Longitudinal Model-Based Meta-Analysis (MBMA) for rheumatoid arthritis with Monolix

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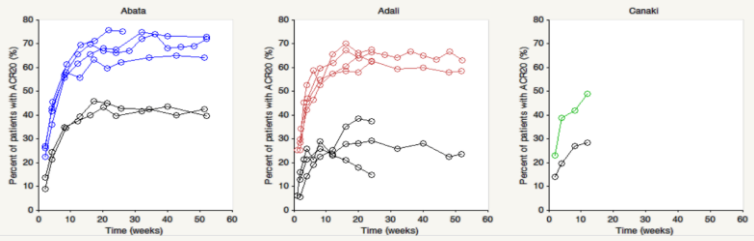
Introduction

MBMA uses published aggregate data from many studies to develop a study-level model and support the decision process.
The problem can be formulated as non-linear mixed effect model with a between study variability (BSV, equivalent to IIV), between treatment arm variability (BTAV, equivalent to IOV) and a residual error. The BTAV and residual error must be weighted by the number of individuals per arm.

How to implement a MBMA model in Monolix?

We propose a case study inspired from Demin et al. (2012), focusing on the drug Canakinumab, a candidate for rheumatoid arthritis (RA). As surrogate for efficacy we use the ACR20, the percentage of patients achieving 20% improvement.

Does Canakinumab has a chance to be more efficacious than Adalimumab and Abatacept, which are already on the market?



Model formulation

To model the ARC20 (in [0,100]), we propose an Emax model:

$$\begin{cases} \text{logit}(y_{ijk}) = \text{logit}\left(\text{Emax}_{ik}\dfrac{t}{t+\text{T50}_{ik}}\right) + \varepsilon_{ijk} \quad \text{res. error} \\ \text{logit}(\text{Emax}_{ik}) = \text{logit}(\text{Emax}_{\text{pop},d}) + \eta_i^0 + \eta_{ik}^1 \\ \log(\text{T50}_{ik}) = \log(\text{T50}_{\text{pop},d}) \end{cases} \qquad \begin{array}{l} \varepsilon_{ijk} \sim \mathcal{N}\left(0, \dfrac{\sigma^2}{N_{ik}}\right) \\ \eta_i^0 \sim \mathcal{N}(0, \omega^2) \\ \eta_i^1 \sim \mathcal{N}\left(0, \dfrac{\gamma^2}{N_{ik}}\right) \end{array}$$

BSV: η_i^0 — BTAV: η_{ik}^1

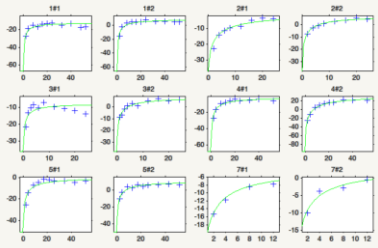
with i = study, j = time, k = treatment arm, d = drug

- observations in the data set and predictions in the model must be transformed due to weightening of residual error by N_{ik}
- parameters with BSV/BTAV must be decomposed into the fixed effect, the BSV and the BTAV term and reformed in the model file, to take into account the weightening of BTAV by N_{ik}

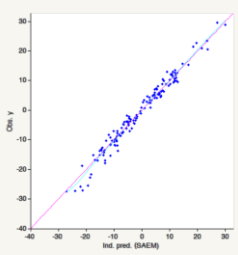
```
[LONGITUDINAL]
input = {EmaxFE, T50, etaBSVEmax, etaBTAVEmax, Narm}
Narm = {use=regressor}

EQUATION:
tEmax = logit(EmaxFE)
tEmaxRE = tEmax + etaBSVEmax + etaBTAVEmax/sqrt(Narm)
EmaxRE = 1 / (1+ exp(-tEmaxRE) )

ACR20 = EmaxRE * (t / (T50 + t))
pred = logit(ACR20)*sqrt(Narm)

OUTPUT:
output = pred
```

Model results

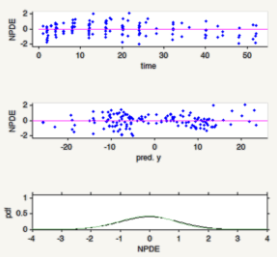
The model properly captures the study-level data of the ACR20 for the three drugs.



Individuals fits



Obs. vs Pred.



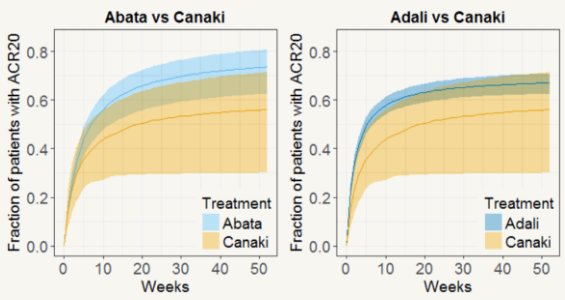
Residuals (NPDE)

The estimated parameter values and RSE are:

	parameter	s.e. (lin)	r.s.e.(%)	p-value
EmaxFE_pop	0.386	0.034	9	
beta_EmaxFE_tDRUG_abata	1.85	0.17	9	< 1e-010
beta_EmaxFE_tDRUG_adali	1.34	0.18	13	< 1e-010
beta_EmaxFE_tDRUG_canaki	0.94	0.62	66	0.13
T50_pop	3.55	0.45	13	
beta_T50_tDRUG_abata	0.187	0.14	76	0.19
beta_T50_tDRUG_adali	-0.569	0.17	30	0.00071
beta_T50_tDRUG_canaki	-0.351	0.65	186	0.59
etaBSVEmax_pop	0	-	-	
etaBTAVEmax_pop	0	-	-	
omega_EmaxFE	0	-	-	
omega_T50	0	-	-	
omega_etaBSVEmax	0.268	0.095	35	
omega_etaBTAVEmax	0	-	-	
gamma_EmaxFE	0	-	-	
gamma_T50	0	-	-	
gamma_etaBSVEmax	0	-	-	
gamma_etaBTAVEmax	2.24	1.1	51	
a	2.45	0.15	6	

Simulations for decision support

We compare the true efficacy (over an infinitely large population - BSV, BTAV and residual error were removed) of Canaki versus Abata and Adali, taking into account the uncertainty of population parameters.



At week 52, there are 5.8% chances that Canaki is better than Abata and 15.6% chances it is better than Adali.

```
NbStudy <- 1000
paramWithUncertainty <- simpopmlx(n=4*NbStudy, project='./project.mlxtran')
out <- list(name='ACR20',time=seq(0,52,by=1))
cov <- data.frame(id=1:(4*NbStudy),
                  tDRUG=rep(c('abata','adali','canaki','placebo'),each=NbStudy))
res <- simulx(model=myModel,
              parameter=list(cov,paramWithUncertainty),
              output = out)
```

Available online

- full case study with downloadable material
- guidelines to implement your own MBMA model