eAppendix for "Causal mediation analysis with survival data" by TJ VanderWeele

Equivalence of Product and Difference Method for the Accelerated Failure Time Model with No Exposure-Mediator Interaction

Suppose that the model (2) in the text for the mediator is correctly specified:

$$E[M|a,c] = \beta_0 + \beta_1 a + \beta_2' c. \tag{2}$$

along with model (4) for the outcome with the exposure and mediator so that:

$$\log(T) = \theta_0 + \theta_1 A + \theta_2 M + \theta_4' C + \nu\varepsilon. \tag{4}$$

Suppose also a model is fit for the outcome with just the exposure, not the mediator:

$$\log(T) = \phi_0 + \phi_1 A + \phi_4' c + \varkappa\varepsilon.$$

The difference method uses $\phi_1 - \theta_1$ as a measure of the indirect effect; the product method uses $\beta_1\theta_2$. We show that if all of the models are correctly specified these two are equal. This is because by the model for the outcome without the mediator we have:

$$E[\log(T)|a,c] = \phi_0 + \phi_1 a + \phi_4' c + \varkappa E[\varepsilon]$$

and by model (4) we have:

$$\begin{aligned}
E[\log(T)|a,c] &= E[E[\log(T)|a,M,c]] \\
&= \theta_0 + \theta_1 a + \theta_2 E[M|a,c] + \theta_4' c + \nu E[\varepsilon] \\
&= \theta_0 + \theta_1 a + \theta_2\{\beta_0 + \beta_1 a + \beta_2' c\} + \theta_4' c + \nu E[\varepsilon] \\
&= \{\theta_0 + \theta_2\beta_0\} + \{\theta_1 + \theta_2\beta_1\}a + \{\theta_4' + \theta\beta_2'\}c + \nu E[\varepsilon]
\end{aligned}$$

Because this holds for all a, we must have $\phi_1 = \{\theta_1 + \theta_2\beta_1\}$ and thus $\phi_1 - \theta_1 = \theta_2\beta_1$.

Formulas for Natural Direct and Indirect Effects for the Accelerated Failure Time Model with An Exposure-Mediator Interaction

Under model (2) for the mediator and model (5) for the outcome:

$$\log(T) = \theta_0 + \theta_1 A + \theta_2 M + \theta_3 AM + \theta_4' C + \nu\varepsilon \tag{5}$$

we have that

$$\begin{aligned}
E(T_{aM_{a^*}}|c) &= \int E[T_{am}|c, M_{a^*} = m]dP_{M_{a^*}}(m|c) \\
&= \int E[T_{am}|c]dP_{M_{a^*}}(m|c) \\
&= \int E[T|a,m,c]dP_M(m|a^*,c) \\
&= \int E[e^{\theta_0+\theta_1 a+\theta_2 m+\theta_3 am+\theta_4' c+\nu\varepsilon}]dP_M(m|a^*,c) \\
&= e^{\theta_0+\theta_1 a+\theta_4' c}E[e^{\nu\varepsilon}]E[e^{\theta_2 M+\theta_3 aM}] \\
&= e^{\theta_0+\theta_1 a+\theta_4' c}E[e^{\nu\varepsilon}]e^{(\theta_2+\theta_3 a)(\beta_0+\beta_1 a^*+\beta_2' c)+\frac{1}{2}(\theta_2+\theta_3 a)^2\sigma^2}
\end{aligned}$$

where the first equality follows by the law of iterated expectations, the second by assumption (iv), the third by assumptions (i)-(iii), the fourth by the acclerated failure time model, and the final one by the fact that

M is normally distributed and has constant variance σ^2. Thus,

$$\log\{E(T_{aM_{a^*}}|c)\} = \log(E[e^{\nu\varepsilon}]) + \theta_0 + \theta_1 a + \theta_4' c + (\theta_2 + \theta_3 a)(\beta_0 + \beta_1 a^* + \beta_2' c) + \frac{1}{2}(\theta_2 + \theta_3 a)^2\sigma^2$$

and so

$$\begin{aligned}
\log\{E(T_{aM_a}|c)\} - \log\{E(T_{aM_{a^*}}|c)\} &= (\theta_2\beta_1 + \theta_3\beta_1 a)(a - a^*) \\
\log\{E(T_{aM_{a^*}}|c)\} - \log\{E(T_{a^*M_{a^*}}|c)\} &= \{\theta_1 + \theta_3(\beta_0 + \beta_1 a^* + \beta_2' c + \theta_2\sigma^2)\}(a - a^*) + 0.5\theta_3^2\sigma^2(a^2 - a^{*2}).
\end{aligned}$$

Formulas for Natural Direct and Indirect Effects for the Proportional Hazards Model with Exposure-Mediator Interaction and a Rare Outcome

Under model (2) for the mediator and model (6) for the outcome:

$$\lambda_T(t|a,m,c) = \lambda_T(t|0,0,0)e^{\gamma_1 a + \gamma_2 m + \gamma_3 am + \gamma_4' c}. \tag{6}$$

we have that

$$\lambda_{T_{aM_{a^*}}}(t|c) = \frac{f_{T_{aM_{a^*}}}(t|c)}{S_{T_{aM_{a^*}}}(t|c)}$$

where $f_{T_{aM_{a^*}}}(t|c)$ and $S_{T_{aM_{a^*}}}(t|c)$ denote the conditional density and survival functions respectively for $T_{aM_{a^*}}$. We have that

$$\begin{aligned}
f_{T_{aM_{a^*}}}(t|c) &= \int f_{T_{am}}(t|c, M_{a^*} = m)dP_{M_{a^*}}(m|c) \\
&= \int f_{T_{am}}(t|c)dP_{M_{a^*}}(m|c) \text{ by assumption (iv)} \\
&= \int f_T(t|a,m,c)dP_M(m|a^*,c) \text{ by assumptions (i)-(iii)} \\
&= \int \lambda_T(t|0,0,0)e^{\gamma_1 a + \gamma_2 m + \gamma_3 am + \gamma_4' c}\exp(-\Lambda_T(t|0,0,0)e^{\gamma_1 a + \gamma_2 m + \gamma_3 am + \gamma_4' c})dP_M(m|a^*,c)
\end{aligned}$$

where $\Lambda_T(t|0,0,0) = \int_0^t \lambda_T(t|0,0,0)dt$. Likewise,

$$S_{T_{aM_{a^*}}}(t|c) = \int \exp(-\Lambda_T(t|0,0,0)e^{\gamma_1 a + \gamma_2 m + \gamma_3 am + \gamma_4' c})dP_M(m|a^*,c).$$

Thus,

$$\lambda_{T_{aM_{a^*}}}(t|c) = \lambda_T(t|0,0,0)\exp(\gamma_1 a + \gamma_4' c)r(t;a,a^*,c)$$

where

$$r(t;a,a^*,c) = \frac{\int e^{(\gamma_2+\gamma_3 a)m}\exp(-\Lambda_T(t|0,0,0)e^{\gamma_1 a + \gamma_2 m + \gamma_3 am + \gamma_4' c})dP_M(m|a^*,c)}{\int \exp(-\Lambda_T(t|0,0,0)e^{\gamma_1 a + \gamma_2 m + \gamma_3 am + \gamma_4' c})dP_M(m|a^*,c)}.$$

Since M is normally distributed we have that (cf. Lin et al.[16]):

$$\begin{aligned}
r(t;a,a^*,c) &= e^{(\gamma_2+\gamma_3 a)(\beta_0+\beta_1 a^*+\beta_2' c)+\frac{1}{2}(\gamma_2+\gamma_3 a)^2\sigma^2} \\
&\quad\times\frac{\int \exp(-\Lambda_T(t|0,0,0)e^{(\gamma_2+\gamma_3 a)^2+\gamma_1 a+\gamma_2 m+\gamma_3 am+\gamma_4' c})\exp(-\frac{(m-(\beta_0+\beta_1 a^*+\beta_2' c))^2}{2})dm}{\int \exp(-\Lambda_T(t|0,0,0)e^{\gamma_1 a+\gamma_2 m+\gamma_3 am+\gamma_4' c})\exp(-\frac{(m-(\beta_0+\beta_1 a^*+\beta_2' c))^2}{2})dm}
\end{aligned}$$

which can be approximated by $e^{(\gamma_2+\gamma_3 a)(\beta_0+\beta_1 a^*+\beta_2' c)+\frac{1}{2}(\gamma_2+\gamma_3 a)^2\sigma^2}$ if $\Lambda_T(t|0,0,0)$ is small (i.e. if the outcome is relatively rare). Thus

$$\lambda_{T_{aM_{a^*}}}(t|c) \approx \lambda_T(t|0,0,0)e^{\gamma_1 a+\gamma_4' c}e^{(\gamma_2+\gamma_3 a)(\beta_0+\beta_1 a^*+\beta_2' c)+\frac{1}{2}(\gamma_2+\gamma_3 a)^2\sigma^2}$$

and

$$\log\{\lambda_{T_{aM_{a^*}}}(t|c)\} = \log(\lambda_T(t|0,0,0)) + \gamma_1 a + \gamma_4' c + (\gamma_2+\gamma_3 a)(\beta_0+\beta_1 a^* + \beta_2' c) + \frac{1}{2}(\gamma_2+\gamma_3 a)^2\sigma^2.$$

From this it follows that,

$$\begin{aligned}
\log\{\lambda_{T_{aM_a}}(t|c)\} - \log\{\lambda_{T_{aM_{a^*}}}(t|c)\} &= (\gamma_2\beta_1 + \gamma_3\beta_1 a)(a-a^*) \\
\log\{\lambda_{T_{aM_{a^*}}}(t|c)\} - \log\{\lambda_{T_{a^*M_{a^*}}}(t|c)\} &= \{\gamma_1 + \gamma_3(\beta_0+\beta_1 a^* + \beta_2' c + \gamma_2\sigma^2)\}(a-a^*) + 0.5\gamma_3^2\sigma^2(a^2 - a^{*2}).
\end{aligned}$$

Equivalence of Product and Difference Method for the Proportional Hazards Model with No Exposure-Mediator Interaction and a Rare Outcome

Suppose that the model (2) in the text for the mediator is correctly specified:

$$E[M|a,c] = \beta_0 + \beta_1 a + \beta_2' c. \tag{2}$$

along with proportional hazards model (3):

$$\lambda_T(t|a,m,c) = \lambda_T(t|0,0,0)e^{\gamma_1 a+\gamma_2 m+\gamma_4' c} \tag{3}$$

Suppose also a proportional hazards model is also fit without the mediator:

$$\lambda_T(t|a,c) = \lambda_T(t|0,0)e^{\phi_1 a+\phi_4' c}.$$

The difference method uses $\phi_1 - \gamma_1$ as a measure of the indirect effect; the product method uses $\beta_1\gamma_2$. We show that if all of the models are correctly specified and the outcome is rare these two are approximately equal. This is because by the proportional hazards model without the mediator:

$$\lambda_T(t|a,c) = \lambda_T(t|0,0)e^{\phi_1 a+\phi_4' c}$$

and by model (3)

$$\begin{aligned}
\lambda_T(t|a,c) &= \frac{f_T(t|a,c)}{S_T(t|a,c)} \\
&= \frac{\int f_T(t|a,m,c)dP_M(m|a,c)}{\int S_T(t|a,m,c)dP_M(m|a,c)} \\
&= \frac{\int \lambda_T(t|0,0,0)e^{\gamma_1 a+\gamma_2 m+\gamma_4' c}\exp(-\Lambda_T(t|0,0,0)e^{\gamma_1 a+\gamma_2 m+\gamma_4' c})dP_M(m|a,c)}{\int \exp(-\Lambda_T(t|0,0,0)e^{\gamma_1 a+\gamma_2 m+\gamma_4' c})dP_M(m|a,c)} \\
&= \lambda_T(t|0,0,0)\exp(\gamma_1 a + \gamma_4' c)r(t;a,c)
\end{aligned}$$

where

$$r(t;a,c) = \frac{\int e^{\gamma_2 m}\exp(-\Lambda_T(t|0,0,0)e^{\gamma_1 a+\gamma_2 m+\gamma_4' c})dP_M(m|a,c)}{\int \exp(-\Lambda_T(t|0,0,0)e^{\gamma_1 a+\gamma_2 m+\gamma_4' c})dP_M(m|a,c)}.$$

As in the previous proof, since M is normally distributed we have that (cf. Lin et al.[16]):

$$r(t;a,c) = e^{\gamma_2(\beta_0+\beta_1 a+\beta_2' c)+\frac{1}{2}\gamma_2^2\sigma^2} \times \frac{\int \exp(-\Lambda_T(t|0,0,0)e^{\gamma_2^2+\gamma_1 a+\gamma_2 m+\gamma_4' c})\exp(-\frac{(m-(\beta_0+\beta_1 a+\beta_2' c))^2}{2})dm}{\int \exp(-\Lambda_T(t|0,0,0)e^{\gamma_1 a+\gamma_2 m+\gamma_4' c})\exp(-\frac{(m-(\beta_0+\beta_1 a+\beta_2' c))^2}{2})dm}$$

which can be approximated by $e^{\gamma_2(\beta_0+\beta_1 a+\beta_2' c)+\frac{1}{2}\gamma_2^2\sigma^2}$ if $\Lambda_T(t|0,0,0)$ is small (i.e. if the outcome is relatively rare). Thus

$$\lambda_T(t|a,c) \approx \{e^{\gamma_2\beta_0+\frac{1}{2}\gamma_2^2\sigma^2}\lambda_T(t|0,0,0)\}e^{(\gamma_1+\gamma_2\beta_1)a+(\gamma_2\beta_2+\gamma_4)' c}.$$

Because this holds for all a, we must have $\phi_1 \approx \{\gamma_1+\gamma_2\beta_1\}$ and thus $\phi_1-\gamma_1 \approx \gamma_2\beta_1$.

The Product Method for the Proportional Hazards Model with Common Outcome Yields a Valid Test of the Presence of Any Mediated Effect

We assume models (2) and (3) are correctly specified and that assumptions (i)-(iv) hold. In counterfactual notation, these are that for all a, a^*, m, (i) $T_{am} \perp\!\!\!\perp A|C$, (ii) $T_{am} \perp\!\!\!\perp M|C$, (iii) $M_a \perp\!\!\!\perp A|C$ and (iv) $T_{am} \perp\!\!\!\perp M_{a^*}|C$ where $X \perp\!\!\!\perp Y|Z$ denotes that X is independent of Y conditional on Z. On any causal diagram for which (iv) holds, it also follows that $(T_{am}, T_{am^*}) \perp\!\!\!\perp (M_a, M_{a^*})|C$. If in models (2) and (3) we have that $\gamma_2\beta_1 \neq 0$ then from this it follows that $\gamma_2 \neq 0$ and $\beta_1 \neq 0$. If $\beta_1 \neq 0$ then by assumption (iii) it follows that A has an effect on M in the sense that for some a and a^* there are individuals $\omega \in \Theta_1$ such that, $M_a(\omega) - M_{a^*}(\omega) \neq 0$. Let $m = M_a(\omega)$ and $m^* = M_{a^*}(\omega)$. If $\gamma_2 \neq 0$ then by assumptions (i) and (ii) it follows that M has an effect on Y with A fixed at a in the sense that there are individuals $\omega \in \Theta_2$ such that $T_{am}(\omega) - T_{am^*}(\omega) \neq 0$. Since $(T_{am}, T_{am^*}) \perp\!\!\!\perp (M_a, M_{a^*})|C$, it follows that there are individuals $\omega \in \Theta_1 \cap \Theta_2$ and thus for $\omega \in \Theta_1 \cap \Theta_2$, $0 \neq T_{am}(\omega) - T_{am^*}(\omega) = T_{aM_a}(\omega) - T_{aM_{a^*}}(\omega)$ i.e. $T_{aM_a}(\omega) \neq T_{aM_{a^*}}(\omega)$ so there are some individuals for whom the natural indirect effect is non-zero.

The argument given here that the product method constitutes a valid test for the presence of a natural indirect effect holds more generally for other models for the mediator and the outcome provided that the models are correctly specified and assumptions (i)-(iv) hold.