

Objectives

Mediation analyses can provide strong support for biomarker development by demonstrating that a biomarker mediates a (large) part of the treatment effect on a clinical outcome [1,2].

Mediation analysis **decomposes a total treatment effect** into two parts :

- an **indirect effect** that is mediated by the mediator (i.e. biomarker) of interest
- a **direct effect** that is not mediated.

Given the potential complexity of PK-PD models (which may violate assumptions in the traditional mediation approach), the more advanced **causal mediation analysis** approach can be more appropriate in certain applications. Here, we will illustrate the concepts used in causal mediation analysis in a pharmacometrics context.

Model of exposure (AUC), mediator M and outcome Y

The concepts were numerically illustrated with a PK-PD model:

$$AUC = DOSE(in \mu g)/CL, \text{ with typical } CL \text{ of } 10 \text{ L/h.}$$

$$M = 100 * \exp(-0.001 * AUC).$$

$$Y = EMAX * AUC/(AUC+EC50) - 0.01 * M,$$

with $E_{max} = 0.15$ and $EC50 = 300 \text{ ng} \cdot \text{h/ml}$.

For sake of simplicity of the illustration of the counterfactuals of causal mediation analysis, variability (residual and inter-individual) is absent in this example

Figure 1. Schematic of the PK-PD model. The total effect of AUC on Y can be decomposed into a direct and indirect effect. The direct effect is reflected by the arrow from AUC to Y, while the indirect effect is reflected by the consecutive effect of AUC on M and M on Y.

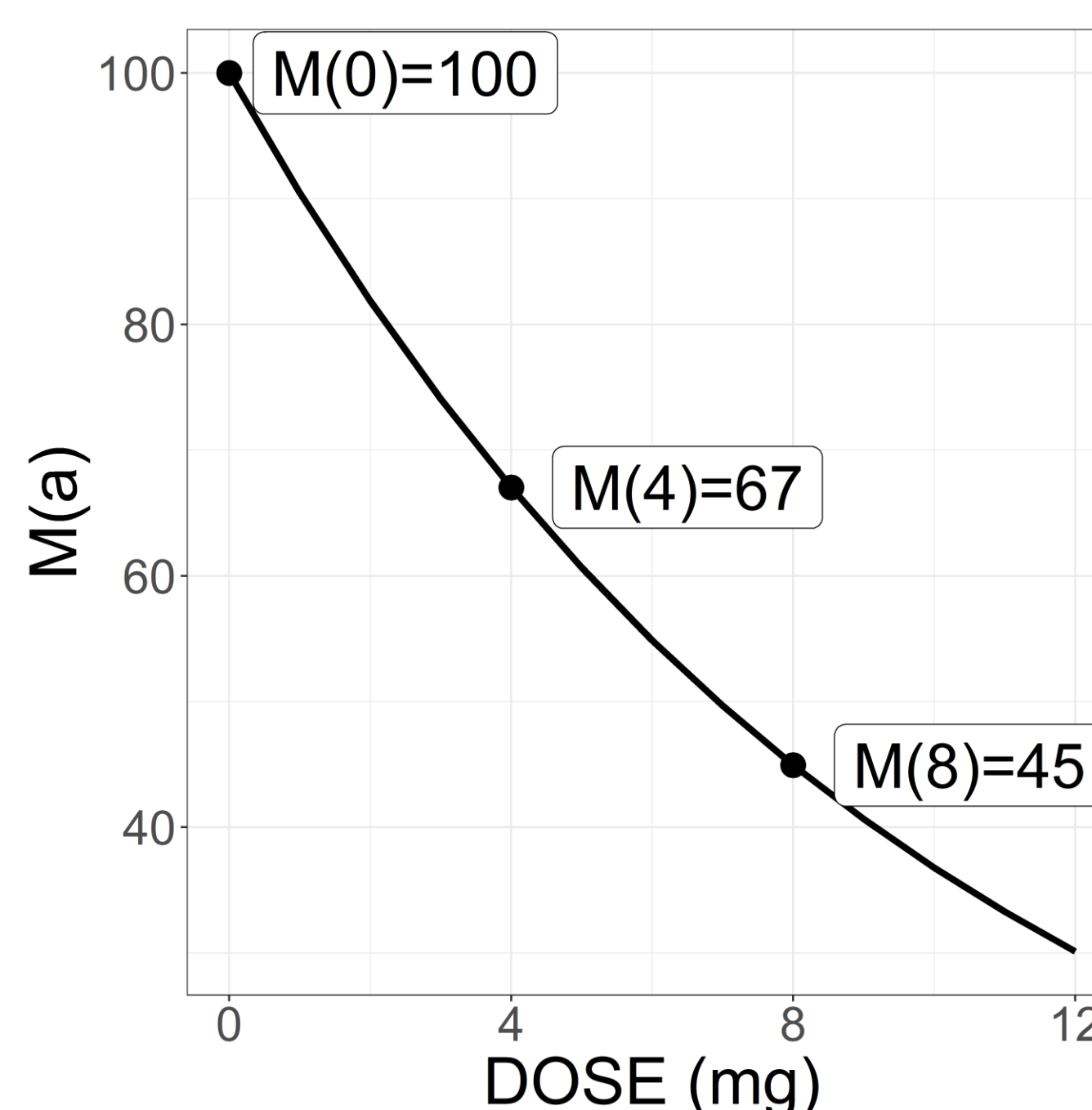
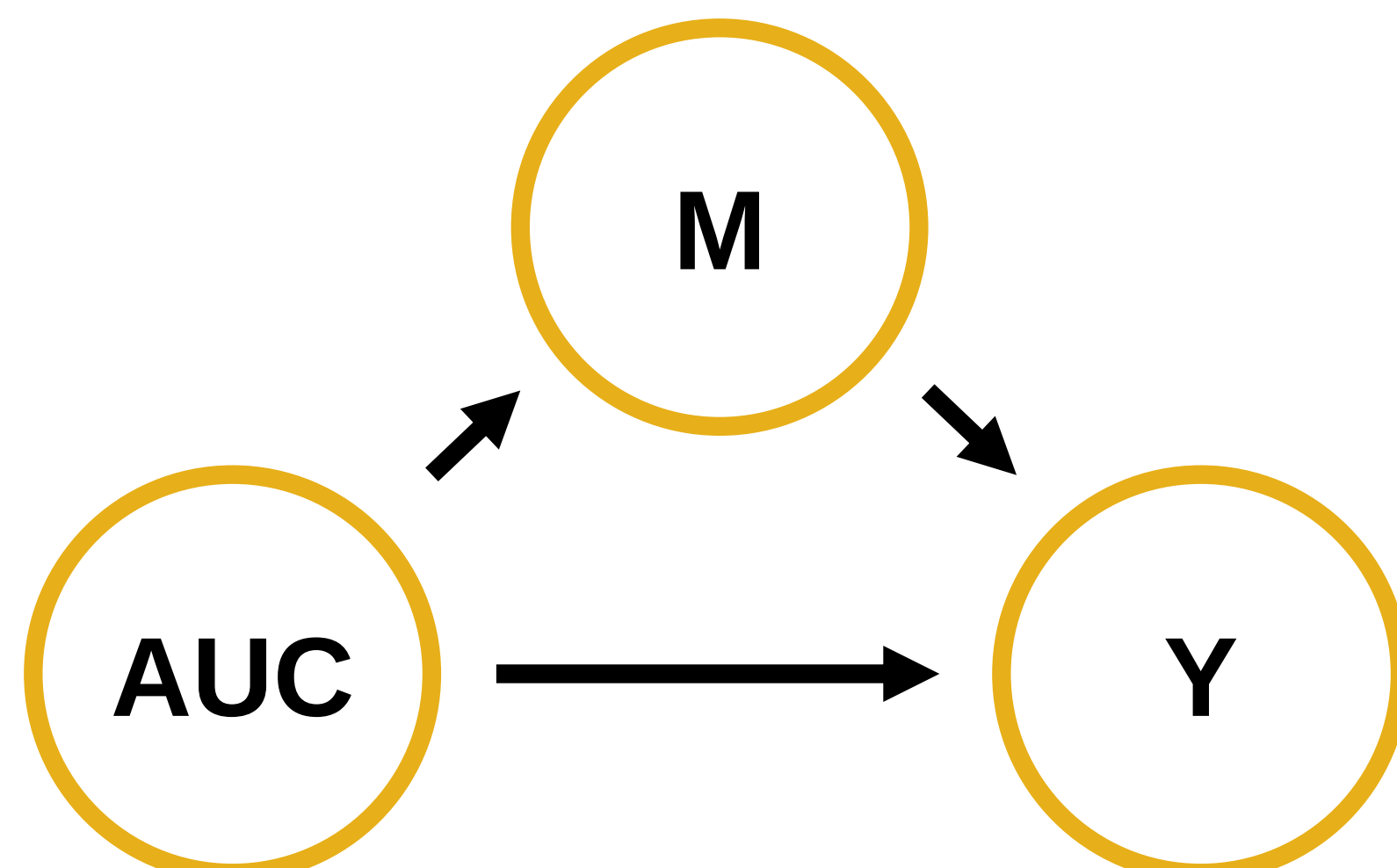


Figure 2. Illustrated dose-response relationship for mediator M

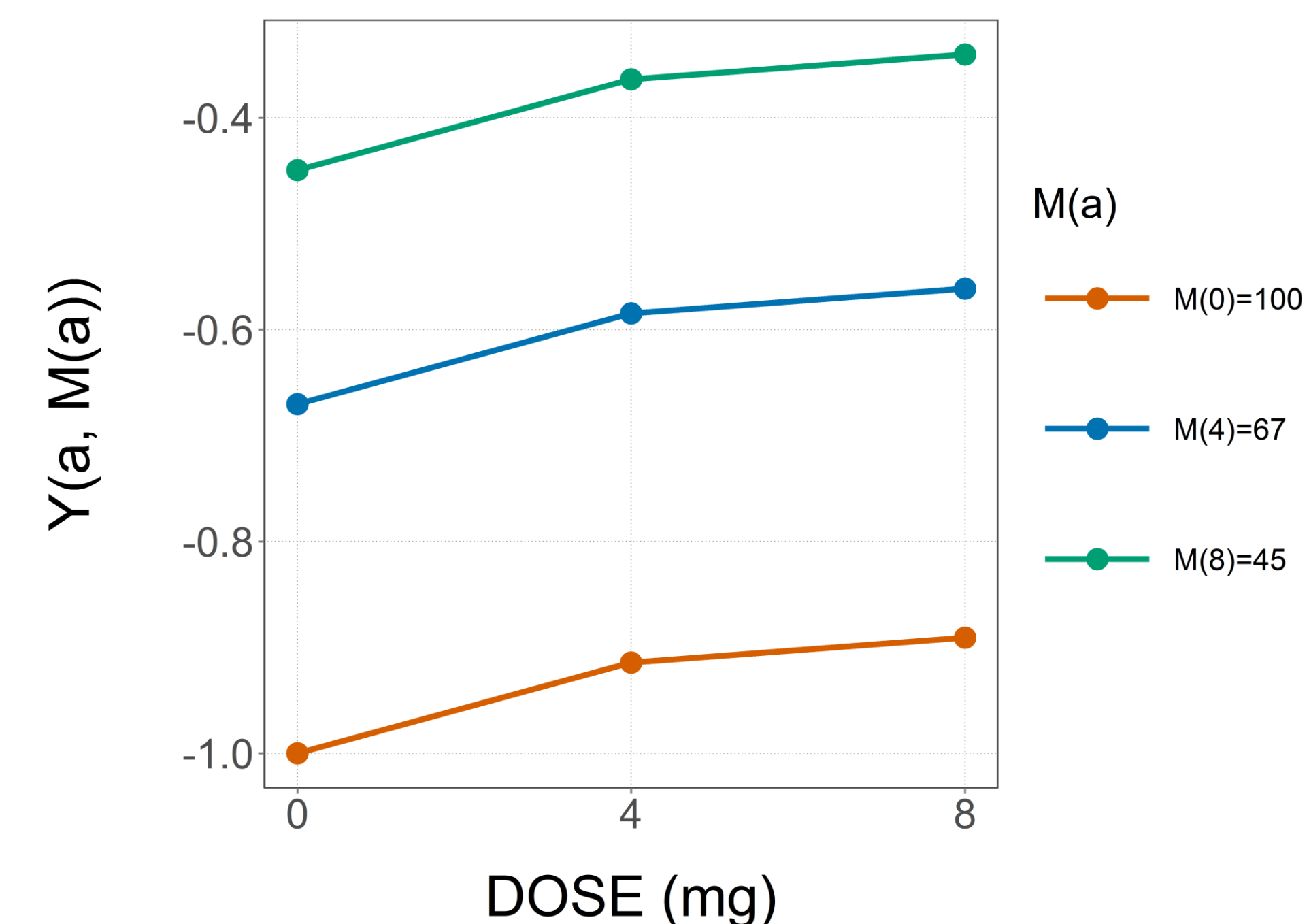


Figure 3. Illustrated dose-response relationship for Y, conditional on M

Results

Using PK-PD models for the mediator and outcome, the counterfactual definitions of the causal mediation analysis (TE and PIE) were estimated through simulation for a typical subject (for a 4 mg and 8 mg dose).

The relevant counterfactual effects can then be simulated using the PK-PD model (illustrated in Figure 2):

$$TE(4 \text{ mg}) = Y(4, M(4)) - Y(0, M(0)) = -0.585 - -1 = 0.415$$

$$PIE(4 \text{ mg}) = Y(0, M(4)) - Y(0, M(0)) = -0.670 - -1 = 0.330$$

$$\text{Proportion mediated} = PIE(4 \text{ mg})/TE(4 \text{ mg}) = 79.4\%$$

$$TE(8 \text{ mg}) = Y(8, M(8)) - Y(0, M(0)) = -0.340 - -1 = 0.660$$

$$PIE(8 \text{ mg}) = Y(0, M(8)) - Y(0, M(0)) = -0.449 - -1 = 0.551$$

$$\text{Proportion mediated} = PIE(8 \text{ mg})/TE(8 \text{ mg}) = 83.5\%$$

Due to saturation of the direct effect of AUC on Y (E_{max} relationship), the proportion mediated increased at higher doses with this PK-PD model.

Causal mediation analysis: Counterfactuals

Causal mediation analysis uses counterfactual definitions from causal inference to formally define the direct and indirect effects [3]. These counterfactual definitions (defined below) can be seen as ‘what if’ questions and may be estimated through simulations [4].

$M(a)$ is the value of mediator M with treatment a. $Y(a, M(a))$ is the value of the outcome Y and depends on the treatment a and the value of the mediator M (Figure 1).

$$\text{Total effect (TE) of 4 mg treatment} = Y(4 \text{ mg}, M(4 \text{ mg})) - Y(0 \text{ mg}, M(0 \text{ mg}))$$

$$\text{Pure indirect effect (PIE) of 4 mg treatment} = Y(0 \text{ mg}, M(4 \text{ mg})) - Y(0 \text{ mg}, M(0 \text{ mg}))$$

$$\text{Proportion mediated by M} = PIE/TE$$

PIE reflects the effect that the treatment would have if (potentially contrary to fact) its only effect would be to change the mediator. While $Y(0, M(4 \text{ mg}))$ can, by definition, not be observed in any particular subject, under certain assumptions of non-confounding, it can be simulated to calculate PIE [4].

Conclusion

Here, we illustrated the concepts of **causal mediation analysis** with a simple pharmacometrics example.

Key strengths of the causal mediation analysis approach for PKPD models:

- **General definitions** for direct and indirect effects, independent of parametric structure of the model
- **Widely applicable** to the diverse models used in pharmacometrics (e.g. non-linearities, interaction effects, non-continuous data)

The simulations used here to calculate the level of mediation for a typical subject, can be extended to:

- Calculate the **average level of mediation for a population** and study design of interest (when using population simulations).
- Calculate **confidence intervals** when including model parameter uncertainty
- Investigate **inter-individual differences** in the level of mediation

[1] Fleming et al. Ther Innov Regul Sci (2023) 57:109–120.

[2] Goulooze et al. CPT Pharmacometrics Syst Pharmacol (2024) 13:1285–1288.

[3] VanDerWeele et al. Annu Rev Public Health (2016) 37:17–32.

[4] Imai et al. Psychol Method (2010) 15:309–334.