A Bayesian Model for the Validation of Magnetic Resonance Imaging (MRI) as a Surrogate Endpoint for a Clinical Endpoint

Leacky Muchene
Hasselt University
Research team

Academia

- Uhasselt
  - Leacky Muchene
  - Ziv Shkedy
- Uantwerpen
  - Jelle Praet
  - Marleen Verhoye
  - Annemie Vanderlinden

Industry

- Janssen
  - Luc Bijnens
  - Darrel Pemberton
  - Marc Schmidt
  - Others
- Icometrix
- Histogenix
- Open Analytics
- The MRI Consortium
Introduction

- Alzheimer disease: age-dependent, irreversible.
- Non-invasive screening tools desirable for early detection and management.
- Identification and validation of potential bio-markers crucial— a lot of ongoing research.
- Evaluate the use of Magnetic Resonance Imaging (MRI) as a surrogate for disease progression
MR Image acquisition

Images downloaded from: TREM, MR Solutions

Numeric values for different parameters
- Diffusion kurtosis imaging
  - Mean Kurtosis (MK)
  - Axial Kurtosis (AK)
  - Radial Kurtosis (RK)
- Diffusion tensor imaging
  - Mean Diffusivity (MD)
  - Axial Diffusivity (AD)
  - Radial Diffusivity (RD)
  - Fractional Anisotropy (FA)

Note: MRI can be acquired longitudinally
Different histology stains enable detection of different structures

Plague deposits are quantified
- % stained area
- Mean intensity

Numeric values for statistical analysis
- MBP staining
- GFAP staining
- Iba1 staining
- 4G8 staining

Note: Only one set of histology measurements per animal
Data

- Histology can only be acquired once per animal.
- Cross-sectional studies at 2, 4, 6 and 10 months with MRI and histology available.
- Longitudinal MRI study with histology at 8 months
- Resulting into 4 cross-sectional (multivariate) datasets
- 23 brain ROI, 7 MRI parameters, 4 histology parameters
- $23 \times 7 \times 4 = 664$ models
Evaluation of MRI as biomarker for histology

- Methodology: surrogate endpoints in clinical trials.
  - Histology: “true” endpoint.
  - MRI: “surrogate” endpoint.

- Can we use MRI as a surrogate to histology?
- Can we replace histology with MRI?
Illustration: Disease Effects

A covariate with 4 levels = 4 age groups.

Effect of level j compared to the reference group.

Correlation

Transgenic
Wildtype
Two-stage Surrogacy Model

Given a ‘True’ endpoint T and a surrogate endpoint S,

The two-stage model for surrogacy can generally be denoted as:

\[
\begin{align*}
\left( \begin{array}{c}
T_{ij} \\
S_{ij}
\end{array} \right) & \sim N \left( \begin{array}{c}
\mu_{Tj} + \alpha_j Z_i \\
\mu_{sj} + \beta_j Z_i
\end{array} \right), \Sigma_k \\
\left( \begin{array}{c}
\alpha_j \\
\beta_j
\end{array} \right) & \sim N \left( \begin{array}{c}
\bar{\alpha} \\
\bar{\beta}
\end{array} \right), D
\end{align*}
\]

Component for deriving individual-level surrogacy

Component for deriving trial-level surrogacy
For a given region in the brain, MRI parameter and histology stain

\[
T_{ij} = \mu_{T_j} + \alpha_j Z_i + \varepsilon_{T_{ij}}
\]

\[
S_{ij} = \mu_{S_j} + \beta_j Z_i + \varepsilon_{S_{ij}}
\]

\[
\begin{pmatrix}
\varepsilon_{T_{ij}} \\
\varepsilon_{S_{ij}}
\end{pmatrix}
\sim N\left(\begin{pmatrix}0 \\
0\end{pmatrix}, \Sigma_k\right), k = 1, 2
\]

**Transgenic**: \(\Sigma_1 = \begin{pmatrix}
\sigma^2_{\text{App, hist}} & \sigma_{\text{App, hist;mri}} \\
\sigma_{\text{App, hist;mri}} & \sigma^2_{\text{App, mri}}
\end{pmatrix}\)

**Wildtype**: \(\Sigma_2 = \begin{pmatrix}
\sigma^2_{\text{Wt, hist}} & \sigma_{\text{Wt, hist;mri}} \\
\sigma_{\text{Wt, hist;mri}} & \sigma^2_{\text{Wt, mri}}
\end{pmatrix}\)
Two Measures of Surrogacy

1: Individual-level surrogacy

\[ \Sigma_k \Rightarrow \rho(MRI, Hist.) \]

*Transgenic*: \( \rho_1 = \frac{\sigma_{App, hist,mri}}{\sqrt{\sigma_{App,mri}^2 \cdot \sigma_{App,hist}^2}} \)

*Wildtype*: \( \rho_2 = \frac{\sigma_{Wt, hist,mri}}{\sqrt{\sigma_{Wt,mri}^2 \cdot \sigma_{Wt,hist}^2}} \)

2: Disease-level surrogacy

- Correlation between the disease effects

\[ D \Rightarrow \rho(\alpha_j, \beta_j) \]

\[ \rho_D = \frac{\sigma_{\alpha,\beta}}{\sqrt{\sigma_{\alpha}^2 \cdot \sigma_{\beta}^2}} \]

- Predicting effects in histology by the effects in MRI
Bayesian Prior Specification

\[ \mu_{S_j} \sim \mathcal{N}(0.0, \tau_{SS}), \]
\[ \mu_{T_j} \sim \mathcal{N}(0.0, \tau_{TT}), \]
\[ \tau_{SS} \sim \text{Gamma}(0.001, 0.001), \]
\[ \tau_{TT} \sim \text{Gamma}(0.001, 0.001), \]
\[ \Sigma_1^{-1} \sim \text{Wishart}(R_W, \phi), \]
\[ \Sigma_2^{-1} \sim \text{Wishart}(R_A, \phi), \]
\[ \begin{pmatrix} \alpha_j \\ \beta_j \end{pmatrix} \sim \mathcal{N} \left( \left( \begin{array}{c} \bar{\mu}_S \\ \bar{\mu}_T \end{array} \right), D_{22} \right), \]
\[ D_{22}^{-1} \sim \text{Wishart}(R_{D_{22}}, \phi), \]
\[ \bar{\mu}_S \sim \mathcal{N}(0.0, 1.0E-6), \]
\[ \bar{\mu}_T \sim \mathcal{N}(0.0, 1.0E-6). \]
Example 1
Cortex Motor: MRI-AK with GFAP Staining
Cortex Motor: Observed Data (MRI-AK with GFAP)
**Results: Cortex Motor (MRI-AK with GFAP)**

- **MRI (AK) is a good biomarker for histology at disease-level**
- We can predict the effect in histology using the effect in MRI

- **Poor individual-level surrogacy**
- We cannot predict histology values from MRI values for an individual
Example 2
Cortex Motor: MRI-RD with GFAP Staining
Cortex Motor: Observed Data (MRI-RD with GFAP)

- **Graph Description:**
  - **Y-axis:** GFAP % staining
  - **X-axis:** RD
  - **Genotype:**
    - TRANSGENIC
    - WILDLTYPE
  - **Month:**
    - 2
    - 4
    - 6
    - 8
    - 10

- **Key Points:**
  - The graph shows the observed data for GFAP % staining across different RD values for both genotypes across various months.
Results: Cortex Motor (MRI-RD with GFAP)

- MRI (AK) is a **poor biomarker** for histology at **disease-level**
- We can **NOT** predict the effect in histology using the effect in MRI

**Poor individual-level surrogacy**
- We **cannot** predict histology values from MRI values for an individual
Conclusion

- MRI has potential to be a biomarker at disease level
- Surrogacy depends on MRI parameters, histology stain and brain region
- Assess model improvement at resolution higher than the ROI (unit level analysis)
- Evaluation of multivariate markers jointly?