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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

Outline

- Introduction
- Quantitative analysis of DCE-MRI
- Standard analysis for longitudinal studies
- LoMIS model
- Breast cancer study
- Head and neck cancer study
- Extensions

DCE-MRI

- Dynamic Contrast-Enhanced Magnetic Resonance Imaging
- Usually a contrast agent (Gd-DTPA) is injected to enhance perfusion, *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

DCE-MRI in oncology

- 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

Data example

[image removed]

Data example

[image removed]

Compartment model

[image removed]

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

Kinetic model & parameters

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

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

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

$v_e = K^{trans} / k_{ep}$: 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

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

- 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 ($K^{trans} > 10$)

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:

$$\log(K^{trans}) \sim N(0,1)$$

$$\log(k_{ep}) \sim N(0,1)$$

$$v_p \sim \text{Beta}(1,19)$$

- Estimation via MCMC
- Estimates are more robust, biological realistic

[image removed]

Schmid, Whitcher, Padhani, Taylor, Yang, IEEE TMI (2006), 25:12, 1627-1636

Breast cancer study
Data

- 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

Breast cancer study
Standard analysis

- For each scan, an average time curve in the ROI was computed
- A kinetic model was fitted to the averaged concentration
- Change of K^{trans} values between pre treatment and post treatment scans is tested via Wald test

p = 0.055

Patient	Pre	Post
1	0.208	0.161
2	0.355	0.120
3	0.255	0.031
4	0.230	0.245
5	0.199	0.208
6	0.154	0.173
7	0.264	0.327
8	0.198	0.223
9	0.305	0.122
10	0.267	0.221
11	0.432	0.111
12	0.174	0.113

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

[image removed]

Schmid, Whitcher, Padhani, Taylor, Yang, MRM (2009), 61, 163-174

$$C_{t,is}(t) = v_{p,is} C_p(t) + K_{is}^{trans} C_p(t) \otimes \exp(-tk_{ep,is}) + e_{tis}$$

$$\log(K_{is}^{trans}) = \alpha^T z + \beta x_s + \gamma_i + \delta_i x_s + \varepsilon_{is}$$

$$\log(k_{ep}) = \tilde{\alpha}^T z + \tilde{\beta} x_s + \tilde{\gamma}_i + \tilde{\delta}_i x_s + \tilde{\varepsilon}_{is}$$

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

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

$$\gamma_i, \delta_i \sim \text{IG}(1,1), \varepsilon_{is} \sim \text{IG}(1,10^{-5})$$

Breast cancer study
Treatment effect

[image removed]

p = 0.001

Breast cancer study
Patient/interaction effect

[image removed]

Breast cancer study
K^{trans} per voxel

[image removed]

Head and 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

Head and Neck cancer study
K^{trans} map

[image removed]

Head and Neck Cancer study
LoMIS results 1

p = 0.30

[image removed]

Whitcher, Schmid, Collins, Orton, Koh *et al*., MRI 2010 (accepted)

Head and Neck Cancer study
LoMIS results 2

[image removed]

Head and Neck Cancer study
LoMIS results 3

[image removed]

Head and Neck Cancer study
LoMIS results 4

[image removed]

- Update of mixed effects is easy (multivariate Gaussian)
- Update of voxel effects is ugly, similar to update of log(K^{trans}) and log(k_{ep})

$$p(\theta \mid .) \propto \exp\left(-c_1\theta^2 - c_2 \exp(c_3\theta^2) + c_4 \exp(c_5\theta)\right)$$

- Lot of data:
  - 1000 – 10000 voxel per scan
  - 40 – 50 time points per scan
  - ~ 1 – 2 million data points

Extensions

- 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

Conclusions

- 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

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Thank you for your attention!