bar{a}_t}), \qquad t = 0, 1, \ldots, T$$

Under sequential conditional exchangeability, consistency and **positivity** we have:

$$\mathbb{E}(Y_t^{\bar{a}_t}) \quad = \quad \mathbb{E}(\ldots \mathbb{E}(\mathbb{E}(Y_t | \bar{A}_t = \bar{a}_t, \mathbf{H}_t) | \bar{A}_{t-1} = \bar{a}_{t-1}, \mathbf{H}_{t-1}) \ldots | A_0 = a_0, \mathbf{L}_0)).$$

$\rightarrow$ substitution estimation (sequential g-computation)

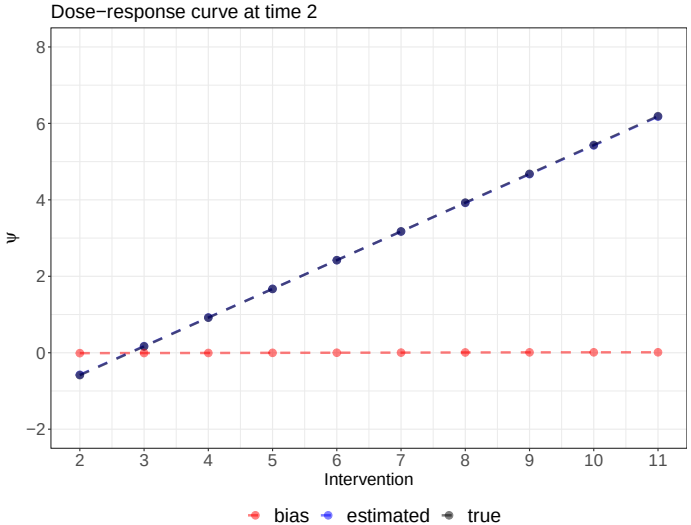
Positivity: (strong version)

$$\inf_{a_t \in \bar{\mathcal{A}}_t} g(a_t \mid \mathbf{h}_t) > 0 \quad \text{whenever} \quad p_0(\mathbf{l}_t \mid A_{t-1} = a_{t-1}, \mathbf{H}_{t-1} = \mathbf{h}_{t-1}) > 0 \quad \forall t, \bar{a}_t, \bar{\mathbf{l}}_t .$$

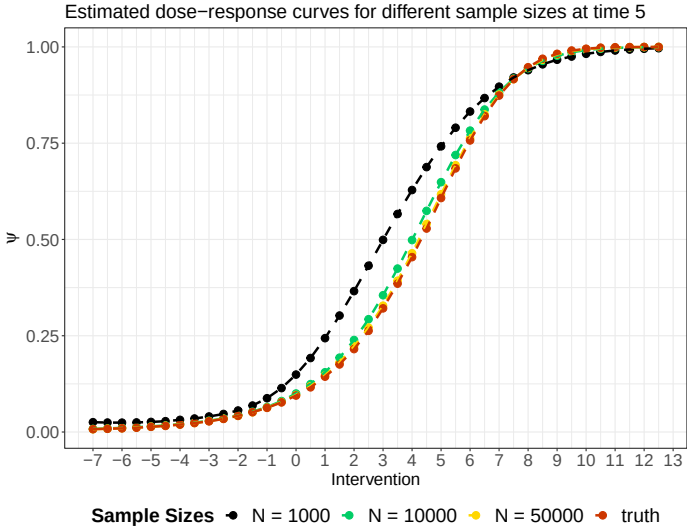
where $\bar{\mathcal{A}}_t$ denotes the set of all relevant strategies $\bar{a}_t = (a_0, \ldots, a_t)$

$\rightarrow$ What if we simply assume positivity and apply g-computation for many $\bar{a}_t$?

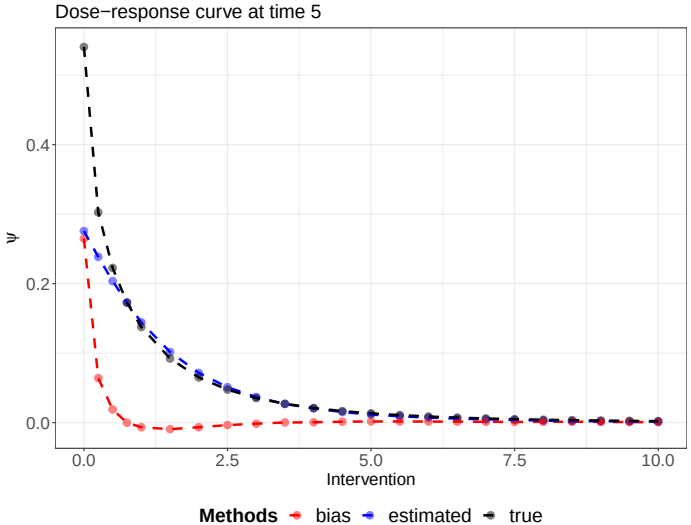
Simulation (simple)



Simulation (survival)



Simulation (complex, as in data)



Overall Consideration

The **tradeoff** to make is between

estimating the CDRC as closely as possible, at the risk of bias due to positivity violations because of the continuous intervention

and

minimizing the risk of bias due to positivity violations, at the cost of redefining the estimand

Alternative proposal: make a compromise!

Proposal: Weighted Estimand (1 Time Point)

The general dose-response curve $m : a \mapsto E(Y^a)$ can be identified[2] with the g-formula as

$$m(a) = \int E(Y \mid A = a, \mathbf{L} = \mathbf{l}) p_0(\mathbf{l}) d\nu(\mathbf{l}) \,,$$

Proposal: instead, rather use

$$m_w(a) = \int E(Y \mid A = a, \mathbf{L} = \mathbf{l}) w(a, \mathbf{l}) p_0(\mathbf{l}) d\nu(\mathbf{l})$$

with

$$w(a, \mathbf{l}) = \begin{cases} 1 & \text{if } g(a \mid \mathbf{l}) > c \\ \frac{g(a|l)}{g(a)} & \text{otherwise.} \end{cases}$$

[2] under consistency, positivity and conditional exchangeability

Weighted Estimand – Implications

- yields the desired dose-response curve under enough support (i.e., $g(a \mid \mathbf{l}) > c$)
- otherwise the estimand is $E(Y|A = a)$

  $\rightarrow$ not a causal quantity but does not require positivity assumption

Example: $a = 0.5$ mg/L

$\rightarrow$ for all patients with confounders $\mathbf{l}$ that have $g(0.5 \mid \mathbf{l}) > c$ we still target $E(Y^a)$

$\rightarrow$ but for those where this does not hold we target $E(Y|a)$

(plausible example: $g(0.5 \mid \mathit{ultraslow}, \mathit{adherent}) = 0$)

Weighted Estimand – Multiple Time Points

$$w_t(a_{t+1}, \mathbf{h}_{t+1}, c) = \begin{cases} 1 & \text{if } g_t(a_{t+1} \mid \mathbf{h}_{t+1}) > c\,, \\ \frac{g_t(a_{t+1}|\mathbf{h}_{t+1})}{g_t(a_{t+1}|a_t,\mathbf{h}_t)} & \text{if } g_t(a_{t+1} \mid \mathbf{h}_{t+1}) \leq c \text{ and } g_t(a_{t+1} \mid a_t, \mathbf{h}_t) > c\,, \\ \frac{g_t(a_{t+1}|\mathbf{h}_{t+1})}{g_t(a_{t+1}|a_{t-1},\mathbf{h}_{t-1})} & \text{if } g_t(a_{t+1} \mid \mathbf{h}_{t+1}) \leq c \text{ and } g_t(a_{t+1} \mid a_t, \mathbf{h}_t) \leq c \\ & \text{and } g_t(a_{t+1} \mid a_{t-1}, \mathbf{h}_{t-1}) > c\,, \\ \vdots & \vdots \\ \frac{g_t(a_{t+1}|\mathbf{h}_{t+1})}{g_t(a_{t+1})} & \text{otherwise}\,. \end{cases}$$

Weighted Estimand – Implications

- Targets still $E(Y_t^{\bar{a}_t})$ if there is enough conditional support in terms of $g_t(a_t \mid \mathbf{h}_t) > c \quad \forall t$

- Targets $E(Y_t \mid \bar{a}_t)$ if there is not enough conditional support $\forall t$

  $\rightarrow$ not a causal quantity but does not require positivity assumption.

- For units where there is support at some points, but not at others, the weights will be 1 at some time points, but not at all $t \rightarrow$ we deviate from the CDRC only when necessary.

Interpretation

We stick to the actual research question as long as possible, and calculate the CDRC in regions of enough support.

For some patients however, it may be unlikely (or even biologically impossible!) to actually observe some intervention trajectory of interest: those patients then "receive" *individual* concentration levels which generate outcomes that are typical for children with $\bar{a}_t$ mg/l.

For this, we make use of associations and require no positivity assumption.

The weighted curve acts like a magnifying class and sensitivity tool if we don't want to rely on parametric extrapolation in regions of low support, where fixing the concentration to a specific level seems unrealistic.

Weighted Estimand – Estimation

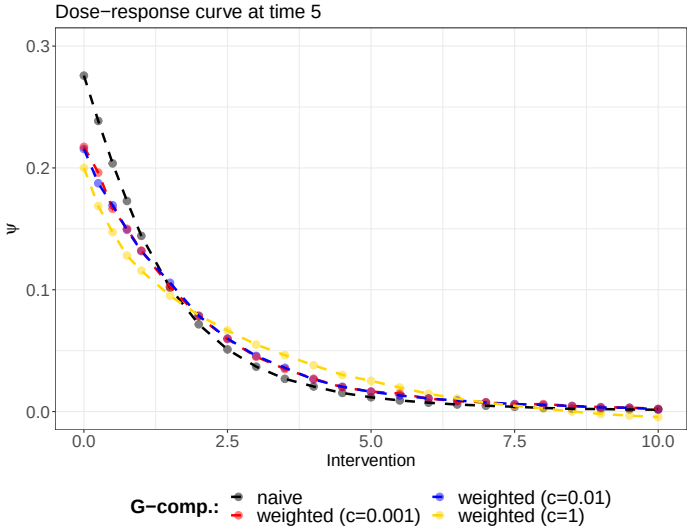
For example, substitution estimator based on the following expression:

$$\tilde{m}_{w,t} \quad = \quad \mathbb{E}(\mathbb{E}(\ldots \mathbb{E}(\, \mathbb{E}(\, Y_t w_t | \bar{A}_t = \bar{a}_t, \bar{\mathbf{L}}_t)\, w_{t-1} | \bar{A}_{t-1} = \bar{a}_{t-1}, \bar{\mathbf{L}}_{t-1}\,) \ldots)\, w_0 | A_0 = a_0, \mathbf{L}_0\,)\,)$$

$\rightarrow$ can also re-expressed into parametric g-formula-type expression, but then requires estimation of conditional *densities*, not only expectations

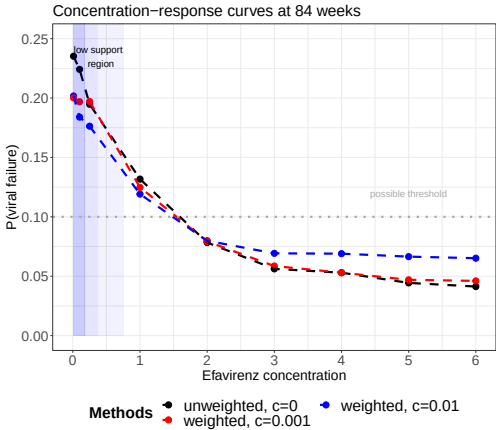
Note: even if Y_t is normal, $w_t Y_t$ may not be normal; so we may need a data-adaptive approach

Simulation (complex, as in data)



Data Analysis

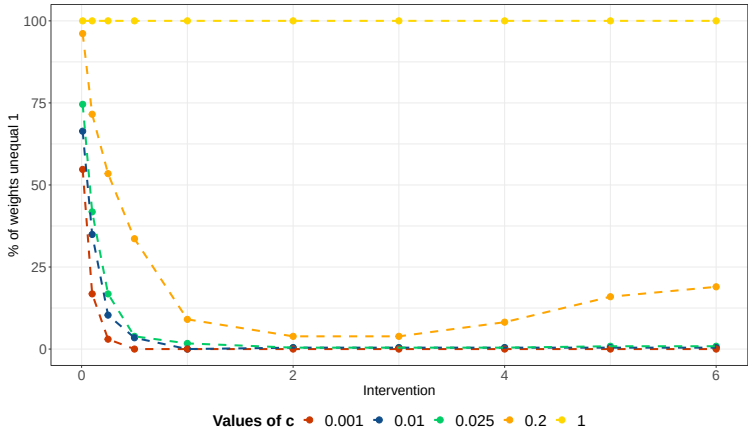
Based on a complete case analysis[3] of $n = 58$. Weighted curve deviates from estimated CDRC in areas of low support kids.



[3] See https://arxiv.org/abs/2402.14562 on why complete cases are used

Data Analysis – conditional support and weight behaviour

Percentage of weights which are unequal 1, as a function of c and concentration values, averaged over all visits.



Possibly present both estimands

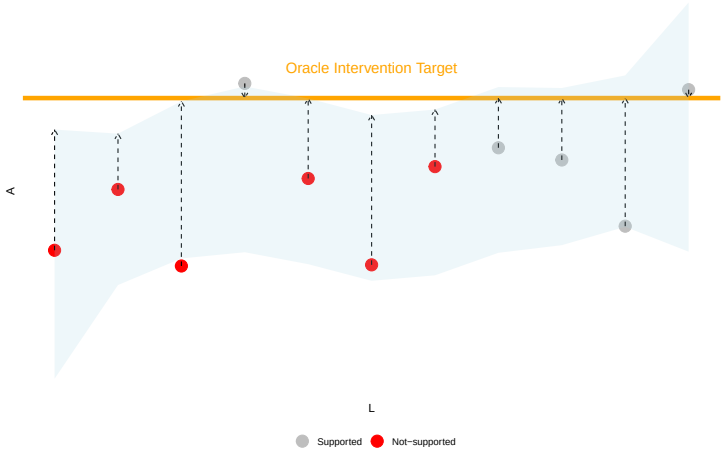
- Whenever an estimate of the conditional treatment density is close to zero, we do not necessarily know whether this is a finite sample / estimation / sparsity issue, or due to "infeasibility", i.e. an illogical intervention given the history of a patient.
- Presenting the CDRC shows the case where nothing is infeasible and we rely on extrapolations.
- Presenting the weighted estimand, with multiple $c's$, shows the change in the curve as we consider more intervention trajectories to be infeasible.
- Both estimands together give us a sense if main conclusions could change when positivity violations are addressed differently.

Intermediate conclusions

- Standard g-computation can be used for continuous interventions
  - + targets the CDRC of interest
  - – relies on positivity assumption
- Simulations show that strategy may work, but can be problematic in regions of low support or with limited sample size
- Weighted curves offer a compromise, don't enforce unrealistic interventions, and do not require the positivity assumption (+)
  - – interpretation is difficult
- – Also: so far relatively simple approach to define "positivity violations" (sparsity)

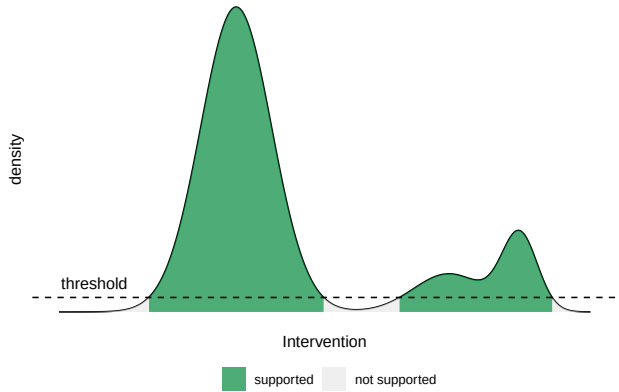
Outlook 1: *Feasible* interventions

Improve interpretation, while still requiring “minimal” (or no) positivity



Source: Han Bao (arXiv paper available soon)

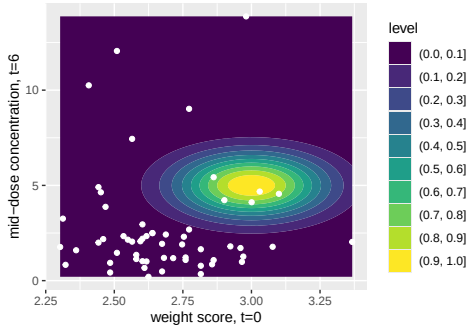
Outlook 2: Different definitions of what positivity violations are



Source: Han Bao (arXiv paper available soon)

Outlook 3: *When to extrapolate, and when to change question?*

We need diagnostics for sparsity....



Source: Katharina Ring (arXiv paper available soon)

Software: *R*-package `CICI`[4]

```
est3 <- sgf(X=EFV,                                          # or gformula()
            Lnodes  = c("adherence.1","weight.1",           # confounders
                        "adherence.2","weight.2",
                        "adherence.3","weight.3",
                        "adherence.4","weight.4"
            ),
            Ynodes  = c("VL.0","VL.1","VL.2","VL.3","VL.4"),      # outcomes
            Anodes  = c("efv.0","efv.1","efv.2","efv.3","efv.4"), # intervent.
            abar=seq(0,10,1),   # intervention trajectories
            Yweights = w$`0.01` # optional outcome weights

)
```

Small tutorial: `https://michaelschomaker.github.io/project/cici/`

Features: Parallelization, additive model framework, model selection and building, custom estimands, survival data, use on imputed data, ...

[4] available on CRAN: `https://cran.r-project.org/web/packages/CICI/index.html`

Read preprint on arXiv

...and test software

https://arxiv.org/abs/2305.06645

Literature

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[2] Iván Díaz, Nicholas Williams, Katherine L. Hoffman, and Edward J. Schenck.
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[3] Edward H. Kennedy, Zongming Ma, Matthew McHugh, and Dylan S. Small.
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[4] Veronica Mulenga, Victor Musiime, Adeodata Kekitiinwa, Adrian D. Cook, George Abongomera, Julia Kenny, Chisala Chabala, Grace Mirembe, Alice Asiimwe, Ellen Owen-Powell, David Burger, Helen McIlleron, Nigel Klein, Chifumbe Chintu, Margaret J. Thomason, Cissy Kityo, A. Sarah Walker, and Diana Gibb.
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[5] M. Schomaker, H. McIlleron, P. Denti, and I. Díaz.
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APPENDIX

Treatment-Confounder Feedback