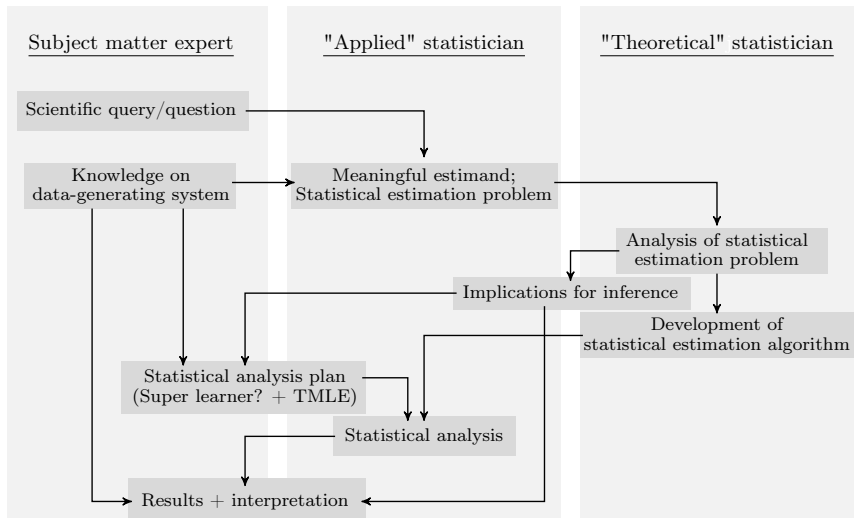


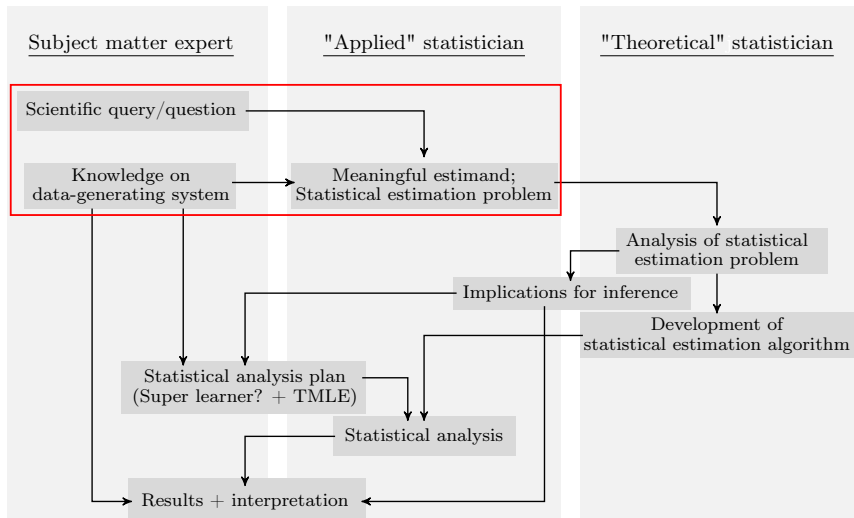
Day 4, Lecture 1

Identification of effects of
time-dependent treatment
interventions

Identifying effects of time-dependent treatment interventions



Identifying effects of time-dependent treatment interventions



Identifying effects of time-dependent treatment interventions

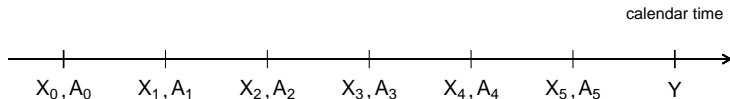
In this lecture, our goal is to:

1. Identify and list the key identification assumptions necessary for a causal interpretation of parameters defined under dynamic treatment interventions, highlighting particularly on the challenges imposed by time-dependent confounding.
2. Explain the identification formulas in presence of time-dependent treatments and confounding, with a specific focus on the identification achieved through sequential regression.

Identifying effects of time-dependent treatment interventions

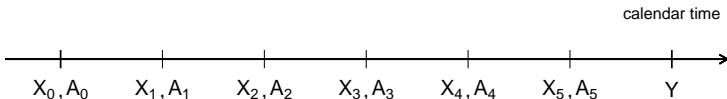
Longitudinal data structure:

- ▶ $O = (X_0, A_0, X_1, A_1, \dots, X_K, A_K, Y) \in (\mathbb{R}^d \times \{0, 1\})^K \times \{0, 1\}$
- ▶ Covariates $X = (X_0, X_1, \dots, X_K)$ change over time
- ▶ Treatment decisions $A = (A_0, A_1, \dots, A_K)$ are updated over time
- ▶ Covariates and treatment decisions interact in complex ways



NB: For now keeping right-censoring (and competing risks) out of the picture.

Identifying effects of time-dependent treatment interventions



Counterfactual outcomes

$$Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}, \quad \text{for,} \quad a_0^*, \dots, a_K^* \in \{0, 1\}$$

= defined by a sequence of treatment decision rules that we choose.

also called:

- ▶ hypothetical treatment **interventions**
- ▶ hypothetical treatment **strategies**
- ▶ hypothetical treatment **regimes**

NB: For now keeping right-censoring (and competing risks) out of the picture.

Overview

1. Identifying assumptions
 - ▶ No unmeasured confounding and positivity
2. Identification formulas
 - ▶ Inverse probability weighting
 - ▶ Sequential regression (iterated expectations)
3. Practical 1

Identifying assumptions

Identifying effects of time-dependent treatment interventions

Identification of $\mathbb{E}[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}]$.

1. Consistency: $Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*} = Y$

if $A_k = a_k^*$ for $k = 0, 1, \dots, K$

2. Exchangeability: $Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*} \perp\!\!\!\perp A_k \mid \bar{X}_k, \bar{A}_{k-1}$

for $k = 0, 1, \dots, K$

3. Positivity:
$$\prod_{k=0}^K \frac{1\{A_k = a_k^*\}}{P(A_k = a_k^* \mid \bar{X}_k, \bar{A}_{k-1})} < \infty$$

for $k = 0, 1, \dots, K$

Notation for histories of variables: $\bar{X}_k = (X_0, X_1, \dots, X_k)$, $\bar{A}_k = (A_0, A_1, \dots, A_k)$.

Identifying effects of time-dependent treatment interventions

Imposing a static regime, like 'always treat',

$$A_0 = 1, A_1 = 1, \dots, A_K = 1$$

may not always be realistic (or even feasible).

Identifying effects of time-dependent treatment interventions

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Example (Robins 1986) Effects of exposure of chemicals on employees: Static regimes cannot be identified since subjects can only be exposed when at work.

Identifying effects of time-dependent treatment interventions

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Another example Development of adverse effects or contraindications (e.g., pregnancy) can force a subject to stop an assigned treatment.

Identifying effects of time-dependent treatment interventions

But the positivity assumption dictates that the treatment level imposed by the intervention cannot in the observed data be deterministically assigned at any time point based on a subject's observed past.

3. Positivity:

$$\prod_{k=0}^K \frac{1\{A_k = a_k^*\}}{P(A_k = a_k^* \mid \bar{X}_k, \bar{A}_{k-1})} < \infty$$

for $k = 0, 1, \dots, K$

Identifying effects of time-dependent treatment interventions

What we can do \Rightarrow change the question/intervention.

- ▶ 'Expose when at work'
- ▶ 'Treat until adverse event or contraindication happen'
- ▶ 'Initiate antidiabetic treatment when HbA1c level increases beyond some level'

Identifying effects of time-dependent treatment interventions

Dynamic treatment regimes

- ▶ A prespecified set of rules which assign treatment over time by responding to a patient's time-varying conditions.

Identifying effects of time-dependent treatment interventions

Dynamic treatment regimes

- ▶ A prespecified set of rules which assign treatment over time by responding to a patient's time-varying conditions.
- ▶ Mathematically, defined as function $\mathcal{S}_k(\bar{X}_k, \bar{A}_{k-1})$ that maps (a subset of) previous covariate/treatment values \bar{X}_k, \bar{A}_{k-1} to a (binary) treatment assignment, e.g.,

$$\mathcal{S}_k(\bar{X}_k, \bar{A}_{k-1}) = \begin{cases} 1 & \text{if } X_k > \theta, \\ 0 & \text{if } X_k \leq \theta. \end{cases}$$

Identifying effects of time-dependent treatment interventions

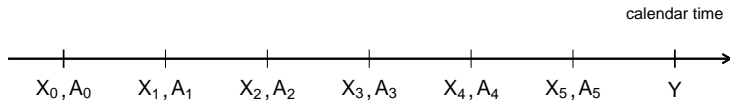
2. Exchangeability: $Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*} \perp\!\!\!\perp A_k \mid \bar{X}_k, \bar{A}_{k-1}$
for $k = 0, 1, \dots, K$



- ▶ Conditional on previous covariate and treatment history, the currently exposed group tells us what would happen to the currently unexposed group and vice versa
- ▶ This is (again) also called no unmeasured confounding
- ▶ The observed history at any point in time is must be sufficient to predict the next treatment decision

Identifying effects of time-dependent treatment interventions

2. Exchangeability: $Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*} \perp\!\!\!\perp A_k \mid \bar{X}_k, \bar{A}_{k-1}$
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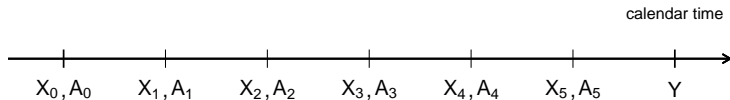


Particularly, we may have that...

- ▶ X_k may be affected by earlier treatment decisions A_{k-1}, \dots, A_1, A_0 .
- ▶ X_k may be a confounder for the effect of A_k, A_{k+1}, \dots, A_K on Y .

Identifying effects of time-dependent treatment interventions

2. Exchangeability: $Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*} \perp\!\!\!\perp A_k \mid \bar{X}_k, \bar{A}_{k-1}$
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} time-dependent confounding

Identifying effects of time-dependent treatment interventions

In presence of time-dependent confounding, "standard methods" may cause bias

- ▶ Multiple regression
- ▶ Random effects models
- ▶ Time-dependent Cox regression

The problem is that:

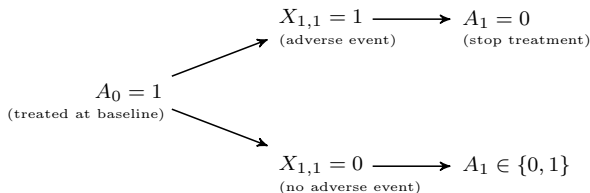
- ▶ If we control for X_k in our model, we will not capture the effect from earlier treatment decisions A_{k-1}, \dots, A_1, A_0 through X_k .
- ▶ But we have to control for X_k to assess the effect of A_k, A_{k+1}, \dots, A_K on Y .

Identifying effects of time-dependent treatment interventions

The simulation setting of Day 3, Practical 2:

- ▶ $X_{0,1}, X_{0,2}, X_{0,3}$ are baseline covariates.
- ▶ $A_0 \in \{0, 1\}$ is a randomized treatment indicator.
- ▶ $X_{1,1}, X_{1,2}$ are follow-up covariates.
- ▶ $A_1 \in \{0, 1\}$ is a follow-up treatment decision.
- ▶ $Y \in \{0, 1\}$ is the final outcome.

Identifying effects of time-dependent treatment interventions



- ▶ The variable $X_{1,1}$ is an indicator of an adverse event from the baseline treatment, an adverse event that causes many treated subjects to switch from 'treatment' ($A_0 = 1$) to 'no treatment' ($A_1 = 0$).
- ▶ The variable $X_{1,2}$ is a marker of being likely to forget to take the medicine (or thinking it is too bothersome) which increases the probability of switching treatment as well.

Identifying effects of time-dependent treatment interventions

We considered the effects of different types of interventions:

1. The **intention-to-treat (ITT) effect** which only sets treatment at baseline and contrasts the two scenarios of being treated at baseline ($A_0 = 1$) and not being treated at baseline ($A_0 = 0$).
2. A **static effect** of being 'always treated' ($A_0 = A_1 = 1$) and 'never treated' ($A_0 = A_1 = 0$).
3. A **dynamic effect** of being treated at baseline ($A_0 = 1$) and only treated at follow-up if the adverse event has not happened, i.e., $X_{1,1} = 0$ — contrasted to being 'never treated' ($A_0 = A_1 = 0$).

Identifying effects of time-dependent treatment interventions

The true ITT average treatment effect:

ITT: -0.93%

The true static average treatment effect:

static: -6.33%

The true dynamic average treatment effect:

dynamic: -5.07%

Identifying effects of time-dependent treatment interventions

We considered two 'naive approaches' to estimate the static effect:

Identifying effects of time-dependent treatment interventions

We considered two 'naive approaches' to estimate the static effect:

1. A logistic regression of the outcome regressed on all treatment variables and covariates: Contrast means of the predictions under $A_0 = A_1 = 1$ to the mean of the predictions under $A_0 = A_1 = 0$.

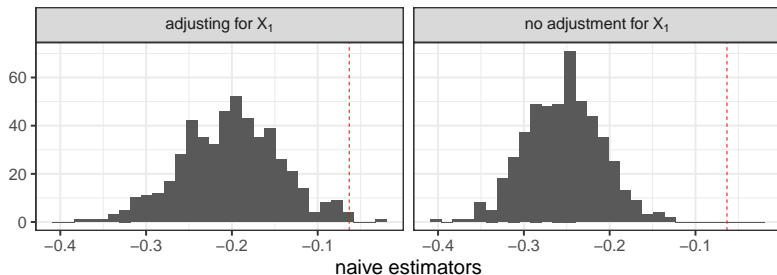
Identifying effects of time-dependent treatment interventions

We considered two 'naive approaches' to estimate the static effect:

1. A logistic regression of the outcome regressed on all treatment variables and covariates: Contrast means of the predictions under $A_0 = A_1 = 1$ to the mean of the predictions under $A_0 = A_1 = 0$.
2. A logistic regression of the outcome regressed on baseline covariates and both treatment variables (leaving out follow-up covariates): Contrast means of the predictions under $A_0 = A_1 = 1$ to the mean of the predictions under $A_0 = A_1 = 0$.

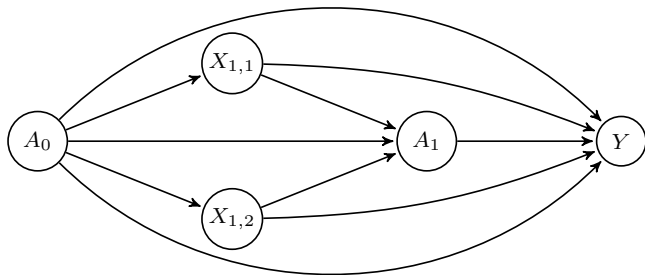
Identifying effects of time-dependent treatment interventions

In a simulation study with $M = 500$ repetitions:



Both naive approaches give biased results — due to time-dependent confounding.

Identifying effects of time-dependent treatment interventions



- ▶ $X_{1,1}$, $X_{1,2}$ are both confounders and mediators.

Identification formulas

Warning: Heavy notation ahead.

Identification formulas

Factorization of the density p of $P \in \mathcal{M}$:¹

$$p(o) = \mu_{X_0}(x_0) \pi_{A_0}(a \mid x_0) \prod_{k=1}^K \mu_{X_k}(x_k \mid \bar{x}_{k-1}, \bar{a}_{k-1}) \pi_{A_k}(a_k \mid \bar{x}_k, \bar{a}_{k-1}) \\ \times \mu_Y(y \mid \bar{x}_K, \bar{a}_K)$$

- ▶ μ_{X_0} is the marginal density of baseline covariates.
- ▶ π_{A_0} is the density of treatment at baseline.
- ▶ $\mu_{X_k}(x_k \mid \bar{x}_{k-1}, \bar{a}_{k-1})$ is the conditional density of X_k given the histories $\bar{X}_{k-1} = \bar{x}_{k-1}, \bar{A}_{k-1} = \bar{a}_{k-1}$, $k = 1, \dots, K$.
- ▶ $\pi_{A_k}(a_k \mid \bar{x}_k, \bar{a}_{k-1})$ is the conditional density of A_k given the histories $\bar{X}_k = \bar{x}_k, \bar{A}_{k-1} = \bar{a}_{k-1}$, $k = 1, \dots, K$.
- ▶ $\mu_Y(y \mid \bar{x}_K, \bar{a}_K)$ is the conditional density of Y given the histories $\bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K$.

¹Statistical model \mathcal{M} for P_0 contains all possible distributions P for the observed data O .

Identification formulas

Factorization of density allows us to write the expectation under P in terms of iterated integrals (Fubini's theorem):

$$\begin{aligned}\mathbb{E}_P[Y] &= \int_{\mathcal{O}} yp(o) d\nu(o) \\ &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \sum_{a_K=0,1} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K) \\ &\quad \pi_K(a_K \mid \bar{x}_K, \bar{a}_K) \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}) d\nu_{X_K}(x_K) \\ &\quad \cdots \pi_0(a_0 \mid x_0) \mu_{X_0}(x_0) d\nu_{X_0}(x_0),\end{aligned}$$

for $P \in \mathcal{M}$.

Identification formulas

We want to identify the treatment-specific mean outcome:

$$\mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}]$$

in terms of the observed data distribution,

using the assumptions of [consistency](#), [exchangeability](#) and [positivity](#):

$$Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*} = Y \quad \text{if } A_k = a_k^* \text{ for } k = 0, 1, \dots, K$$

$$Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*} \perp\!\!\!\perp A_k \mid \bar{X}_k, \bar{A}_{k-1}, \quad \text{for } k = 0, 1, \dots, K$$

$$\prod_{k=0}^K \frac{1\{A_k = a_k^*\}}{P(A_k = a_k^* \mid \bar{X}_k, \bar{A}_{k-1})} < \infty, \quad \text{for } k = 0, 1, \dots, K$$

Identification: g-formula

The claim is that:

$$\begin{aligned} \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\ = \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\ \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \cdots \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \end{aligned}$$

Identification: g-formula

To show the claim from the previous slide, **start from the right hand side**:

1. By consistency, replace Y by $Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}$ in the innermost integral:

$$\begin{aligned} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) &= \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K^*] \\ &= \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*} \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K^*] \end{aligned} \quad (1)$$

2. Drop the last conditioning variable $A_K = a_K^*$ from the conditioning set by exchangeability, and then integrate out over L_K :

$$\begin{aligned} \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \\ = \int_{\mathbb{R}^d} \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*} \mid \bar{X}_K = \bar{x}_K, \bar{A}_{K-1}^* = \bar{a}_{K-1}^*] \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \\ = \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*} \mid \bar{X}_{K-1} = \bar{x}_{K-1}, \bar{A}_{K-1}^* = \bar{a}_{K-1}^*] \end{aligned} \quad (2)$$

3. Note that (2) is the same expression as (1), with K replaced by $K - 1$.
4. Repeat 2. another $K - 1$ times which in the end **gives the left hand side** from the previous slide.

Identification: IP-weighting

We have that:

$$\begin{aligned} & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\ &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\ & \quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \cdots \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \end{aligned}$$

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Identification: g-formula & iterated expectations

The g-formula:

$$\begin{aligned} \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\ = \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\ \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \cdots \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \end{aligned}$$

can also be written as a sequence of iterated conditional expectations.

Identification: g-formula & iterated expectations

$$\begin{aligned} & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\ &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\ & \quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \cdots \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \end{aligned}$$

Identification: g-formula & iterated expectations

$$\begin{aligned}
 & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\
 &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\
 &\quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \cdots \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \\
 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \sum_{a_K=0,1} \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K^*] \\
 &\quad 1\{a_K = a_K^*\} \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \\
 &\quad \cdots 1\{a_0 = a_0^*\} \mu_{X_0}(x_0) d\nu_{X_0}(x_0)
 \end{aligned}$$

Identification: g-formula & iterated expectations

$$\begin{aligned}
 & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\
 &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\
 &\quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \cdots \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \\
 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \sum_{a_K=0,1} \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K] \\
 &\quad 1\{a_K = a_K^*\} \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \\
 &\quad \cdots 1\{a_0 = a_0^*\} \mu_{X_0}(x_0) d\nu_{X_0}(x_0)
 \end{aligned}$$

Identification: g-formula & iterated expectations

$$\begin{aligned}
 & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\
 &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\
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 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \sum_{a_K=0,1} \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K] \\
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 & \quad \cdots 1\{a_0 = a_0^*\} \mu_{X_0}(x_0) d\nu_{X_0}(x_0)
 \end{aligned}$$

Define:

$$\bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K) = \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K]$$

Identification: g-formula & iterated expectations

$$\begin{aligned}
 & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\
 &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\
 &\quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \cdots \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \\
 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \sum_{a_K=0,1} \bar{Q}_{K+1}(\bar{x}_K, a_K^*, \bar{a}_{K-1}) \\
 &\quad 1\{a_K = a_K^*\} \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}) d\nu_{X_K}(x_K) \\
 &\quad \cdots 1\{a_0 = a_0^*\} \mu_{X_0}(x_0) d\nu_{X_0}(x_0)
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Identification: g-formula & iterated expectations

$$\begin{aligned}
 & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\
 &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\
 &\quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \cdots \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \\
 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \bar{Q}_{K+1}(\bar{x}_K, a_K^*, \bar{a}_{K-1}) \\
 &\quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}) d\nu_{X_K}(x_K) \\
 &\quad \cdots 1\{a_0 = a_0^*\} \mu_{X_0}(x_0) d\nu_{X_0}(x_0)
 \end{aligned}$$

Define:

$$\bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K) = \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K]$$

Identification: g-formula & iterated expectations

$$\begin{aligned}
 & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\
 &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\
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 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \bar{Q}_{K+1}(\bar{x}_K, a_K^*, \bar{a}_{K-1}) \\
 &\quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}) d\nu_{X_K}(x_K) \\
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 \end{aligned}$$

Define:

$$\begin{aligned}
 \bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K) &= \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K] \\
 \bar{Q}_K(\bar{x}_{K-1}, \bar{a}_{K-1}) &= \mathbb{E}_P[\bar{Q}_{K+1}(\bar{x}_K, a_K^*, \bar{a}_{K-1}) \mid \bar{X}_{K-1} = \bar{x}_{K-1}, \bar{A}_{K-1} = \bar{a}_{K-1}]
 \end{aligned}$$

Identification: g-formula & iterated expectations

$$\begin{aligned}
 & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\
 &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\
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 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \bar{Q}_{K+1}(\bar{x}_K, a_K^*, \bar{a}_{K-1}) \\
 &\quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}) d\nu_{X_K}(x_K) \\
 &\quad \cdots 1\{a_0 = a_0^*\} \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \\
 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \sum_{a_{K-1}=0,1} \bar{Q}_K(\bar{x}_{K-1}, \bar{a}_{K-1}) \\
 &\quad 1\{a_{K-1} = a_{K-1}^*\} \mu_{X_{K-1}}(x_{K-1} \mid \bar{x}_{K-2}, \bar{a}_{K-2}) d\nu_{X_{K-1}}(x_{K-1}) \\
 &\quad \cdots 1\{a_0 = a_0^*\} \mu_{X_0}(x_0) d\nu_{X_0}(x_0)
 \end{aligned}$$

Define:

$$\bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K) = \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K]$$

$$\bar{Q}_K(\bar{x}_{K-1}, \bar{a}_{K-1}) = \mathbb{E}_P[\bar{Q}_{K+1}(\bar{x}_K, a_K^*, \bar{a}_{K-1}) \mid \bar{X}_{K-1} = \bar{x}_{K-1}, \bar{A}_{K-1} = \bar{a}_{K-1}]$$

Identification: g-formula & iterated expectations

$$\begin{aligned}
 & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\
 &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\
 &\quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \cdots \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \\
 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \bar{Q}_{K+1}(\bar{x}_K, a_K^*, \bar{a}_{K-1}) \\
 &\quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}) d\nu_{X_K}(x_K) \\
 &\quad \cdots 1\{a_0 = a_0^*\} \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \\
 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \bar{Q}_K(\bar{x}_{K-1}, a_{K-1}^*, \bar{a}_{K-2}) \\
 &\quad \mu_{X_{K-1}}(x_{K-1} \mid \bar{x}_{K-2}, \bar{a}_{K-2}) d\nu_{X_{K-1}}(x_{K-1}) \\
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 \end{aligned}$$

Define:

$$\begin{aligned}
 \bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K) &= \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K] \\
 \bar{Q}_K(\bar{x}_{K-1}, \bar{a}_{K-1}) &= \mathbb{E}_P[\bar{Q}_{K+1}(\bar{x}_K, a_K^*, \bar{a}_{K-1}) \mid \bar{X}_{K-1} = \bar{x}_{K-1}, \bar{A}_{K-1} = \bar{a}_{K-1}]
 \end{aligned}$$

Identification: g-formula & iterated expectations

$$\begin{aligned}
 & \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] \\
 &= \int_{\mathbb{R}^d} \cdots \int_{\mathbb{R}^d} \sum_{y=0,1} y \mu_Y(y \mid \bar{x}_K, \bar{a}_K^*) \\
 &\quad \mu_{X_K}(x_K \mid \bar{x}_{K-1}, \bar{a}_{K-1}^*) d\nu_{X_K}(x_K) \cdots \mu_{X_0}(x_0) d\nu_{X_0}(x_0) \\
 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \bar{Q}_{K+1}(\bar{x}_K, a_K^*, \bar{a}_{K-1}) \\
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 &= \int_{\mathbb{R}^d} \sum_{a_0=0,1} \cdots \int_{\mathbb{R}^d} \bar{Q}_K(\bar{x}_{K-1}, a_{K-1}^*, \bar{a}_{K-2}) \\
 &\quad \mu_{X_{K-1}}(x_{K-1} \mid \bar{x}_{K-2}, \bar{a}_{K-2}) d\nu_{X_{K-1}}(x_{K-1}) \\
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 \end{aligned}$$

Define:

$$\begin{aligned}
 \bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K) &= \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K] \\
 \bar{Q}_K(\bar{x}_{K-1}, \bar{a}_{K-1}) &= \mathbb{E}_P[\bar{Q}_{K+1}(\bar{x}_K, a_K^*, \bar{a}_{K-1}) \mid \bar{X}_{K-1} = \bar{x}_{K-1}, \bar{A}_{K-1} = \bar{a}_{K-1}]
 \end{aligned}$$

Identification: g-formula & iterated expectations

Full steps that represent $\mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}]$ as a sequence of iterated conditional expectations:

$$\bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K) = \mathbb{E}_P[Y \mid \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K]$$

$$\bar{Q}_K(\bar{x}_{K-1}, \bar{a}_{K-1}) = \mathbb{E}_P[\bar{Q}_{K+1}(\bar{X}_K, a_K^*, \bar{A}_{K-1}) \mid \bar{X}_{K-1} = \bar{x}_{K-1}, \bar{A}_{K-1} = \bar{a}_{K-1}]$$

$$\vdots$$

$$\bar{Q}_k(\bar{x}_{k-1}, \bar{a}_{k-1}) = \mathbb{E}_P[\bar{Q}_{k+1}(\bar{X}_k, a_k^*, \bar{A}_{k-1}) \mid \bar{X}_{k-1} = \bar{x}_{k-1}, \bar{A}_{k-1} = \bar{a}_{k-1}]$$

$$\vdots$$

$$\bar{Q}_2(\bar{x}_1, \bar{a}_1) = \mathbb{E}_P[\bar{Q}_3(\bar{X}_2, a_2^*, \bar{A}_1) \mid \bar{X}_1 = \bar{x}_1, \bar{A}_1 = \bar{a}_1]$$

$$\bar{Q}_1(x_0, a_0) = \mathbb{E}_P[\bar{Q}_2(\bar{X}_1, a_1^*, A_0) \mid X_0 = x_0, A_0 = a_0]$$

$$\mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] = \mathbb{E}_P[\bar{Q}_1(x_0, a_0^*)].$$

Identification (summary)

1. IP-weighting:

$$\Psi(P) = \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] = \mathbb{E}_P\left[\frac{\prod_{k=0}^K 1\{A_k = a_k^*\}}{\prod_{k=0}^K \pi_{A_k}(a_k^* | \bar{X}_k, \bar{A}_{k-1})} Y\right]$$

2. Sequence of iterated conditional expectations:

$$\bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K) = \mathbb{E}_P[Y | \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K]$$

and iteratively for $k = K, K-1, \dots, 1$,

$$\bar{Q}_k(\bar{x}_{k-1}, \bar{a}_{k-1}) = \mathbb{E}_P[\bar{Q}_{k+1}(\bar{X}_k, a_k^*, \bar{A}_{k-1}) | \bar{X}_{k-1} = \bar{x}_{k-1}, \bar{A}_{k-1} = \bar{a}_{k-1}]$$

so that

$$\Psi(P) = \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] = \mathbb{E}_P[\bar{Q}_1(X_0, a_0^*)].$$

Identification (summary)

1. IP-weighting:

$$\psi(P) = \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] = \mathbb{E}_P\left[\frac{\prod_{k=0}^K 1\{A_k = a_k^*\}}{\prod_{k=0}^K \pi_{A_k}(a_k^* | \bar{X}_k, \bar{A}_{k-1})} Y\right]$$

2. Sequence of iterated conditional expectations:

$$\bar{Q}_{K+1}(\bar{x}_K, \bar{a}_K) = \mathbb{E}_P[Y | \bar{X}_K = \bar{x}_K, \bar{A}_K = \bar{a}_K]$$

and iteratively for $k = K, K-1, \dots, 1$,

$$\bar{Q}_k(\bar{x}_{k-1}, \bar{a}_{k-1}) = \mathbb{E}_P[\bar{Q}_{k+1}(\bar{X}_k, a_k^*, \bar{A}_{k-1}) | \bar{X}_{k-1} = \bar{x}_{k-1}, \bar{A}_{k-1} = \bar{a}_{k-1}]$$

so that

$$\psi(P) = \mathbb{E}_P[Y^{A_0=a_0^*, A_1=a_1^*, \dots, A_K=a_K^*}] = \mathbb{E}_P[\bar{Q}_1(X_0, a_0^*)].$$

SMALL EXERCISE:

For $K = 1$, write up the steps to identify the target parameter in terms of 1. IP-weighting, and 2. iterated conditional expectations.

Identification in R via iterated expectations for the simulated example

```
set.seed(15)
(sim.data <- sim.fun(2000))
```

	X0.1	X0.2	X0.3	A0	X1.1	X1.2	A1	Y
1:	0.40845618	-0.19620228	0	1	1	0	0	1
2:	-1.21982429	0.59503302	1	1	0	0	1	0
3:	1.86583493	-1.60888231	0	1	0	0	0	0
4:	0.60362212	0.04123507	0	1	0	0	1	0
5:	-0.53171243	-1.25139144	0	0	0	1	0	0

1996:	-0.72294993	-0.43541869	0	1	0	0	0	1
1997:	-0.13592934	-0.80204340	0	0	0	0	0	0
1998:	-1.67193359	-1.57095686	0	0	0	1	0	0
1999:	0.68115948	-0.72905589	0	1	0	0	1	0
2000:	0.04187752	0.10649384	0	0	0	0	0	1

Identification in R via iterated expectations for the simulated example

```
fit.Q2 <- glm(Y ~ A1 + X1.1 + X1.2 + A0 + X0.1 + X0.2 + X0.3,  
             family=binomial, data=sim.data)  
sim.data[, pred.Q2:=predict(fit.Q2, newdata=copy(sim.data)[,  
          A1:=1], type="response")]
```

Identification in R via iterated expectations for the simulated example

```
fit.Q2 <- glm(Y ~ A1 + X1.1 + X1.2 + A0 + X0.1 + X0.2 + X0.3,  
             family=binomial, data=sim.data)  
sim.data[, pred.Q2:=predict(fit.Q2, newdata=copy(sim.data)[,  
             A1:=1], type="response")]
```

```
fit.Q1 <- glm(pred.Q2 ~ A0 + X0.1 + X0.2 + X0.3,  
             family=quasibinomial, data=sim.data)  
sim.data[, pred.Q1:=predict(fit.Q1, newdata=copy(sim.data)[,  
             A0:=1], type="response")]
```


Identification in R via iterated expectations for the simulated example

```
fit.Q2 <- glm(Y ~ A1 + X1.1 + X1.2 + A0 + X0.1 + X0.2 + X0.3,  
             family=binomial, data=sim.data)  
sim.data[, pred.Q2:=predict(fit.Q2, newdata=copy(sim.data)[,  
             A1:=1], type="response")]
```

```
fit.Q1 <- glm(pred.Q2 ~ A0 + X0.1 + X0.2 + X0.3,  
             family=quasibinomial, data=sim.data)  
sim.data[, pred.Q1:=predict(fit.Q1, newdata=copy(sim.data)[,  
             A0:=1], type="response")]
```

```
(est1.g.formula <- sim.data[, mean(pred.Q1)])
```

```
[1] 0.228188
```

Identification in R via iterated expectations for the simulated example

```
fit.Q2 <- glm(Y ~ A1 + X1.1 + X1.2 + A0 + X0.1 + X0.2 + X0.3,  
             family=binomial, data=sim.data)  
sim.data[, pred.Q2:=predict(fit.Q2, newdata=copy(sim.data)[,  
            A1:=0], type="response")]
```

Identification in R via iterated expectations for the simulated example

```
fit.Q2 <- glm(Y ~ A1 + X1.1 + X1.2 + A0 + X0.1 + X0.2 + X0.3,  
             family=binomial, data=sim.data)  
sim.data[, pred.Q2:=predict(fit.Q2, newdata=copy(sim.data)[,  
             A1:=0], type="response")]
```

```
fit.Q1 <- glm(pred.Q2 ~ A0 + X0.1 + X0.2 + X0.3,  
             family=quasibinomial, data=sim.data)  
sim.data[, pred.Q1:=predict(fit.Q1, newdata=copy(sim.data)[,  
             A0:=0], type="response")]
```

Identification in R via iterated expectations for the simulated example

```
fit.Q2 <- glm(Y ~ A1 + X1.1 + X1.2 + A0 + X0.1 + X0.2 + X0.3,  
             family=binomial, data=sim.data)  
sim.data[, pred.Q2:=predict(fit.Q2, newdata=copy(sim.data)[,  
             A1:=0], type="response")]
```

```
fit.Q1 <- glm(pred.Q2 ~ A0 + X0.1 + X0.2 + X0.3,  
             family=quasibinomial, data=sim.data)  
sim.data[, pred.Q1:=predict(fit.Q1, newdata=copy(sim.data)[,  
             A0:=0], type="response")]
```

```
(est0.g.formula <- sim.data[, mean(pred.Q1)])
```

```
[1] 0.371784
```

Practical 1: Kreif et al. (2017) as an example

In this practical we discuss the study by Kreif et al. as an example:

- ▶ Data structure, static and dynamic intervention, time-dependent treatment interventions.
- ▶ IP-weighting, g-formula, TMLE.

Questions for the paper that you should go over can be found in: **day3_practical1.pdf**.