A New High Dimensional Surrogacy Measure Based on Bayesian Variable Selection Approach

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Outline

- Background of the study
- Methodology
- Application to a high dimensional data
- Conclusion and further research

Part 1 : Surrogacy in clinical trials

Introduction

- Clinical trials : most credible indicator of drug/therapy response.
- In clinical trials: focus on clinical relevant endpoints.
  Examples are: Survival in cancer studies.
  Quality of life assessment with multi-dimensional instrument.
  Cachexia in malnutition and loss of muscle study.
- Therapy: improve clinical endpoint relevant to patients.
- Goal: estimate treatment effect on the primary endpoint.

Issues with primary endpoints

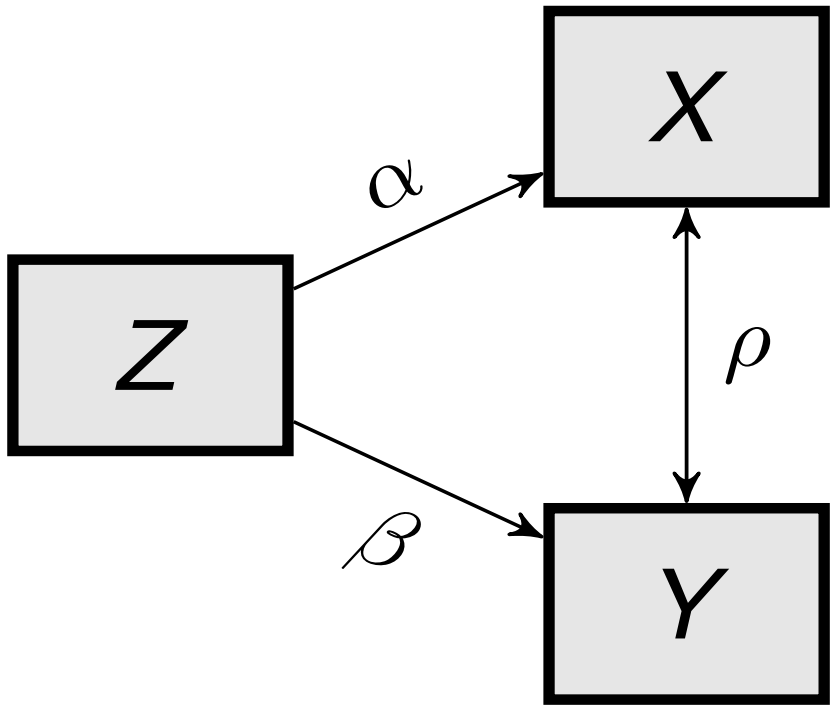
Possible problems

- Long follow up time.
- Costly to measure.
- Difficult and risky to measure.

Possible solution

- Surrogate endpoint to replace the primary endpoint.
- By measuring the treatment effect on the surrogate.

Surrogacy measure and evaluation



Evaluation of surrogate endpoint

Two level of surrogacy

- Trial level surrogacy
  Can we predict β with information about α?

- Individual level surrogacy
  The association between X and Y given Z.

Focus of today's talk

- Focus on individual level surrogacy.
- Surrogacy measure for high dimensional data.

Part 2 : Validation and evaluation of surrogate endpoint

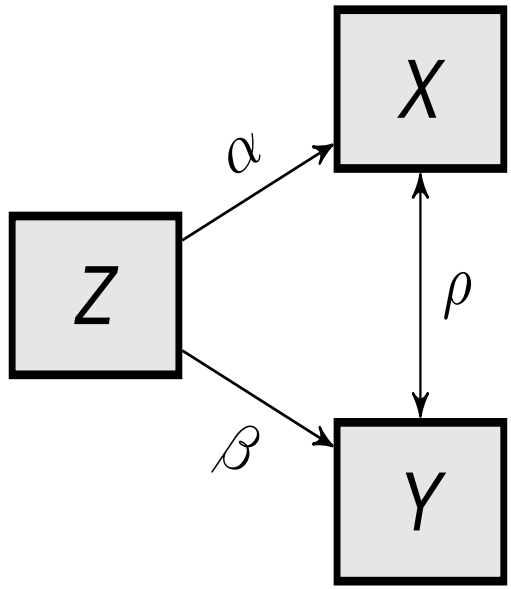
(Individual level surrogacy)

What is new?

- An easy and simple measure.
- Applied to any type of endpoints combination.
- Model uncertainty is taken into account.
- It is related to other measures for surrogacy (will be discussed later).
- Based on a probability measure which gives the importance of an endpoint as a biomarker.

Biomarker/Surrogacy setting

- The Joint modelling approach (Buyse and Molenberghs, 1998).



$$\begin{pmatrix} X_i \\ Y_i \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} \mu_X + \alpha Z_i \\ \mu_Y + \beta Z_i \end{pmatrix}, \sum \right)$$

The Joint modelling approach

where;

$$\sum = \begin{pmatrix} \delta_{XX} & \delta_{XY} \\ \delta_{XY} & \delta_{yy} \end{pmatrix}$$

Surrogacy measure: adjusted association

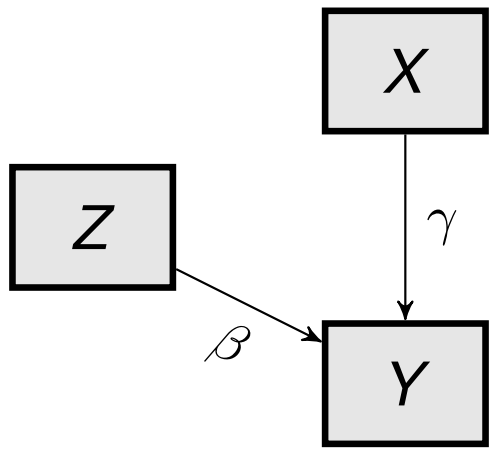
$$\rho = \frac{\delta_{XY}}{\sqrt{\delta_{XX}\delta_{YY}}}$$

$$\rho = \begin{cases} 1, & \text{X is a perfect surrogate,} \\ 0, & \text{Independent.} \end{cases} \qquad \text{and} \qquad 0 \leq \rho \leq 1.$$

$$\rho = 0 \implies \sum = \begin{pmatrix} \delta_{XX} & 0 \\ 0 & \delta_{yy} \end{pmatrix}$$

Biomarker/Surrogacy setting

- The Information theory approach (Alonso and Molenberghs, 2001).



$$M_o = Y|Z \sim \mathcal{N}(\mu_X + \beta Z, \delta_o^2)$$
$$M_1 = Y|ZX \sim \mathcal{N}(\mu_X + \beta Z + \gamma X, \delta_1^2)$$

$$G^2 = -2[\text{loglik}(M_0) - \text{loglik}(M_1)]$$
$$R_h^2 = 1 - \exp\frac{-G^2}{N}$$

The Information theory approach

$$0 \leq R_h^2 \leq 1$$

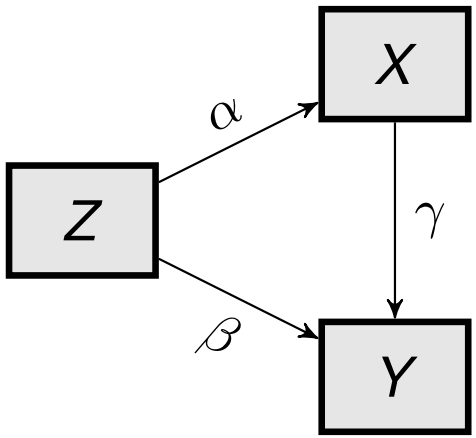
$$\rho = \sqrt{R_h^2} \text{ normal endpoints}$$

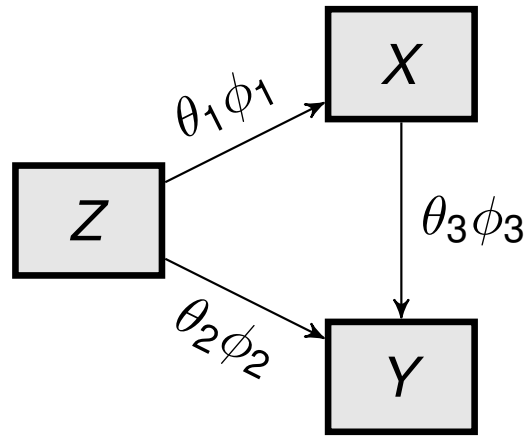
$$R_h^2 = 1 \implies \text{X is aperfect surrogate}$$

$$R_h^2 = 0 \implies \text{independent}$$

Biomarker/Surrogacy setting

- A Bayesian Variable Selection approach.





$$\begin{pmatrix} X \\ Y \end{pmatrix} \sim \mathcal{N}\left(\begin{matrix} \mu_X + \alpha Z \\ \mu_Y + \beta Z + \gamma X \end{matrix} , \quad \sum \right)$$

$$\begin{pmatrix} X \\ Y \end{pmatrix} \sim \mathcal{N}\left(\begin{matrix} \mu_X + \theta_1 \phi_1 Z \\ \mu_Y + \theta_2 \phi_2 Z + \theta_3 \phi_3 X \end{matrix} , \quad \sum \right)$$

$$\alpha = \phi_1{}^* \theta_1, \qquad \beta = \phi_2{}^* \theta_2, \qquad \gamma = \phi_3{}^* \theta_3.$$

Bayesian Variable Selection (prior specification)

$$\phi_i \sim B(\pi_i) \quad \text{and} \quad \pi_i \sim U(0,1)$$

$$\phi_i = \begin{cases} 1, & \theta_i \text{ is included in the model,} \\ 0, & \theta_i \text{ is not included in the model.} \end{cases}$$

$$\theta_1, \theta_2, \theta_3 \sim \mathcal{N}(0, 0.00001)$$

$$\Sigma^{-1} \sim dwish(W, df)$$

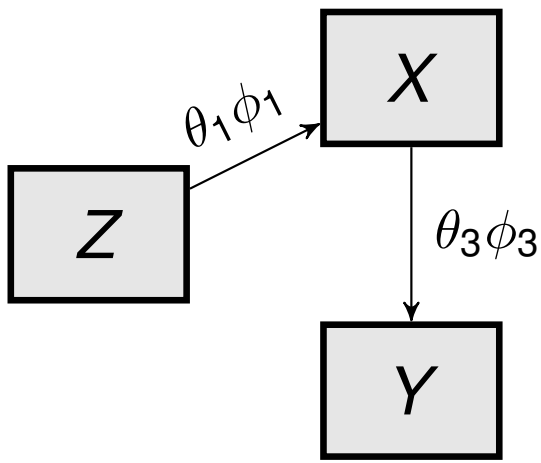
$$W = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$$

$$df = 2$$

Configuration of the inclusion parameters

$$\phi = \{\phi_1, \phi_2, \phi_3\}$$

- The configuration of ϕ define uniquely all possible models;
- Example: If $\phi = \{1, 0, 1\}$ then;



- Z influences Y indirectly via X.

Inclusion probability

- Inclusion probability as measure of surrogacy.
- $\pi_i = P(\phi_i = 1 | \text{data}, \text{model paramters})$.
- Example:
  $P(\phi_3 = 1 | \text{data}, \text{model paramters}) =$
  $P(\text{X is included in the model})$.

Relationship between the joint model and the BVS model

- Joint model approach.

$$\begin{pmatrix} X_i \\ Y_i \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} \mu_X + \alpha Z_i + \epsilon_{Xi} \\ \mu_Y + \beta Z_i + \epsilon_{Yi} \end{pmatrix}, \sum = \begin{pmatrix} \delta_{xx} & \delta_{xy} \\ \delta_{xy} & \delta_{yy} \end{pmatrix} \right)$$

$$\Downarrow$$

$$Y|X, Z \sim \mathcal{N}[\delta_0 + \delta_1 Z_i + \delta_2 X_i + \tilde{\epsilon_{Yi}}, \tilde{\delta}]$$

$$\delta_1 = \beta - \delta_{xy}\delta_{xx}^{-1}\alpha$$

$$\delta_2 = \delta_{xy}\delta_{xx}^{-1}$$

$$var(\tilde{\delta}) = \delta_{yy} - \delta_{xy}^2\delta_{xx}^{-1}$$

Relationship between the information theory approach and the BVS model

$$P(\phi_3 = 0 | \text{data, model parameters})$$

$$\Downarrow$$

$$Y|X, Z \sim \mathcal{N}[\delta_0 + \delta_1 Z_i, \delta^2]$$

and in this case;

$$R_h^2 = 0$$

Relationship between the information theory approach and the BVS model

$$\rho = 0 \implies \sum = \begin{pmatrix} \delta_{xx} & 0 \\ 0 & \delta_{yy} \end{pmatrix}$$

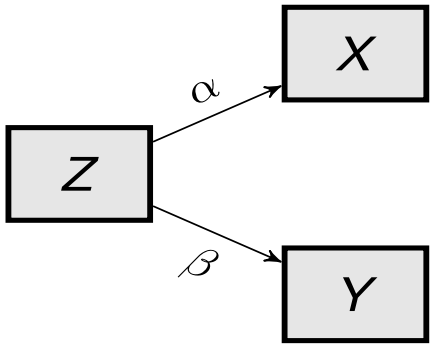
$$\delta_2 = 0 \implies Y_i | X_i Z_i \sim \mathcal{N}(\mu_Y + \beta Z, \delta_0^2)$$

$$\implies R_h^2 = 0$$

This implies that for $P(\phi_3 = 0 | \text{data, parameters})$ then $\rho = 0$

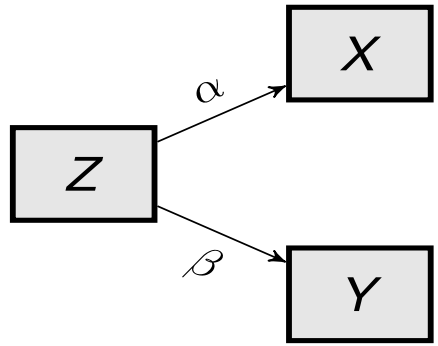
Pictorial representation

The Joint model approach



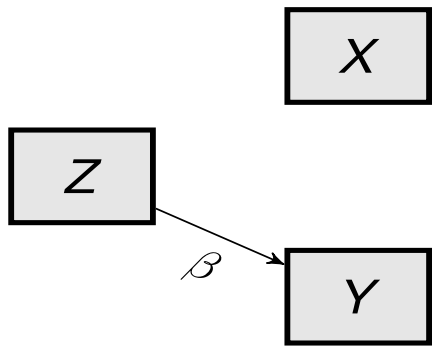
$$\rho = 0$$

The BVS approach



$$\phi_3 = 0$$

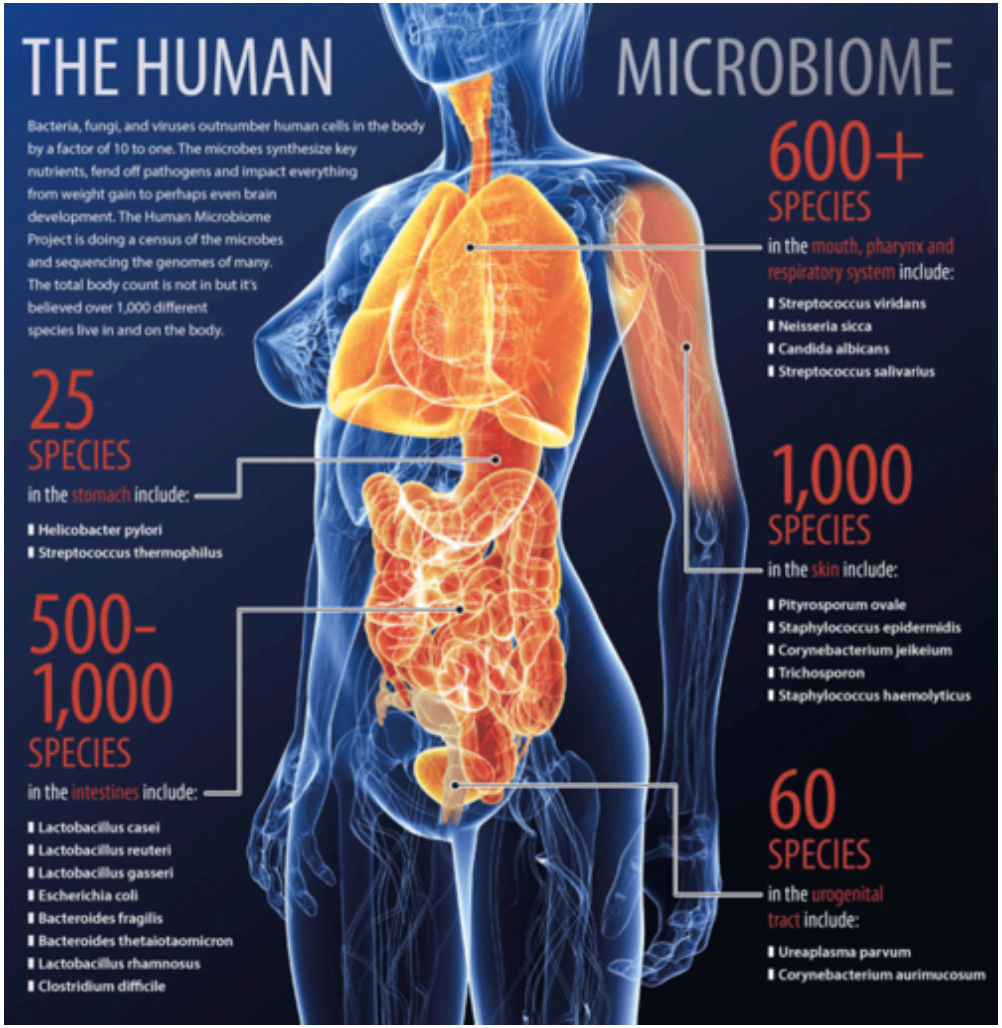
The information theory approach



$$R_h^2 = 0$$

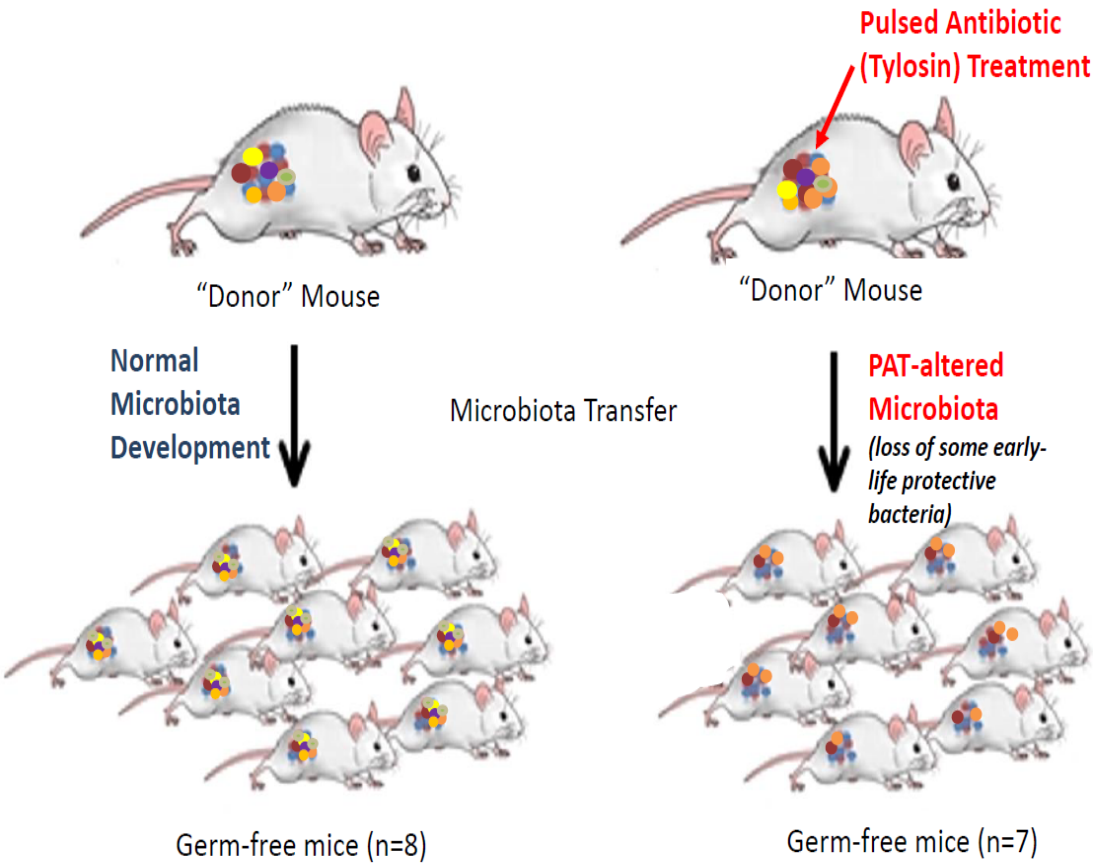
Part 3: The TRANSpat study

The Microbiome



- Composition : Homes billions form of bacteria.
- GUT: a major site for interactions between microbiome and the immune system
- Developmental features and operations of the immune system
- Stimulation of the immunoglobulin A
- The microbiota differs from one individual to another

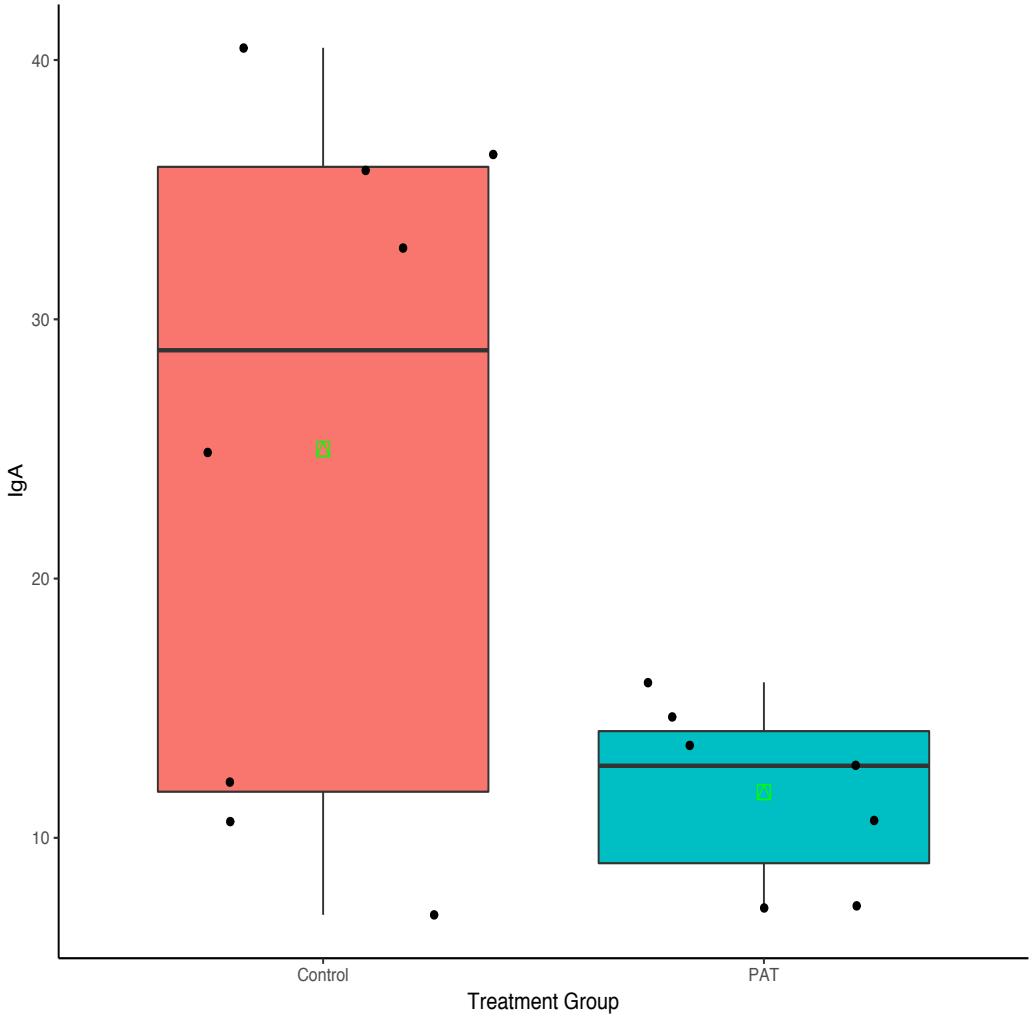
The transPAT study



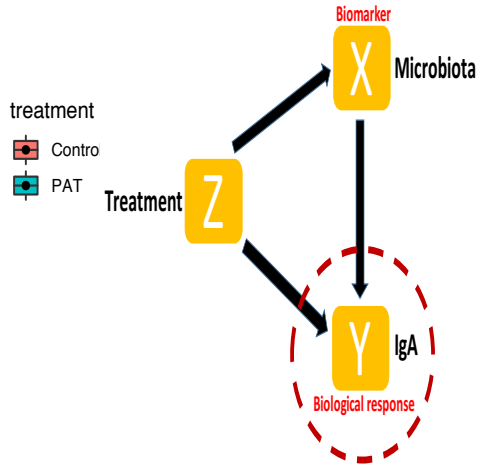
- Measurements:
  1. Microbiome Data
  2. Immunological Data

- Research question:
  Is the PAT altered Microbiota sufficient to alter Intestinal Immunity?

Immunological data

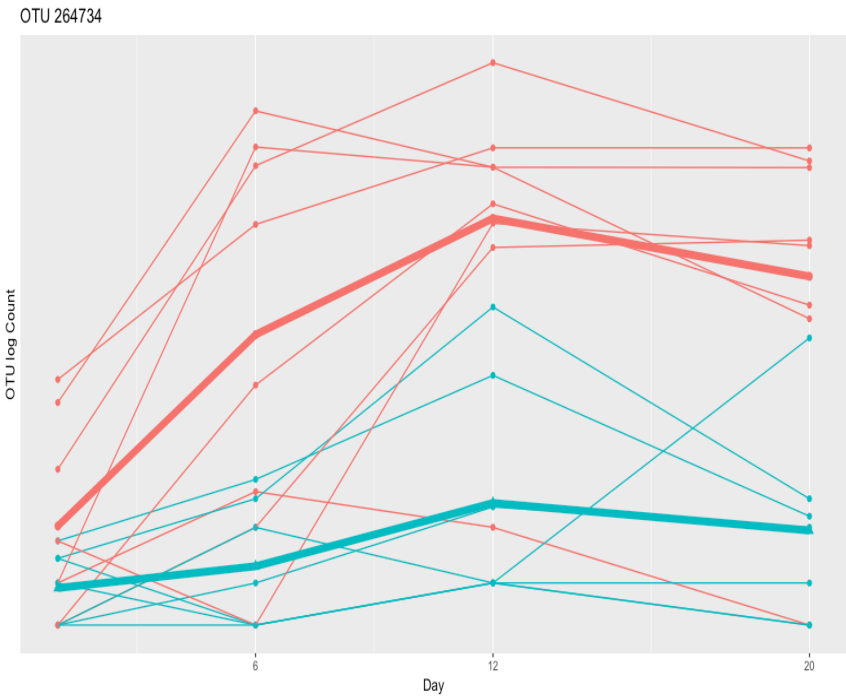


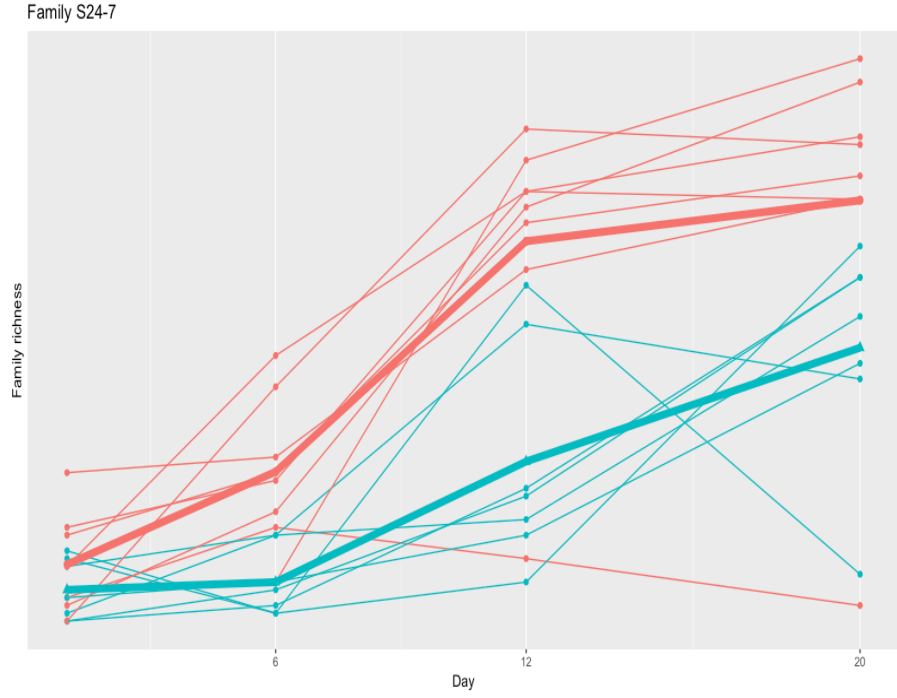
- Immunity: Measured by IgA level
- Analysis: Truncated at Day20



Microbiome data(1)

KINGDOM → PHYLUM → CLASS → ORDER → FAMILY → GENUS → SPECIES/OTU





OTU Level (OTU count)

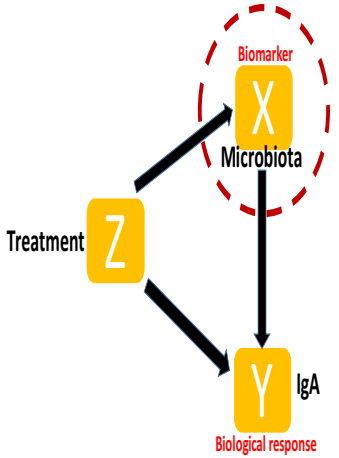
FAMILY Level (Richness)

Microbiome data(2)

$$
\underbrace{\begin{pmatrix}
x_{1,1} & x_{1,2} & \cdots & x_{1,8} & x_{1,9} & x_{1,10} & \cdots & x_{1,15} \\
x_{2,1} & x_{2,2} & \cdots & x_{2,8} & x_{2,9} & x_{2,10} & \cdots & x_{2,15} \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
x_{j,1} & x_{j,2} & \cdots & x_{j,8} & x_{j,9} & x_{j,10} & \cdots & x_{j,15} \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
x_{355,1} & x_{355,2} & \cdots & x_{355,8} & x_{355,9} & x_{355,10} & \cdots & x_{355,10}
\end{pmatrix}}_{\text{Control Group} \quad \text{PAT altered Group}}
$$

m = 355 OTUs

- Similar in structure to other omics data: gene expression data, metabolic data...



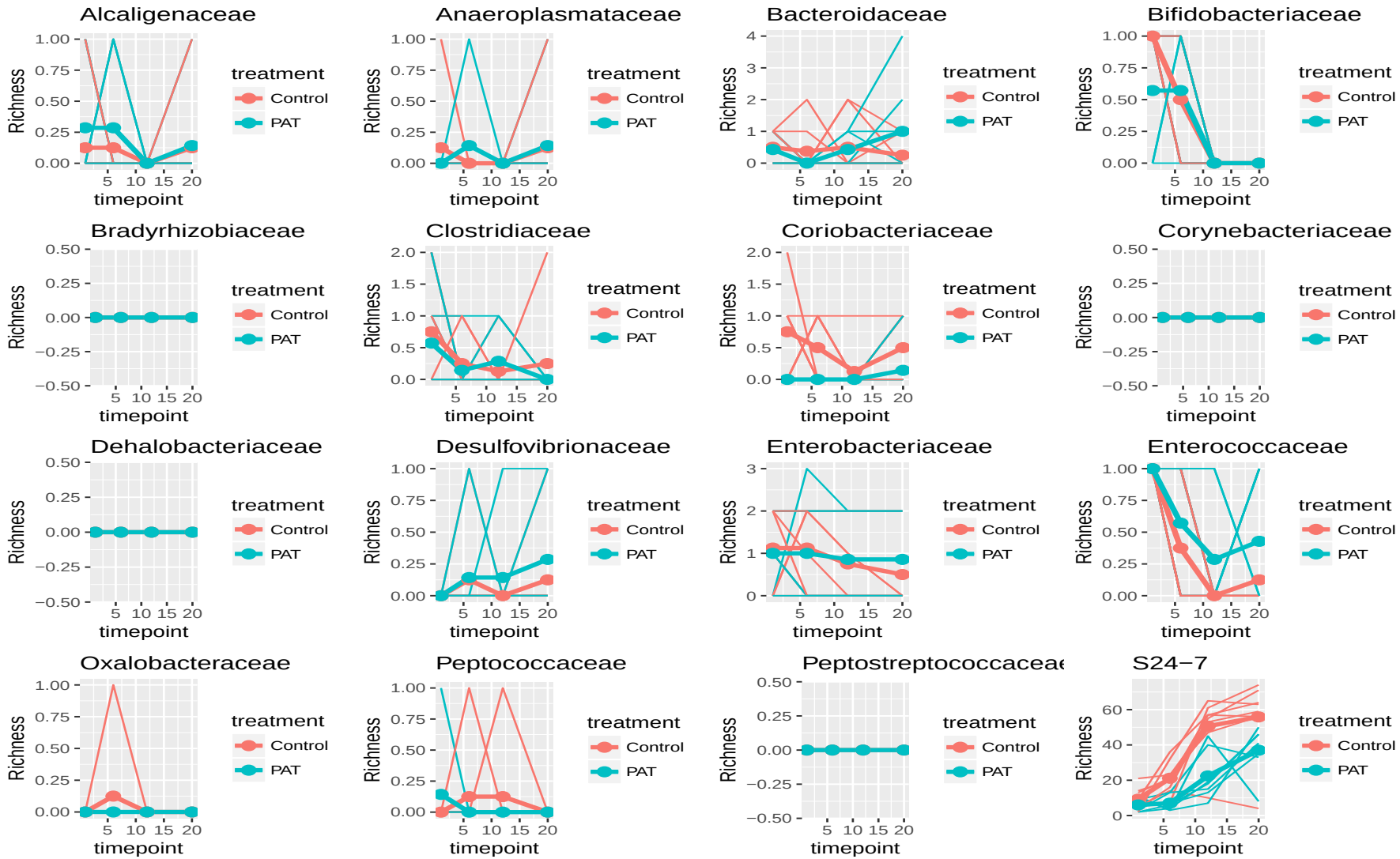
Data structure

- Repeated measurements at 4 time points
- 355 OTU's = 30 families
- A subject : Mouse
- Observation unit = $\{\boldsymbol{Z_i}, \boldsymbol{Y_i}, \boldsymbol{X_{ij}}\}$

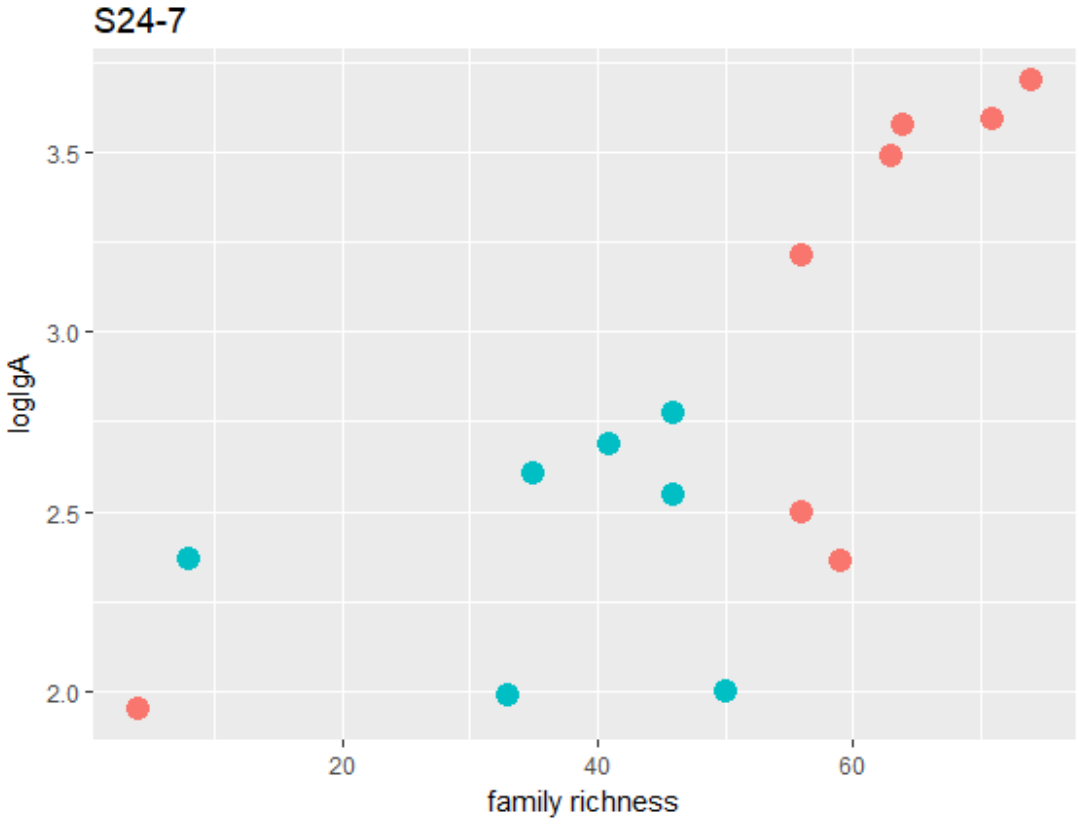
$$Y = \begin{bmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_{15} \end{bmatrix}, X = \begin{bmatrix} X_{1,1} & X_{1,2} & \cdots & X_{1,15} \\ X_{2,1} & X_{2,2} & \cdots & X_{2,15} \\ \vdots & \vdots & \vdots & \vdots \\ X_{30,1} & X_{30,2} & \cdots & X_{30,15} \end{bmatrix}, Z = \begin{bmatrix} Z_1 \\ Z_2 \\ \vdots \\ Z_{15} \end{bmatrix}$$

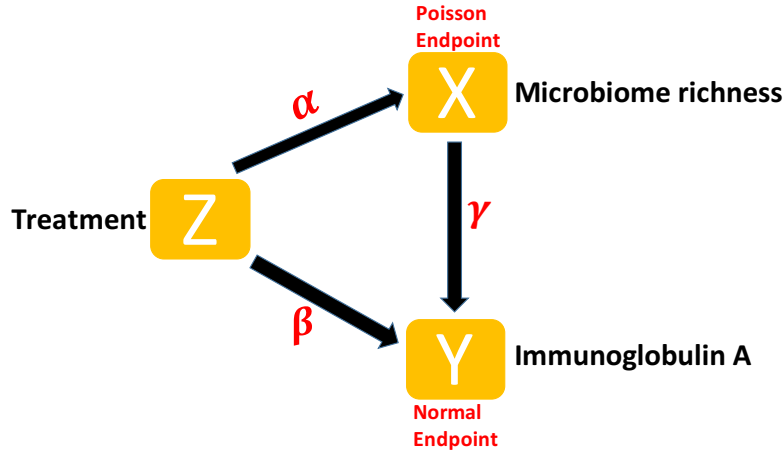
- Richness: Number of nonzero OTUs for a subject
- Family Level richness: Richness belonging to a particular family

Family richness over time



Family richness and IgA: S24-7



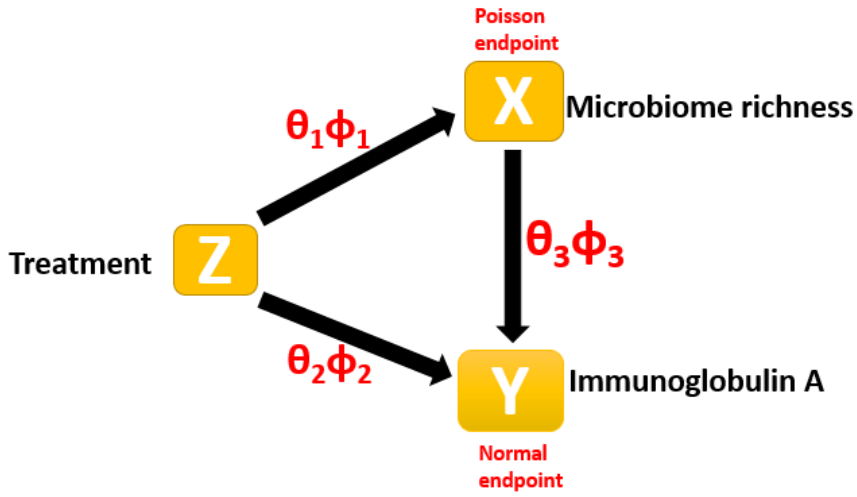


α = Treatment effect on the family richness
β = Treatment effect on the IgA
γ = Effect on the family richness on the IgA

Control group, PAT group

Part 4: Application to the TRANSpat data

Bayesian Variable Selection formulation



$X_i \sim Pois(\lambda_i)$
$log(\lambda_i) = \mu_x + \phi_1{}^*\theta_1 Z_i$

$Y_i \sim N(\mu_i, \tau)$
$\mu_i = \mu_y + \phi_2{}^*\theta_2 Z_i + \phi_3{}^*\theta_3 X_i$

$\alpha = \phi_1{}^*\theta_1$; ϕ_1=1 then $\alpha = \theta_1$
$\beta = \phi_2{}^*\theta_2$; ϕ_2=1 then $\beta = \theta_2$
$\gamma = \phi_3{}^*\theta_3$; ϕ_3=1 then $\gamma = \theta_3$

Priors specification

$\tau \sim Gamma(0.00001, 0.00001)$ $\quad$ $\mu_x, \mu_y, , \alpha, \beta, \gamma \sim N(0, 0.00001)$

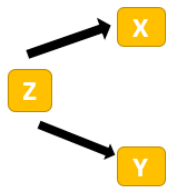
$\phi_i \sim B(\pi_i)$ and $\pi_i \sim U(0, 1)$

Models configuration

- The configuration of ϕ define uniquely the 8 models

For example:

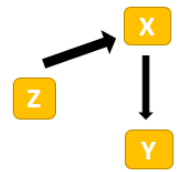
Model 6



$$\phi = \{1, 1, 0\}$$

$$\begin{pmatrix} \log(\lambda_i) \\ \mu_i \end{pmatrix} = \begin{pmatrix} \mu_X + \alpha Z_i \\ \\ \mu_Y + \beta Z_i \end{pmatrix}$$

Model 5



$$\phi = \{1, 0, 1\}$$

$$\begin{pmatrix} \log(\lambda_i) \\ \mu_i \end{pmatrix} = \begin{pmatrix} \mu_X + \alpha Z_i \\ \\ \mu_Y + \gamma X_i \end{pmatrix}$$

Design matrix for the indicators

- Matrix of indicator for the 8 models:

$$\Phi = \left\{ \begin{array}{ccc} \phi_1 & \phi_2 & \phi_3 \\ \hline 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \\ 0 & 1 & 1 \\ 1 & 1 & 1 \end{array} \right\}$$

- Unique identification of a model

$$C = \{1, 2, 4\}$$
$$T_r = 1 + \Phi C^T$$

Models' posterior probability

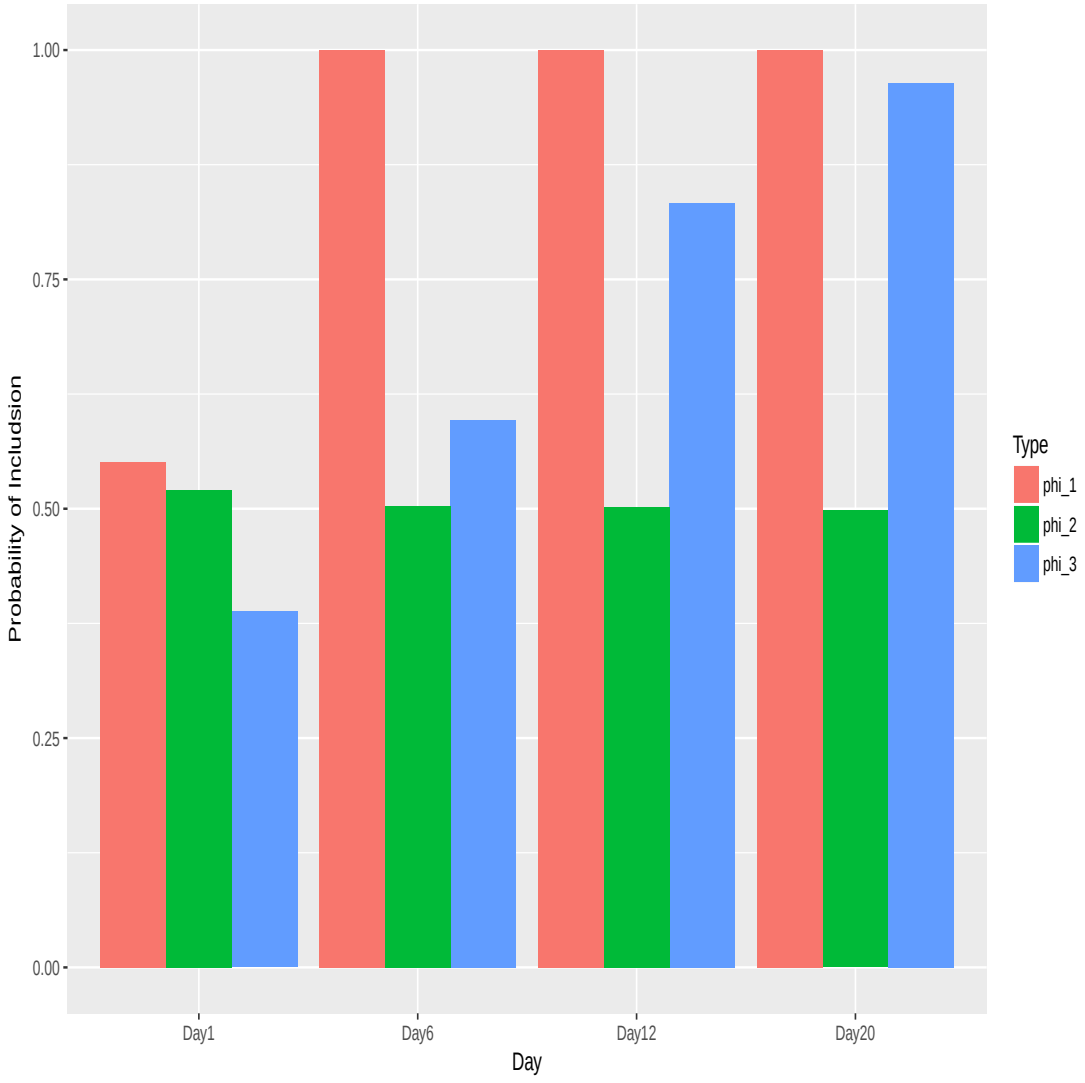
- Transformation rule for each model

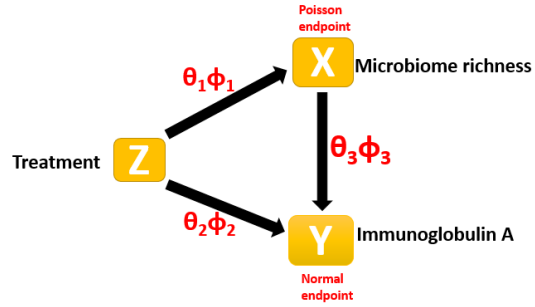
$$T_r = \begin{cases} 1, & \text{for } \phi = (\phi_1 = 0, \ \phi_2 = 0, \ \phi_3 = 0), & \text{model } m_1 \\ 2, & \text{for } \phi = (\phi_1 = 1, \ \phi_2 = 0, \ \phi_3 = 0), & \text{model } m_2 \\ 3, & \text{for } \phi = (\phi_1 = 0, \ \phi_2 = 1, \ \phi_3 = 0), & \text{model } m_3 \\ 5, & \text{for } \phi = (\phi_1 = 0, \ \phi_2 = 0, \ \phi_3 = 1), & \text{model } m_4 \\ 6, & \text{for } \phi = (\phi_1 = 1, \ \phi_2 = 0, \ \phi_3 = 1), & \text{model } m_5 \\ 4, & \text{for } \phi = (\phi_1 = 1, \ \phi_2 = 1, \ \phi_3 = 0), & \text{model } m_6 \\ 7, & \text{for } \phi = (\phi_1 = 0, \ \phi_2 = 1, \ \phi_3 = 1), & \text{model } m_7 \\ 8, & \text{for } \phi = (\phi_1 = 1, \ \phi_2 = 1, \ \phi_3 = 1), & \text{model } m_8 \end{cases}$$

- Posterior probability of transformation

$$p(m_4|\phi, \text{data}) = p(T_r = 5|\phi, \text{data})$$

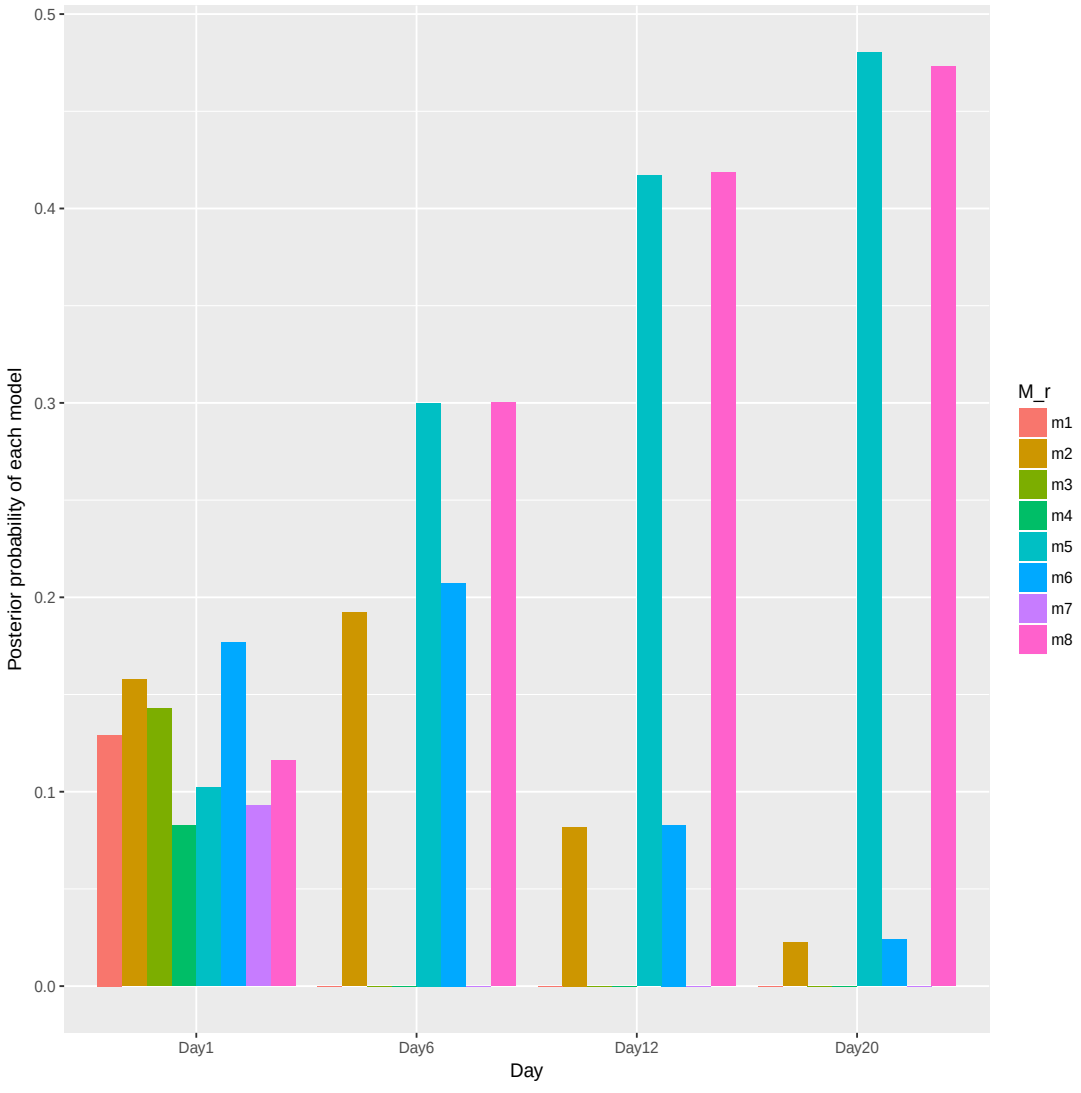
Inclusion probability (per day)

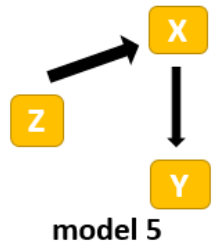




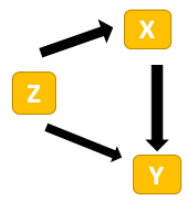
- $P(\phi_3 = 1|data)$ develops over time

Models' posterior probability (per day)



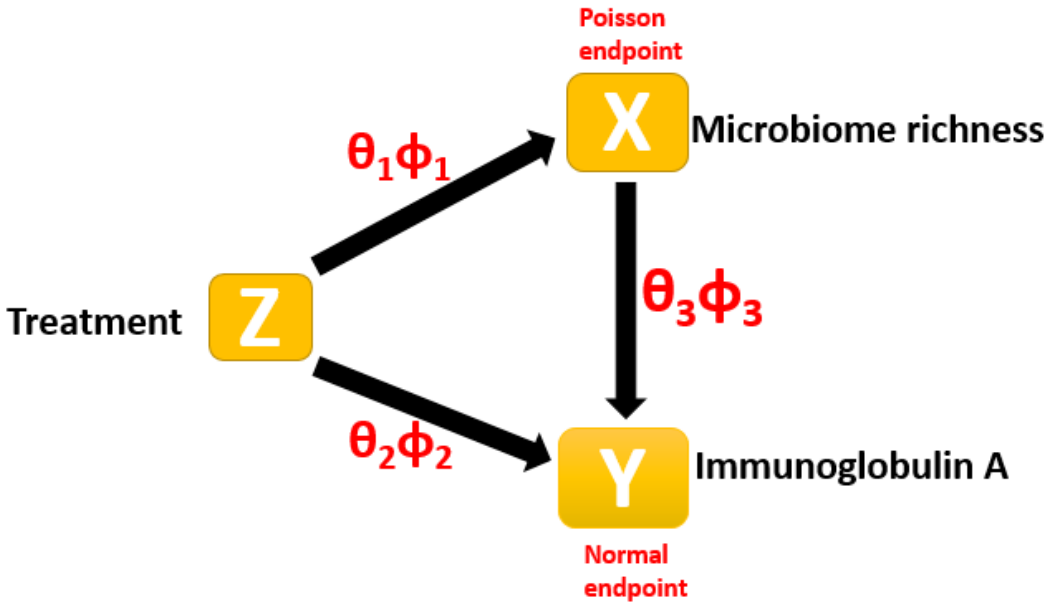


model 5



model 8

What is the probability for X to be a biomarker at day 20?



$$P(\phi_1 = 1|data) = P(m_2) + P(m_5) + P(m_6) + P(m_8) = 0.9996$$
$$P(\phi_2 = 1|data) = P(m_3) + P(m_6) + P(m_7) + P(m_8) = 0.5007$$

Probability that X is a biomarker

$$P(\phi_3 = 1|data) = P(m_4) + P(m_5) + P(m_7) + P(m_8) = 0.96045$$

Conclusion

- Bayesian extension of the JM for all type of distribution
- The probability of inclusion as a measure of surrogacy
- Richness as a biomarker was seen to be highly related to the IgA over time

Further research

- To take into account the longitudinal information
- Incorporate other features
- Testing the method on a better dataset (small sample and few active features)
- To develop credible interval for the measure
- Establish a connection between our method and the information criteria approach through simulation.