Mediation analysis when the mediator is truncated by death

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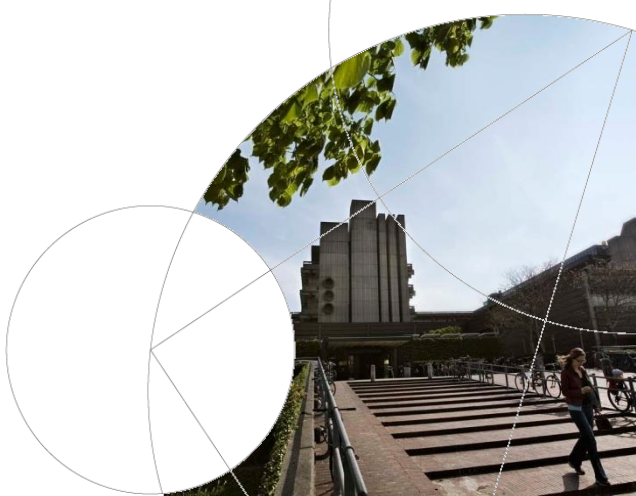


The original problem

- Intravenous fluids are the mainstay of treatment for patients with hypovolemia due to severe sepsis to obtain fast circulatory stabilisation.

- Commonly applied interventions:
  - Crystalloids including saline and dextrose (Ringer's solution)
  - Colloids containing larger molecules such as starch or gelatine.

- Preferred choice in Scandinavian intensive care units (ICU)
  - Hydtroxyethyl starch (HES) 130/0.42

- However: HES 130/0.42 is largely unstudied in patients with severe sepsis

The 6S trial

The 6S trial – details and results

Study population:

- Patients with severe sepsis admitted to an intensive care unit (ICU) who needed fluid for circulatory stabilization

Randomization to:

- Hydroxyethyl starch (HES 130/0.42)
- Ringer's solution

Primary outcome:

- Death or end-stage kidney failure at 90 days after randomization

Results reported in NEJM: (Perner et al. (2012))

- At 90 days after randomization, 201 of 398 assigned to HES had died as compared with 172 of 400 patients assigned to Ringer's acetate. (RR 1.17; 95% confidence interval, 1.01 to 1.36: p=0.03)

Next step after the 6S trial

The simple:

Stop using HES.

The curious:

Try to understand why HES increases mortality.

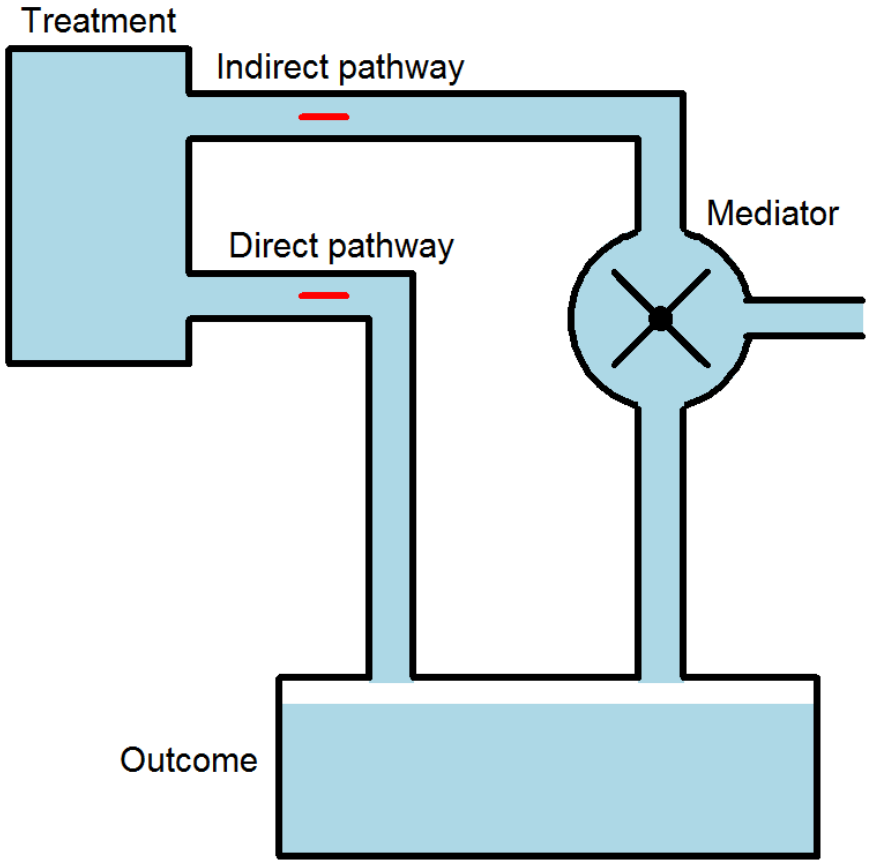
Likely mechanisms linking HES to increased mortality are:

1. Starch is a foreign body, which overtime causes kidney damager leading to kidney related death (this will be the pathway we look at in this talk).
2. Coagulapathy (bleeding disorder).
3. Patients generally have a low immune response, additionally adding foreign bodies could cause there immune system to crash.

Mediation analysis allows you to take the curious approach.

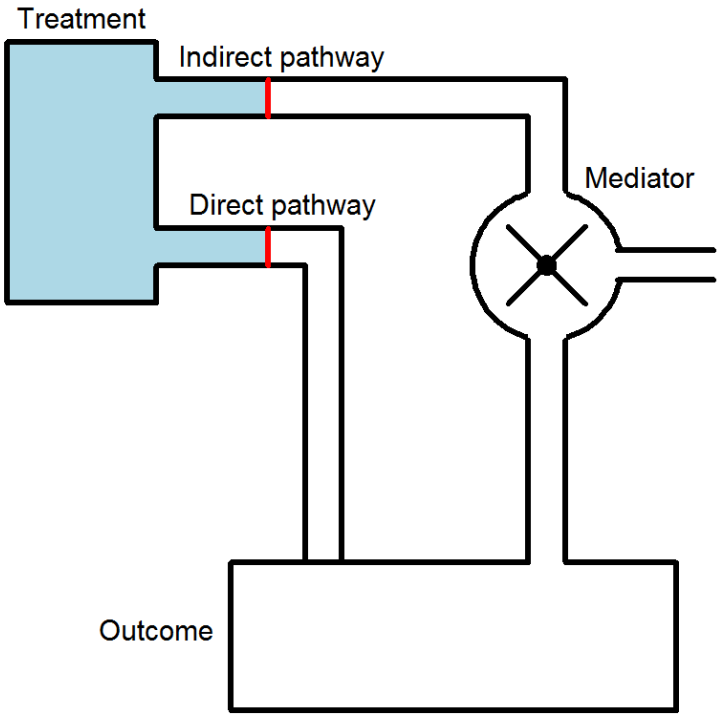
Understanding mediation analysis as systems

The effect of treatment can be thought of as flowing through different channels/body-systems to the outcome.

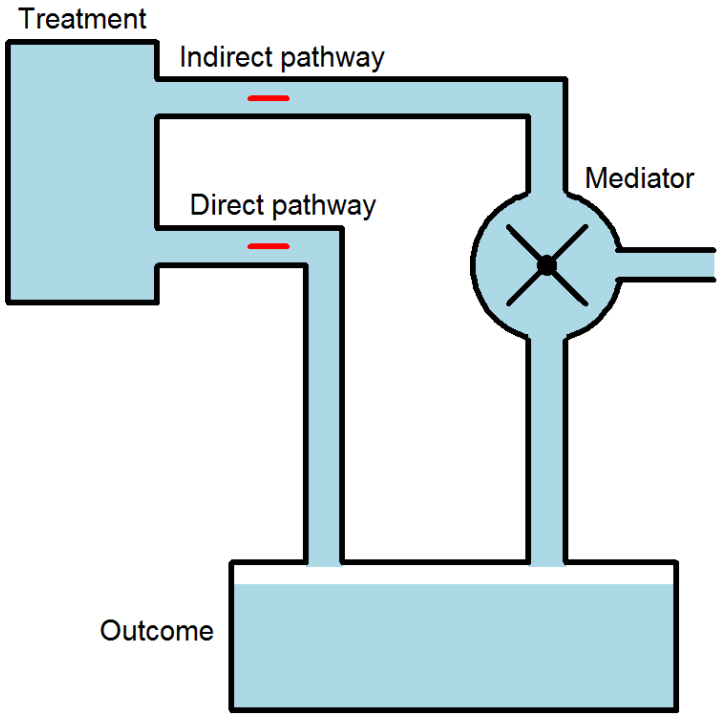


Understanding mediation analysis

The RCT can be visualized as the contrast



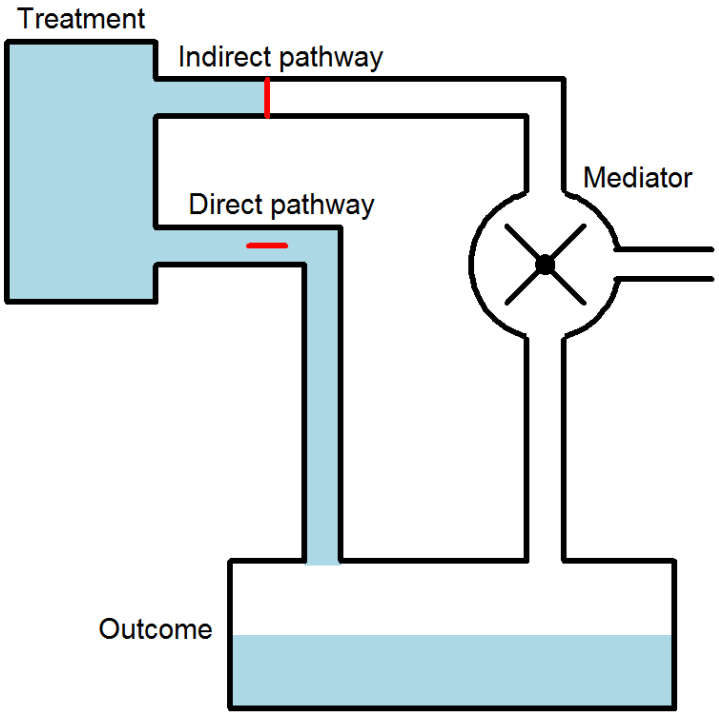
Y_{00}
(placebo)



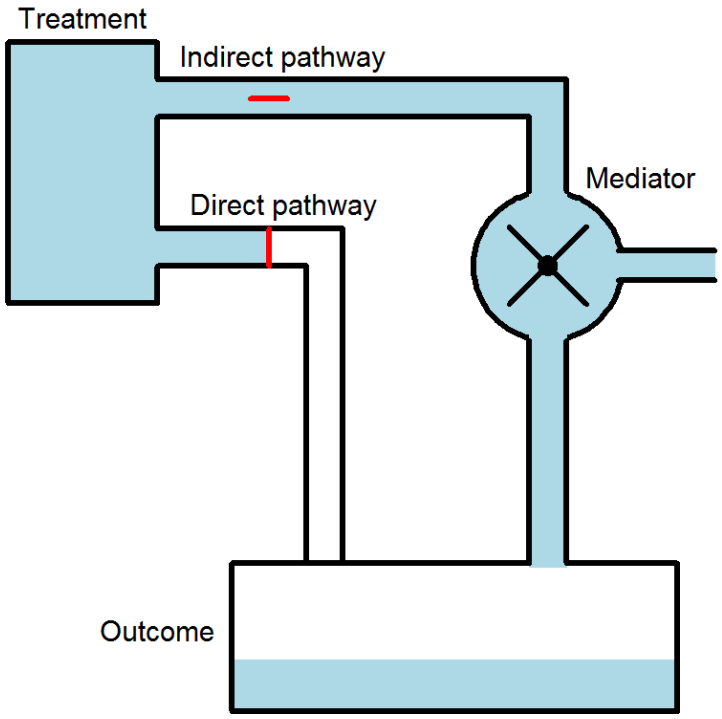
Y_{11}
(active treatment)

Understanding mediation analysis

As a thought experiment: What would happen in only one pathway was active?



Y_{10}
(direct effect)



Y_{01}
(indirect effect)

Understanding mediation analysis

- The the different pathways are quantified by comparing Y_{00} with Y_{01} etc.
- The comparison can be done on any scale (odds ratio, linear regression whatever).
- Natural indirect effect is Y_{00} vs. Y_{01}. Ie. the effect if only the pathway involving the mediator was activated.
- Natural direct effect is Y_{01} vs. Y_{11}. Ie. the effect if only the pathway **not** involving the mediator was activated.
- Total effect is Y_{00} vs. Y_{11} (which is what the RCT estimates).
- The variables Y_{01} etc. are called *nested counterfactuals*.

The traditional interpretation of nested counterfactuals

- Y_{01} is the outcome observed if treatment had been set to 0 and the mediator to the value it would naturally take is the mediator had been set to 1.

- The *natural indirect effect* is then the change in outcome that would be observed if we could change the mediator as much as it would naturally change when exposure was changed without actually changing the exposure.

- Let us call this the intervention-interpretation.

- The systems-interpretation presented on the previous slides results in the same number, but I find the system-interpretation easier.

- More complicated if different mediators for different patients (6S).

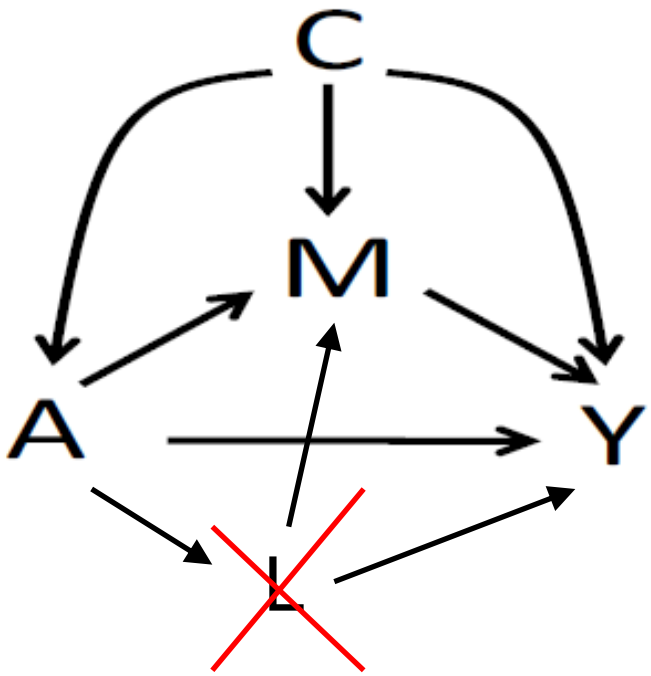
Challenges in mediation analysis

- We never observe patients where only one of the pathways have been activated.
- Either none have (placebo) or both have (active treatment).
- Even in RCTs we do not randomize the mediator, accordingly we need to worry about confounding.
- The solution is assumptions.

Assumptions for natural direct and indirect effects

1: No unmeasured confounders of:

- The exposure-outcome relation
- The exposure-mediator relation
- The mediation-outcome relation



2: No intertwined causal pathways.
(aka. Pearls identifiability condition)

3: Consistency and positivity.
(mostly technical)

REF: Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology*. 1992;3(2): 143–155.

Natural effect models with software solution

- Natural effect models propos (introduced by Vansteelandt and Lange) to use a regression model for the natural effects:

$$g(\mathrm{E}[Y_{ab}|C=c]) = \beta_0 + \beta_1 * a + \beta_2 * b + \beta_3 * c$$

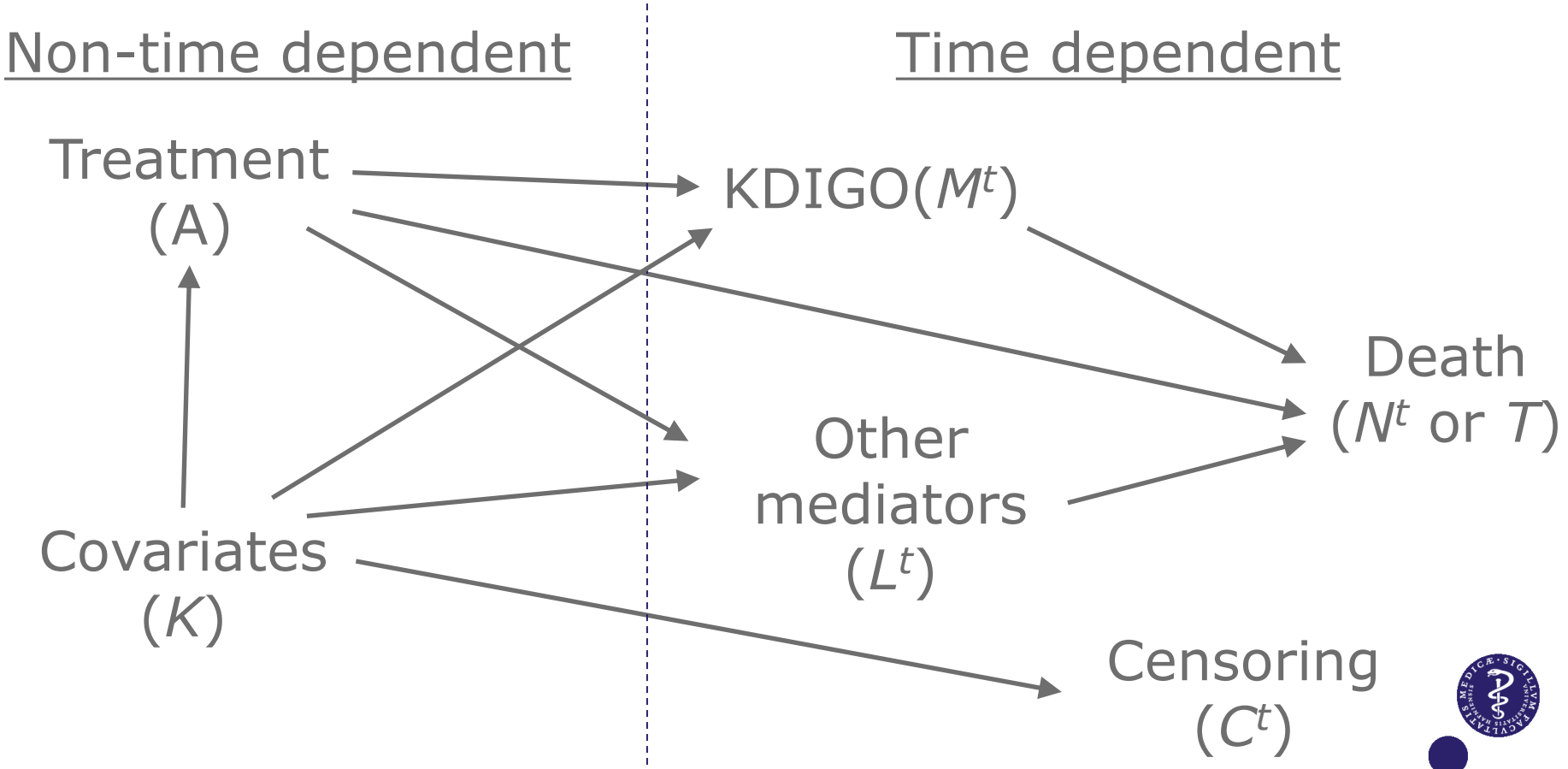
- Coefficients (β_1 and β_2) will be the natural direct and indirect effects, respectively.
- Similar formulations (Cox etc.) for survival outcome.
- Mediator(s) can be of any type and dimensionality.
- The R package medflex can estimate such models in 3 lines of R code.
- More in Liis' talk.

Special problems with 6S data

- In the 6S data the mediator is kidney impairment quantified by the daily KDIGO score.
- The KDIGO score was recorded daily as long as patients were admitted to the ICU.
- If a patient dies the KDIGO score on the following days is not only unknown, but undefined.
- This has the implication that the intervention-interpretation of mediation cannot be employed.
- We risk to "run out of KDIGO scores".
- However, the systems-interpretation is still meaningful.

Local independence graph including death

A local independence graph depicts causal relations among potentially time varying processes.



Goal of the analysis

- To quantify the effect of HES passing through the kidney as described by the KDIGO).
- As outcome is death the effect should be expressed as a hazard ratio.
- To address if the kidney impairment pathways is the most important pathway.
- Solution: estimate a natural effect Cox model for T_{ab} conditional on values of baseline confounders (K).

Assumed model for data generating process

- Assume daily data is sufficient to express the dynamics.

- Then the local independence graph can be expressed using non-parametric structural equations as

$$
\begin{aligned}
C^t &= f_C^t(\overline{C}^{t-1}, K = k, \zeta) \\
M_{a^*}^t &= f_L^t(\overline{M}_a^{t-1}, A = a^*, K = k, \delta_{a^*}^t) \\
L_a^t &= f_M^t(\overline{L}_a^{t-1}, A = a, K = k, \varepsilon_a^t) \\
N_{aa^*}^t &= f_N^t(\overline{M}_{a^*}^t, \overline{L}_a^t, N_{aa^*}^{t-1}, A = a, K = k, \gamma_a^t) \\
T_{aa^*} &= \inf\{t > 0 \text{ for which } N_{aa^*}^t = 1\}. \\
\tilde{C} &= \inf\{t > 0 \text{ for which } C^t = 1\}. \\
\tilde{T}_{aa^*} &= \min\{C, T_{aa^*}\}.
\end{aligned}
$$

- Key-assumption is that the mediator process (M^t) does not depend on other time varying processes (L^t).
- Note that the other mediator process (L^t) does not need to be measured.

Proposed estimation algorithm (1/3)

1. Organize your data in wide format. Censored or dead subjects will have missing for the mediators where they were not observed.

2. Estimate models for the mediator at each measurement time *t* conditional on the assigned treatment *A*, the mediator history (*M*) and baseline confounders *K* by using the original data set.

3. Construct a new dataset; repeating each observation twice and including an additional auxiliary variable *A**, which equal *A* for the first replication and 1-A for the second replication.

4. Add an indicator identifying which data originate from the same subject.

Proposed estimation algorithm (2/3)

4. Apply the predict function twice to predict from the models in step 2, once based on A and once based on A^*. By dividing the predicted values local weights at time s can be obtained as

$$W_j^s = \frac{P(M^s = m_j^s | \overline{M}^{s-1} = \overline{m}_j^{s-1}, A^* = a_j^* \quad K{=}k_j \;)}{P(M^s = m_j^s | \overline{M}^{s-1} = \overline{m}_j^{s-1}, A^* = a_j \quad K{=}k_j \;)}$$

5. Compute the cumulative weights by multiplying the local weights obtained in step 4 from time 1 to the event or censoring time:

$$\overline{W}_j = \prod_{s=1}^{T_j} W_j^s$$

Proposed estimation algorithm (3/3)

6. Fit a suitable outcome model, i.e. the Cox model including A and A^*, possible interactions and baseline covariates. The model should be weighted by the weights from step 5. This model is the natural effects model.

7. Confidence intervals can be obtained using bootstrap.

Intuition for the estimation procedure

- The resulting regression coefficient associated with *A* will capture the natural direct effect while the coefficient of *A** will capture the natural indirect effect.

- The derived weights are a tool to distinguish between direct and indirect effects by giving more weights to observations where the observed mediator trajectory would have been more likely to occur under a different treatment level than actually observed.

- For a constructive illustration see Hong (2010)

Back to the 6S mediation problem

A quick recapitulation:

- Patients selection:
  795 patients admitted to intensive care units
  (396 in HES group vs. 399 Ringer solution)

- Mediator: KDIGO (Kidney Disease: Improving Global Outcome) score, taking values 0, 1, 2, 3 measured daily within the first 5 days of follow-up.
  Mediator model: Multinomial logistic regression

- Outcome: Time to death within 90 days after randomization
  Outcome model: Cox regression

Results

	HR (95% CI)
Direct effect	1.16 (0.95 - 1.40)
Indirect ffect	1.05 (0.98 - 1.12)
Total effect	1.21 (1.01 - 1.47)

Table 1: Natural direct and indirect hazard ratios for mediation through KDIGO comparing HES to Ringer solution.

- Neither direct nor indirect effects are significant.
- However, the magnitude of the direct effect indicates that there could be another important pathway.
- Potential alternative pathways include:
  - Coagulapathy (bleeding disorder)
  - Immune system collapse.

Discussion and perspectives

On mediation analysis in general:

- Mediation analysis can shed light on how a treatment works or if the treatment has positive effects above and beyond its effect on the targeted outcome.
- For simple settings both theory and software is well-developed.
- Mediation analyses are always observational studies.

On mediation analysis with a truncated mediator process:

- Easy to implement in standard software (predict functionality, weighted modeling)
- Generally applicable for various mediator types, although some caution with continuous mediators (unstable weights).
- Can handle treatment-by-mediator interactions.
- Requires that you believe in the different mediator systems to be functioning independently.


QUESTIONS?