Mediation Analysis with Bayesian Nonlinear Joint Models: Evaluating Treatment Pathways via Tumor Growth Kinetics.

Georgios Kazantzidis[1,2], François Mercier[1], Virginie Rondeau[2]

[1]F. Hoffmann-La Roche AG, Basel, Switzerland [2]Bordeaux Population Health, Inserm U1219, France

Background

In oncology, it is crucial to quantify how much of a treatment's survival benefit operates through **tumor dynamics** to inform *surrogacy* and mechanism-of-action claims.

The Proportion of Treatment Effect (PTE) is a well know estimand in mediation analysis.

Tumor size attributes are already practically used as surrogates of overall survival without extensive validation.

Objectives

Introduce a **Bayesian joint-model mediation** framework: a nonlinear Tumor Growth Inhibition (TGI) model for longitudinal tumor size SLD (sum of longest diameters) measurements coupled with a parametric survival model.

Estimate **natural direct/indirect effects** and the **PTE** mediated by tumor kinetics to Overall Survival (OS).

Compare biologically motivated link functions between tumor size attributes and OS.

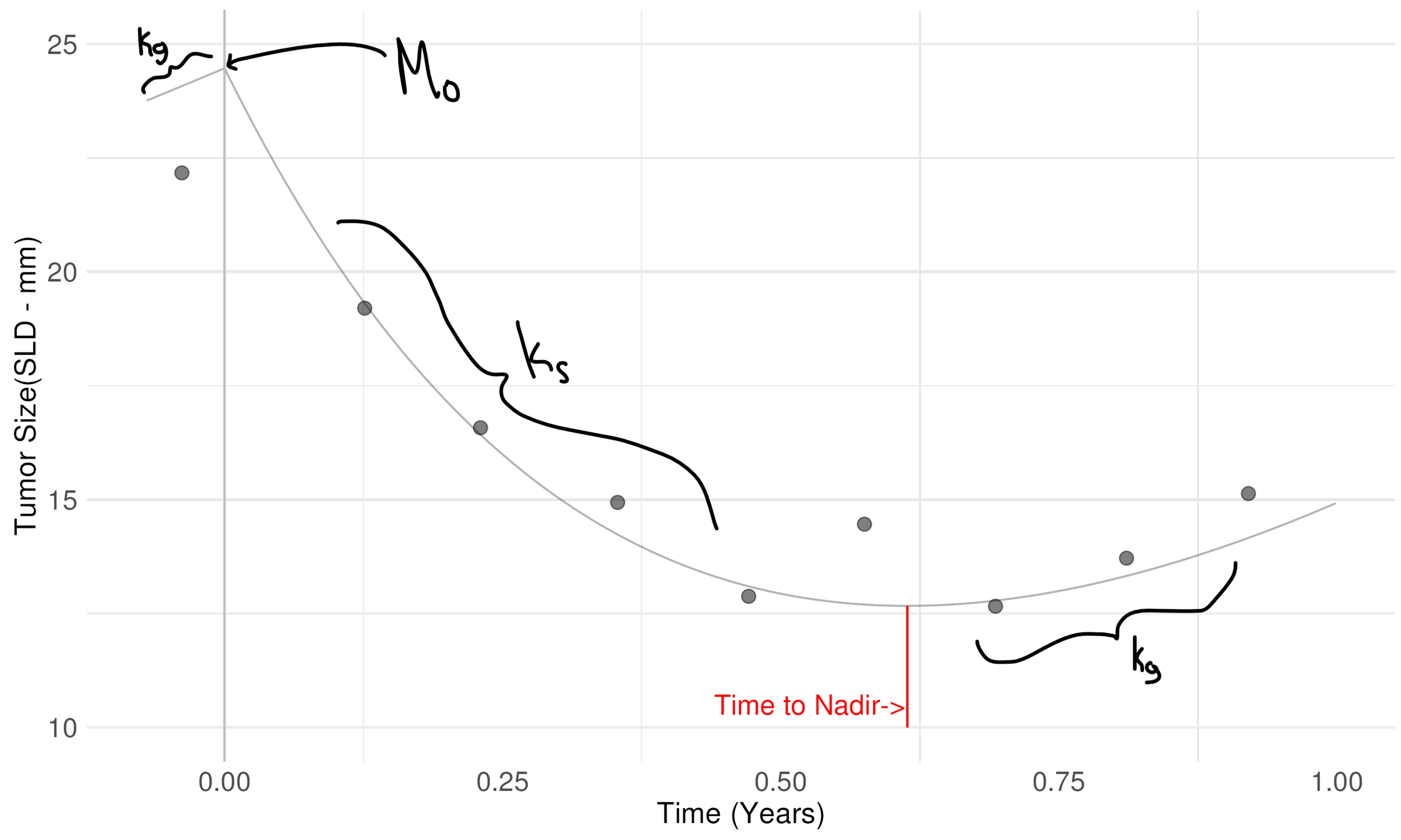
Evaluate bias via simulations; apply to **IMbrave150** clinical trial.

Longitudinal Sub-model: Tumor growth inhibition Stein-Fojo

$$y_{ij} = g_i(t_{ij})(1 + \epsilon_{ij})$$
$$g_i(t) = \underbrace{\mu_{m_0} e^{\xi_{m_{0_i}}}}_{m_0}[exp\{\underbrace{\mu_{k_g} e^{\xi_{k_{g_i}} + \beta_{k_g} Z_i}}_{k_g} t\} + exp\{-\underbrace{\mu_{k_s} e^{\xi_{k_{s_i}} + \beta_{k_s} Z_i}}_{k_s} t\} - 1]$$

y_{ij} Observed SLD for subjet i at time j
$g(t)$ Expected SLD (mm)
k_g Tumor growth rate $(year^{-1})$
k_s Tumor shrinkage rate $(year^{-1})$

m_0 Baseline expected SLD (mm)
$\xi_{k_{s_i}}, \xi_{k_{g_i}}, \xi_{m_{0_i}}$ random effects
$\mu_{k_s}, \mu_{k_g}, \mu_{m_0}$ population effects
$\beta_{k_s}, \beta_{k_g}, Z_i$ Treatment effect and indicator



Survival Sub-model: Proportional hazard

$$\lambda_i(t|h(\cdot)) = \lambda_0(t)\exp\{\eta h(\cdot) + \beta_{os} Z_i\}$$

$\lambda_i(t|h(\cdot))$: Hazard function linked to the TGI process.
$\lambda_0(t)$: Baseline hazard function.
η: Parameter of association.
β_{os}: Parameter of treatment (Z_i) effect on the survival process.
$h(\cdot)$: Link function.

Description	Mathematical Expression
Expected tumor size	$g_i(t)$
Tumor growth	$\log k_{g_i}$
Tumor shrinkage	$\log k_{s_i}$
Slope of tumor size	$g_i'(t)$
Time to nadir	$\frac{\log\left(\frac{k_{s_i}}{k_{g_i}}\right)}{k_{s_i}+k_{g_i}}$

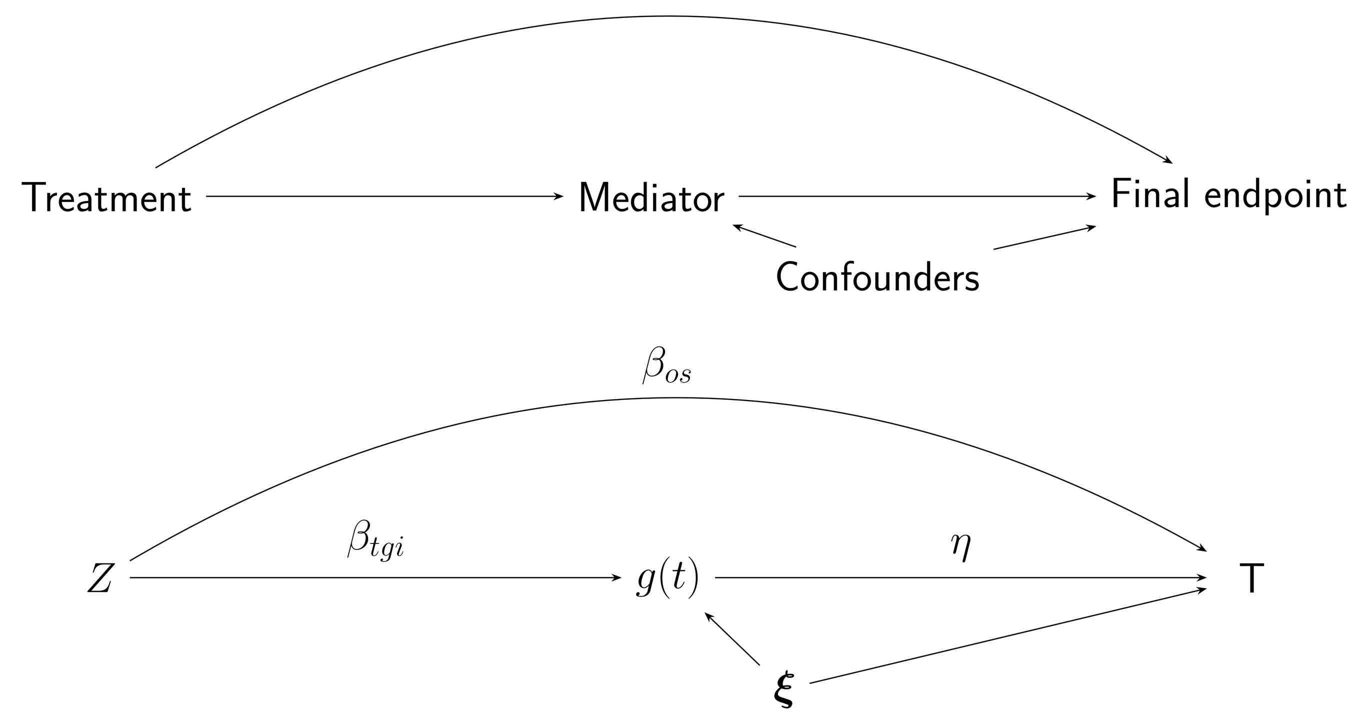
Proportion of Treatment Effect - Counterfactuals

Natural Indirect Effect:
$NIE(t) = \mathbb{S}_{11}(t) - \mathbb{S}_{10}(t)$
Natural Direct Effect:
$NDE(t) = \mathbb{S}_{10}(t) - \mathbb{S}_{00}(t)$

Total Effect:
$TE(t) = \mathbb{S}_{11}(t) - \mathbb{S}_{00}(t)$
Proportion of Treatment Effect:
$PTE(t) = \frac{NIE(t)}{TE(t)}$

Where $\mathbb{S}_{zz'}(t)$ is the counterfactual survival probability for potential treatment regiments z and z'.

Methods: DAG



Simulation Study

Design: Low/average/high mediation; $n = 200$ vs $n = 800$; link functions matching biology.

Results: Survival/tumor parameters recovered with small bias ($\lesssim 5\%$) and high coverage ($\gtrsim 90\%$).

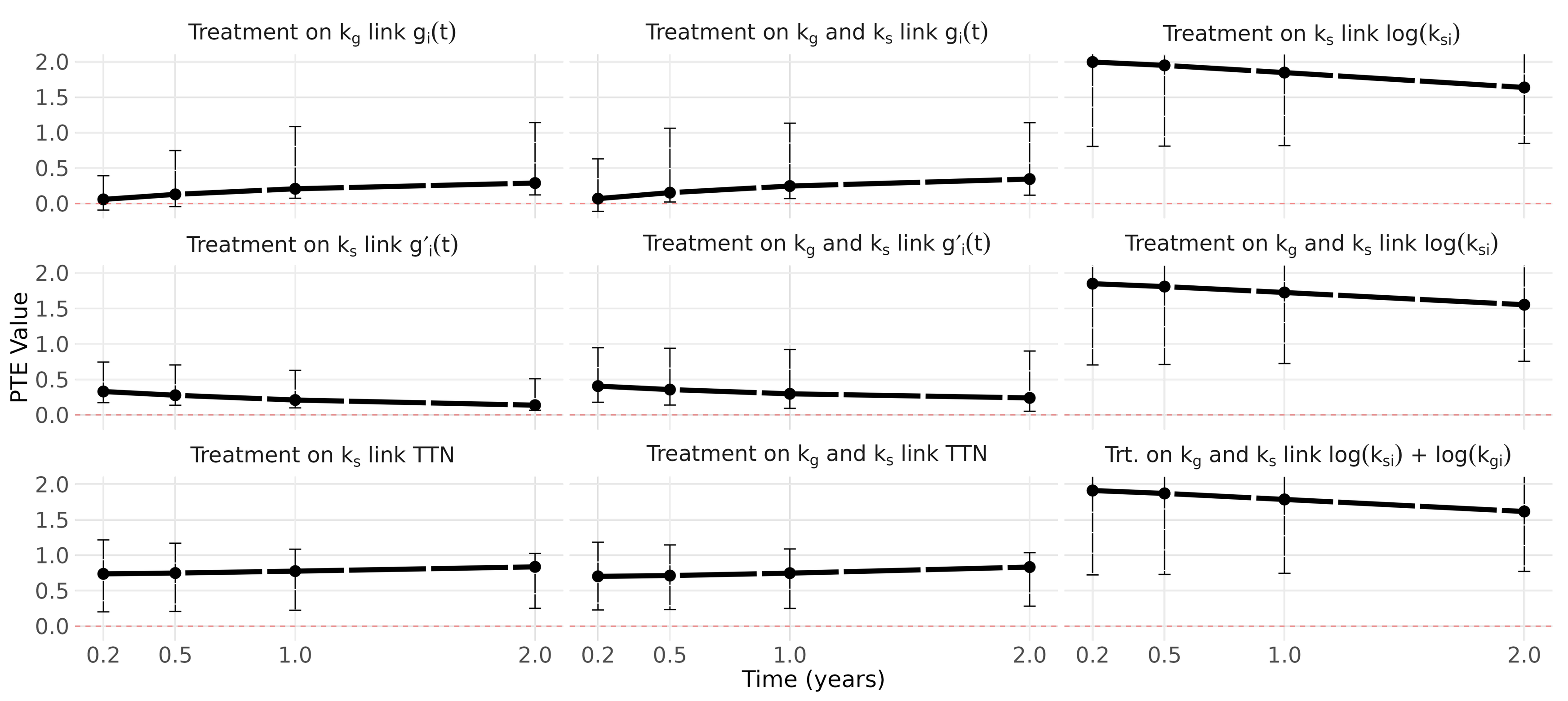
Notes: Slight NIE underestimation at small n; baseline size μ_{m_0} less identifiable.

Application: IMbrave150 (HCC)

Table 1. Best model (by LOOIC): link = *tumor slope*; treatment on both k_s and k_g

Variable	Median	SD	2.5%	97.5%	$\hat{R}$	ESS
Survival Model						
Treatment vs control (β_{os})	-0.307	0.151	-0.597	-0.015	1.00	1735
Association (η)	0.012	0.002	0.009	0.016	1.00	1802
Longitudinal Model						
Treatment on k_s (β_{k_s})	1.091	0.290	0.534	1.661	1.00	973
Treatment on k_g (β_{k_g})	-0.193	0.249	-0.652	0.314	1.01	930
Tumor growth (μ_{k_g})	0.199	0.050	0.118	0.314	1.00	980
Tumor shrinkage (μ_{k_s})	0.163	0.051	0.085	0.284	1.02	1019
Baseline tumor (μ_{m_0})	66.01	2.230	62.02	70.68	1.00	250
σ_{prop}	0.177	0.003	0.172	0.183	1.00	2796

Mediation estimates	0.2 y	0.5 y	1 y	2 y
PTE	0.404	0.354	0.295	0.239
NDE	0.008	0.032	0.071	0.110
NIE	0.005	0.014	0.024	0.022
TE	0.012	0.045	0.095	0.130



Discussion

Framework joins nonlinear TGI with survival in a causal mediation.

Link choice matters: slope/TTN often outperform other links; results decompose the TE differently.

Limitations: Identifiability of μ_{m_0}; LOOIC PSIS diagnostics; no mediator–outcome confounders assumption.

Implication: tumor dynamics mediate a **modest** fraction ($\sim 25\%–40\%$) of survival benefit in IMbrave150.

Conclusions

Provides a robust Bayesian tool to **quantify natural effects** with non linear longitudinal mediators.

Supports **surrogate endpoint** evaluation and mechanism-of-action insights.

Future: extend to a multi-state semi-competing risk join model accounting for **treatment switching**.