Time-dependent mediators in survival analysis: Modeling direct and indirect effects with the additive hazards model

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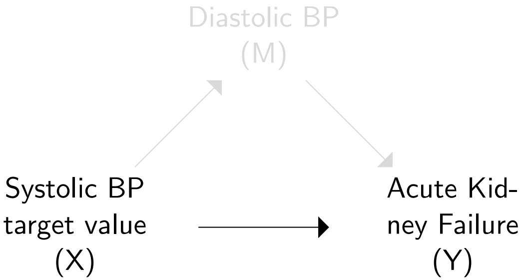
WBS Joint Seminar,
November 29, 2018

Outline

Example from the SPRINT trial

SPRINT = **S**ystolic Blood **P**ressure **In**tervention **T**rial



- **Does** the intervention have side effects?
- **How** do they come about?

  Is there a component of the intervention we can improve to avoid the side effect

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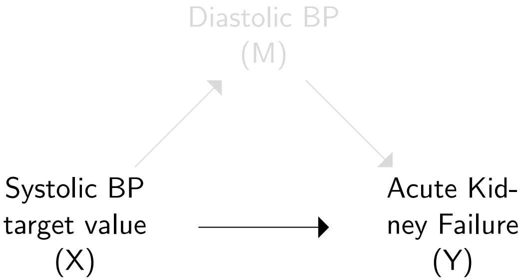

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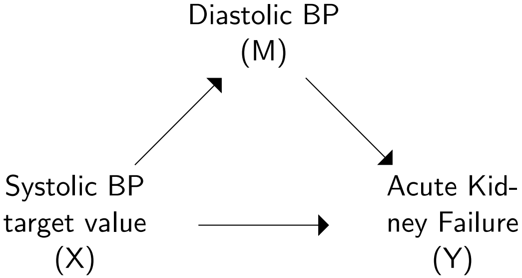

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Particular data structure

- Randomised exposure
- **Time-to-event** outcome
- **Repeated measurements** of the postulated **mediator**
- Large set of (at least) baseline covariates
- Sample size > 9000

Traditional Methods

- Method of **path coefficients**
  - in 'Correlation and causation' **[Wright (1921)]**
  - refinement and further comments in 'The method of path coefficients' **[Wright (1934)]**
- **Distinction between effect-modifier and mediator**
  - in 'The moderator-mediator variable distinction in social psychological research: Conceptual, strategic and statistical consideration' **[Baron and Kenny (1986), almost 60 000 citations]**
    - focus on continuous mediators and outcomes
    - required conditions for mediation (later debated in literature)

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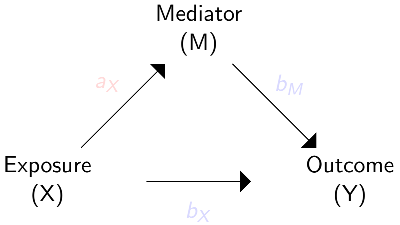
Product method .... 'Baron and Kenny' method

Consider a structure with exposure X, **continuous mediator** M and **continuous outcome** Y



1. $Y = b_0 + b_X X + b_M M + \varepsilon_Y$
2. $M = a_0 + a_X X + \varepsilon_M$

- **Interpretation:**
  - direct effect: :b_x
  - indirect effect: $a_x b_m$ **Path tracing rule**

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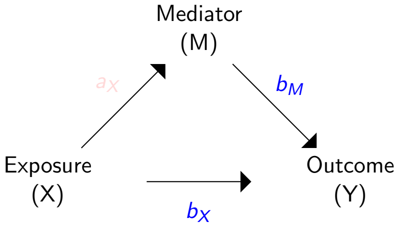

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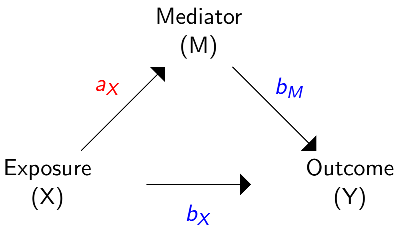

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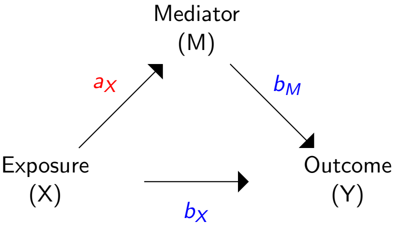

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Limitations of classical methods...

- The **product method** and alternative traditional methods **only coincide** in the simple case **with a continuous mediator and outcome without interactions** (MacKinnon and Dwyer (1993))
  - Can any of them have a causal interpretation?
- Little attention to the importance of **control for confounding**
  - Randomisation does not resolve all issues when it comes to mediation analysis
  - Participants can not be randomised to a certain mediator value
- **Informal definition** of direct and indirect effects:
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- **Randomised controlled trial setting:** Compare the effect of two treatment regimes $X = \{x, x^*\}$ on an outcome Y

$$X \longrightarrow Y$$

- **Ideally:** Compare **potential outcomes** Y_{ix^*} and Y_{ix} for every individual i to estimate the individual causal effect $\theta_i = Y_{ix} - Y_{ix^*}$
- **However**, it is impossible to observe the individual counterfactual
- Instead we can estimate the **average causal effect**:

$$E[\theta] = E[Y_x] - E[Y_{x^*}]$$

- Assumptions
  - Stable unit treatment values assumption
  - Strong Ignorable treatment assumption

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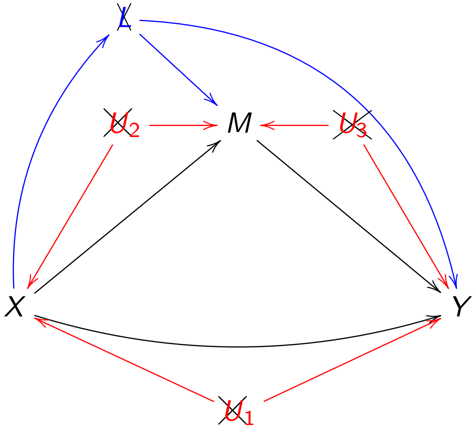
The mediation formula (Pearl, 2001)

- **Nested counterfactual:**
  $Y_{xM_{x^*}}$ denote the composite potential outcome that would have been observed, if X had been set to x, while simultaneously M had been set to the value it would have taken if X had been set to x^*.
- **Effect decomposition**

$$\begin{aligned} TE(Y) &= E[Y_{xM_x}] - E[Y_{x^*M_{x^*}}] \\ &= E[Y_{xM_{x^*}}] - E[Y_{x^*M_{x^*}}] + E[Y_{xM_x}] - E[Y_{xM_{x^*}}] \end{aligned}$$

- Essentially applicable to **'any' type** of mediator and outcome distribution (with additional restricting assumptions for survival outcomes)

Assumptions for identification



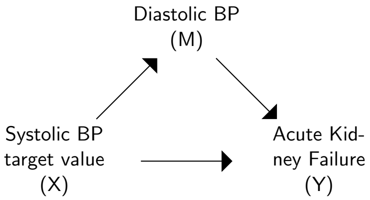
No unmeasured confounding

$$Y_{xm} \perp\!\!\!\perp X|C \quad (1)$$
$$Y_{xm} \perp\!\!\!\perp M|(X, C) \quad (2)$$
$$M_x \perp\!\!\!\perp X|C. \quad (3)$$

'Cross-world assumption'

$$Y_{xm} \perp\!\!\!\perp M_{x^*}|C \quad (4)$$

Back to the practical problem



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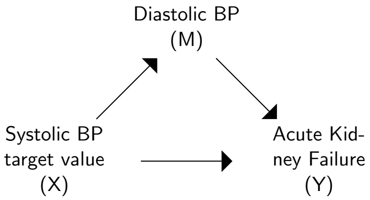

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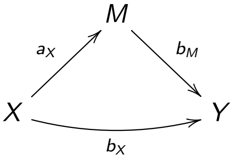
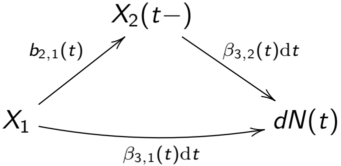
Dynamic path analysis (Fosen et al, 2006)

Traditional path analysis:
Variables measured once



Dynamic path analysis:
Series of time local DAGs



In **both situations** assume:

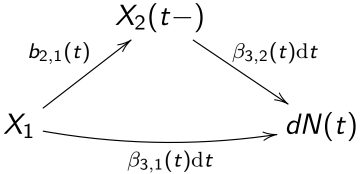
- no unmeasured confounding
- no treatment-mediator interactions

Additionally:

- take time aspect into account
- gain direct and indirect effects as functions of time

Dynamic path analysis - more formal

- **Series of time local DAGs** (directed acyclic graphs) - one defined for each jump in a counting process



- Corresponding **structural equations**

$$
\begin{aligned}
X_1 &= b_{1,0} + W_1 \\
X_2(t) &= b_{2,0}(t) + b_{2,1}(t)X_1 + W_2(t) \\
\lambda(t) &= Y(t)(\beta_{3,0}(t) + \beta_{3,1}(t)X_1 + \beta_{3,2}(s)X_2(t-))
\end{aligned}
$$

where W_1 and $W_2(t)$ are independent at all times t.

Dynamic path analysis - more formal

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$$\begin{tikzcd}
& X_2(t-) \arrow[dr, "\beta_{3,2}(t)\mathrm{d}t"] & \\
X_1 \arrow[ur, "b_{2,1}(t)"] \arrow[rr, bend right, "\beta_{3,1}(t)\mathrm{d}t"'] & & dN(t)
\end{tikzcd}$$

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Quantities of interest

Cumulative path effects
substituting the equation for $X_2(t)$ suggests the following cumulative path effects according to Fosen et al. (2006)

Cumulative **direct** effect

$$X_1 \to N \quad : \quad \int_0^t \beta_{3,1}(s)\mathrm{d}s$$

Cumulative **indirect** effect :

$$X_1 \to X_2 \to N \quad : \quad \int_0^t b_{2,1}(s)\beta_{3,2}(s)\mathrm{d}s,$$

Results from the Systolic Blood Pressure Intervention Trial

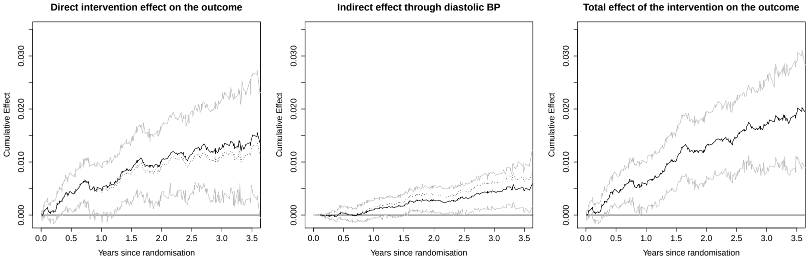
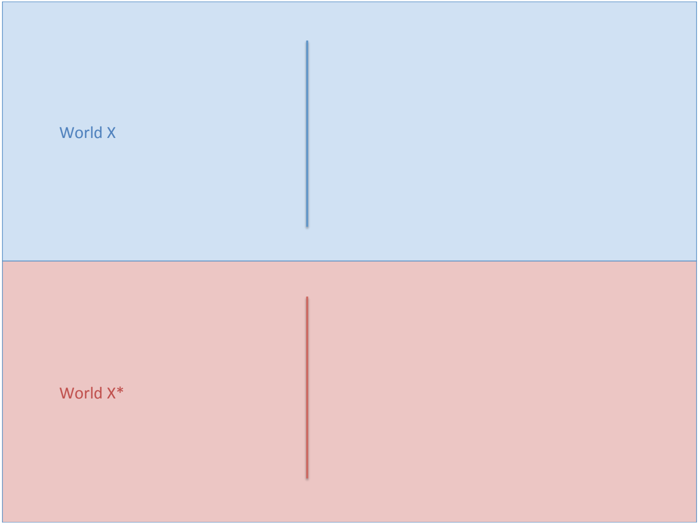


Figure: From Aalen et al, forthcoming

Is it causal?



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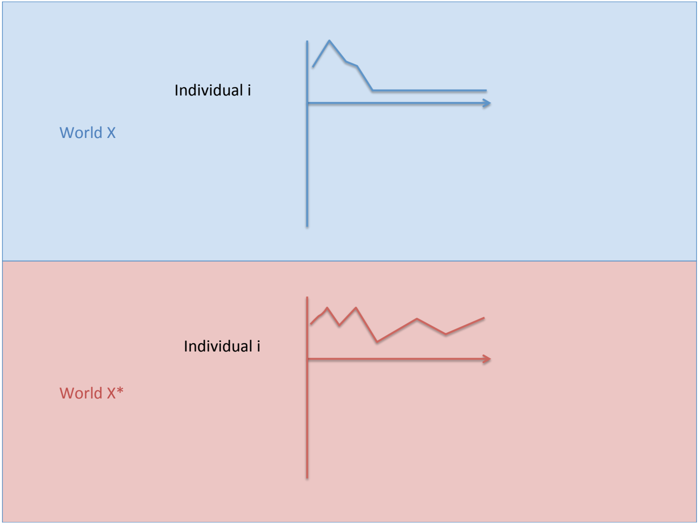

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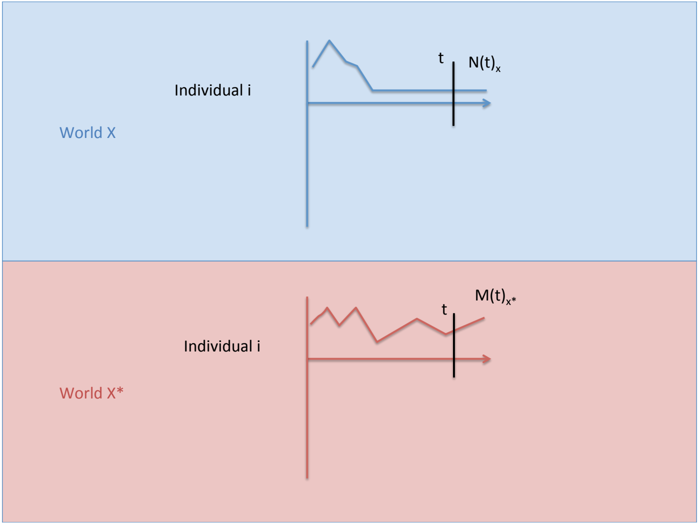

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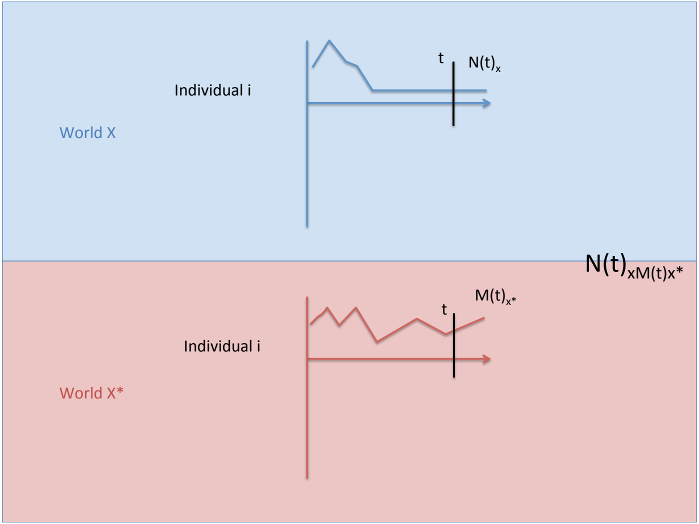

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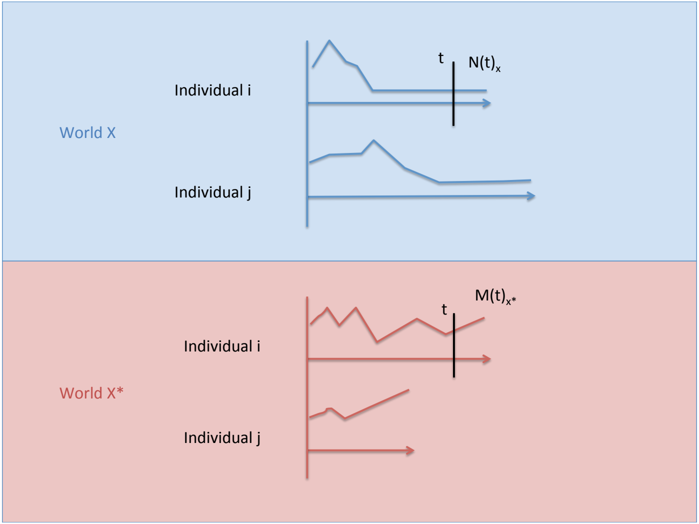
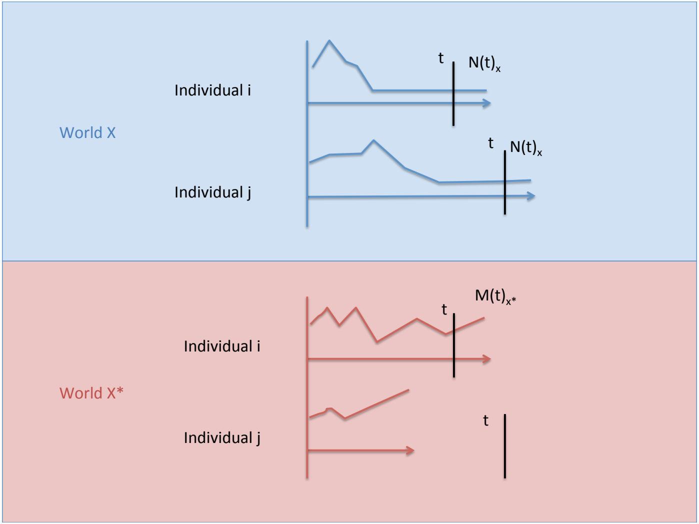

World X
Individual i
t
N(t)x
Individual j
World X*
Individual i
t
M(t)x*
Individual j

Is it causal?



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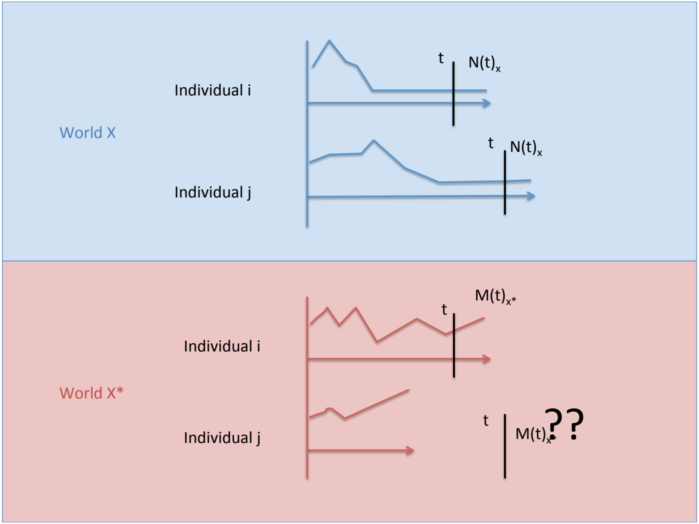

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??

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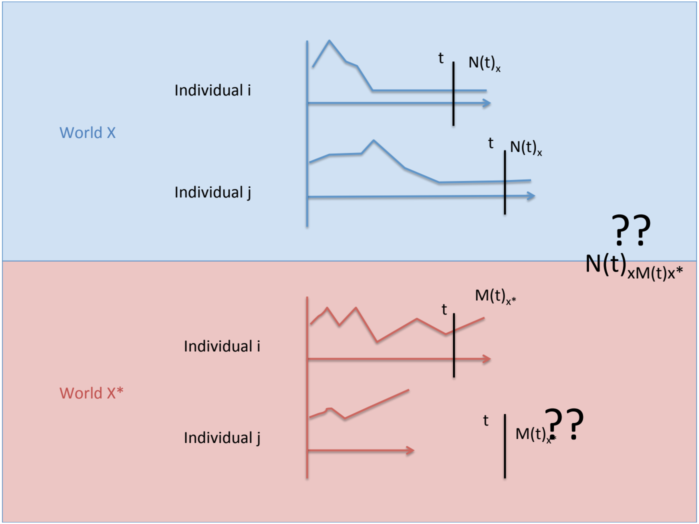
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World X*
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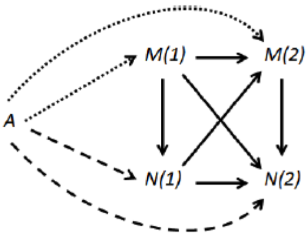
A possible remedy

Explicitly formalise the idea of different components of a treatment



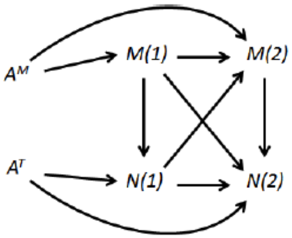


Figure: From Didelez (2018)

Keeping promises

Didelez (2018)

- Treatment separation approach
- Mediational G-formula

VanderWeele (2015)

- Overview on mediation

Fosen et al (2006)

- Dynamic path analysis (DPA)

Strohmaier et al. (2015)

- First causal interpretation for DPA

Aalen et al. (2019)

- Treatment separation approach
- Mediational G-formula
- DPA

Lin et al (2017)

Zheng and van der Laan (2017)

Concluding remarks and future challenges

- **Observational parts** of clinical trials can be utilized in a **useful** manner
- **Mediation is a process** that works in time and that should be taken into account
- **Treatment separation approach** seems more **fruitful**, if biologically plausible
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Key references

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