A Hierarchical Mixed Effect Model for the Analysis of Longitudinal DCE-MRI Studies

Volker J. Schmid
Department of Statistics
Ludwig-Maximilians-University Munich

joint work with
Brandon Whitcher
Clinical Imaging Centre
GlaxoSmithKline, London, UK
• Introduction
• Quantitative analysis of DCE-MRI
• Standard analysis for longitudinal studies
• LoMIS model
• Breast cancer study
• Head and neck cancer study
• Extensions
• Dynamic Contrast-Enhanced Magnetic Resonance Imaging
• Usually a contrast agent (Gd-DTPA) is injected to enhance perfusion, \textit{i.e.}, the blood flow in tissue
• After injection several MR scans are acquired every 5-10 seconds
• In each voxel contrast concentration over time can be computed from the signal
• Quantitative analysis is achieved by fitting pharmacokinetic models to the concentration curves
• Cancerous tissue typically has increased perfusion
• Growth of vessels can be initiated from the tumor (angiogenesis)
• DCE-MRI allows to detect tumors, measure volume, diagnose cancer type, evaluate status of tumor
• Cancer treatment often targets angiogenesis (*inter alia*)
• Hence, success of treatment can be evaluated via DCE-MRI
• Longitudinal drug studies, reduction is perfusion as target
• Typically early phase 1, low patient numbers
[image removed]
Compartment model

Introduction

Standard analysis

LoMIS model

Breast cancer study

Head & neck cancer study

\[ C_t(t) = v_p C_p(t) + C_p(t) \otimes K^{\text{trans}} \exp(-k_{ep}t) \]
\[ C_t(t) = v_p C_p(t) + C_p(t) \otimes K^{\text{trans}} \exp(-k_{ep} t) \]

\( K^{\text{trans}} \): transfer rate between plasma space and EES, main target parameter

\( k_{ep} \): rate constant for transfer between EES and space

\( v_e = K^{\text{trans}} / k_{ep} \): volume of EES

\( v_p \): volume of plasma space

\( C_p \): Arterial input function (AIF), can be measured from large vessels in the field of view or given by literature
Non-linear regression

\[ C_t(t) = \nu_p C_p(t) + C_p(t) \otimes K^{\text{trans}} \exp(-k_{ep}t) \]

- Given a functional form of the AIF, we can use non-linear regression
- Least squares algorithms like Levenberg-Marquardt suffer from a couple of problems:
  - Convergence is not guaranteed
  - Choice of starting values is crucial
  - Estimates can be biological unrealistic \((K^{\text{trans}} > 10)\)
Bayesian non-linear regression

\[ C_t(t) = v_p C_p(t) + C_p(t) \otimes K_{trans} \exp(-k_{ep} t) \]

- As alternative we use a Bayesian approach:
  
  \[
  \log(K_{\text{trans}}) \sim N(0,1) \\
  \log(k_{ep}) \sim N(0,1) \\
  v_p \sim \text{Beta}(1,19)
  \]

- Estimation via MCMC
- Estimates are more robust, biological realistic
Ktrans parameter maps

Introduction
Standard analysis
LoMIS model
Breast cancer study
Head&neck cancer study

• Early phase 1 study of breast cancer patients
• 12 patients were scanned before treatment and two weeks after first treatment
• After the treatment six of these patients were identified as pathological responders, the others were nonresponders
• Regions of interest (ROIs) were drawn manually by an expert radiologist on a scan-by-scan basis
For each scan, an average time curve in the ROI was computed

A kinetic model was fitted to the averaged concentration

Change of \( K_{\text{trans}} \) values between pre treatment and post treatment scans is tested via Wald test

\[
p = 0.055
\]
Introduction

Standard analysis

LoMIS model

Breast cancer study

Head&neck cancer study

Idea of Longitudinal Medical Imaging Studies (LoMIS) model

- Model all curves in all tumor voxels of all scans simultaneously
- Incorporate information about patients and scans (pre/post) similar to a mixed effect model, i.e., decompose kinetic parameters in baseline, treatment, patient, interaction and voxel effect
- Hence, incorporate information about uncertainty in kinetic parameters
- Use posterior of treatment effect to test for success of treatment
- Use posterior of other effects to gain further insight
Breast cancer study
LoMIS model

\[ C_{t,\text{is}}(t) = \nu_{p,\text{is}}C_p(t) + K_{\text{is}}^{\text{trans}}C_p(t) \otimes \exp(-tk_{ep,\text{is}}) + e_{\text{tis}} \]

\[ \log(K_{\text{is}}^{\text{trans}}) = \alpha^T z + \beta x_s + \gamma_i + \delta_i x_s + \epsilon_{\text{is}} \]

\[ \log(k_{ep}) = \tilde{\alpha}^T z + \tilde{\beta} x_s + \tilde{\gamma}_i + \tilde{\delta}_i x_s + \tilde{\epsilon}_{\text{is}} \]

\[ \nu_p \sim \text{Beta}(1,19), e_{\text{tis}} \sim N(0, \sigma_s^2), \sigma_s^2 \sim \text{IG}(1,10^{-2}) \]

\[ p(\alpha) = p(\beta) \propto \text{const.} \]

\[ \gamma_i, \delta_i \sim \text{IG}(1,1), \epsilon_{\text{is}} \sim \text{IG}(1,10^{-5}) \]
Breast cancer study
Treatment effect

[p = 0.001]
[image removed]
Breast cancer study
K\textsubscript{trans} per voxel

Introduction
Standard analysis
LoMIS model
Breast cancer study
Head&neck cancer study
• Nine patients with tumor in head or neck area
• Two sites (Royal Marsden Hospital, London, Vall d’Hebron University Hospital, Barcelona) with different scanners
• Placebo (n=6) and treatment (n=3) group
• Vessels were present in images and a population AIF was computed
• Regions of interest were drawn by an expert radiologist
p = 0.30

Whitcher, Schmid, Collins, Orton, Koh et al., MRI 2010 (accepted)
Head and Neck Cancer study
LoMIS results 3

Introduction
Standard analysis
LoMIS model
Breast cancer study
Head&neck cancer study

V.J. Schmid: Hierachical MEM for longitudinal DCE-MRI studies
Luebeck, 3.12.2009
Head and Neck Cancer study
LoMIS results 4

[head and neck cancer study]

LoMIS:

Introduction
Standard analysis
LoMIS model
Breast cancer study
Head&neck cancer study

V.J. Schmid: Hierachical MEM for longitudinal DCE-MRI studies
Luebeck, 3.12.2009

# 25
• Update of mixed effects is easy (multivariate Gaussian)
• Update of voxel effects is ugly, similar to update of \( \log(K_{\text{trans}}) \) and \( \log(k_{\text{ep}}) \)

\[
p(\theta | .) \propto \exp\left( -c_1 \theta^2 - c_2 \exp(c_3 \theta^2) + c_4 \exp(c_5 \theta) \right)
\]

• Lot of data:
  • 1000 – 10000 voxel per scan
  • 40 – 50 time points per scan
  • \( \sim 1 – 2 \) million data points
• Two pre treatment scans (typically used to evaluate reliability)
• Two or more post treatment scans, gain time line for treatment effect
• Use clinical covariates or genetic expression
• Extensions can easily be included into the mixed effect model
• Use model on other imaging modalities
• DCE-MRI can be used to evaluate treatment success
• Scans are expensive, patient numbers are small
• Standard analysis neglects information given on voxel level
• Mixed effect models can be used to evaluate treatment effect
• We propose to model all concentration curves in all voxels of all scans simultaneously
• Treatment effect can be tested from posterior – power of test is higher
• We gain further insight in patient/treatment interaction and can account for covariates
• Brandon Whitcher, Clinical Imaging Centre, GSK
• Guang-Zhong Yang, Institute of Biomedical Engineering, Imperial College London, UK
• Anwar Padhani, Jane Taylor, Mt Vernon Hospital, Northwood, UK
• David Collins, Matt Orton, Dow-Mu Koh, Institute of Cancer Research UK
• Teams at Royal Marsden Hospital and Vall d’Hebron University Hospital
• BioMed-S: Analysis and modelling of complex systems in biology and medicine (part of the LMUinnovativ initiative)


*Thank you for your attention!*