# Detection of Immunogenicity and Unbiased Estimation of Model Parameters for Monoclonal Antibodies

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## OBJECTIVES

To propose and evaluate methods for detection of immunogenic increase of elimination using concentration-time data and for unbiased estimation of model parameters in the presence of immunogenicity.

## METHODS

**Simulated Data:**

- 1000 subjects
- Model with parallel lineal and Michaelis-Menten elimination; parameters typical for monoclonal antibodies; CV=20% variability on all model parameters; CV=20% residual variability;
- Six 4-week dosing cycles with 2 additional loading doses at days 8 and 15;
- Dense sampling at cycles 1 and 6; pre-dose and post-dose samples at Cycles 2-5;
- 30% subjects with strong immunogenic increase in clearance.

**Immunogenicity Model:**

a) 5-fold increase of clearance following (randomly chosen) doses 3 to 6;
b) 5-fold increase of clearance described by a stiff sigmoid function; inter-subject variability on the magnitude of the increase and time of the onset;

**Detection of immunogenic response:**

- Naïve model without account for immunogenicity but with inter-subject variability on the magnitude of the residual error fitted to the simulated data;
- High magnitude of the residual error ($\eta_\varepsilon > 0$) was assumed to be caused by immunogenicity.

**Estimation of population PK parameters:**

Model 1: Subjects with detected immunogenic response ($\eta_\varepsilon > 0$) were excluded from the dataset;

Model 2a: Mixture model with 5 subpopulations (no immunogenicity or increase in clearance following dose 3, 4, 5, or 6, respectively) fitted to the simulated data;

Model 2b: Mixture model with 2 subpopulations (no immunogenicity or increase in clearance described by the stiff sigmoid function) fitted to the simulated data;

- Parameter estimates of Models 1, 2a, and 2b were compared with the true (simulated) values;
- Ability of each method to identify subjects with immunogenicity was evaluated.

## RESULTS

- The parameter estimates of the model that did not account for immunogenic increase of clearance were significantly biased and the estimates of the inter-individual variability in clearance were greatly inflated;
- Introduction of the random effect on the residual error ($\eta_\varepsilon$) reduced, but not eliminated bias;
- Immunogenic subjects were identified by high magnitude of the residual error;
- When subjects with high residual error were removed from the datasets, bias due to unaccounted immunogenic increase of clearance was eliminated. At the same time, the variance of $\eta_\varepsilon$ decreased to zero indicating that $\eta_\varepsilon$ indeed accounted for immunogenicity;
- Mixture models 2a and 2b provided unbiased estimates of the true parameters. Simulated immunogenic subjects were correctly assigned to the appropriate subpopulations. Thus, the estimates of the mixture model can be used to identify onset and magnitude of immunogenic increase of clearance.

**Figure 1.** Simulated data (circles) and individual predictions (solid lines) for representative subjects from each of Model 2a sub-populations. Blue vertical line: immunogenicity onset

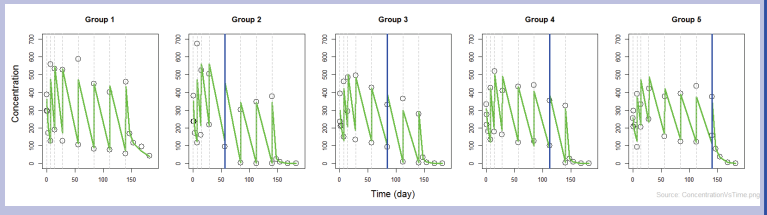
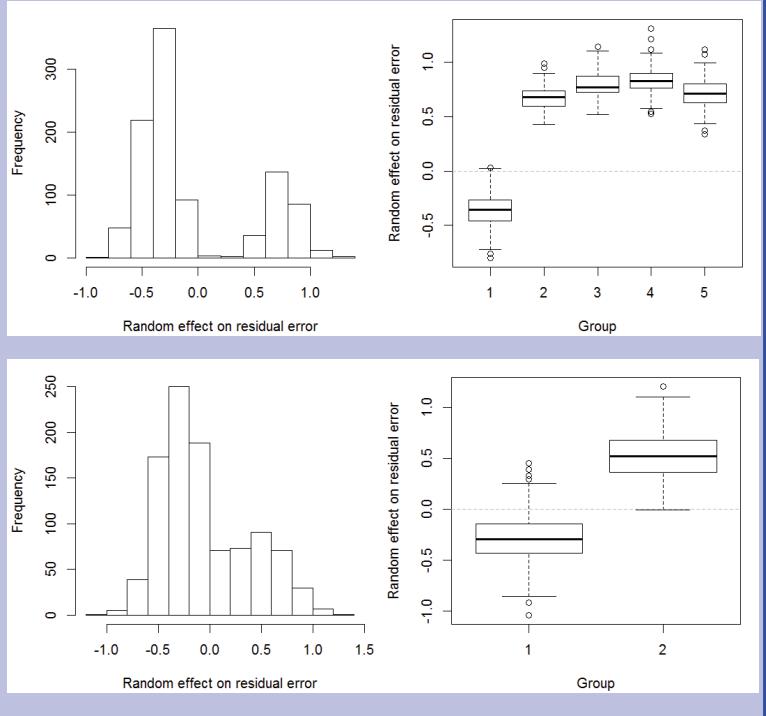



**Figure 2.** Distribution of the individual values of the random effect on residual error $\eta_\varepsilon$ for a naïve model that does not account for immunogenicity. **Left**: histogram; bi-modal distribution is noticeable. **Right**: distribution of $\eta_\varepsilon$ by sub-populations; all subjects with immunogenicity have $\eta_\varepsilon > 0$.
**Top row**: Immunogenicity model (a); **bottom row**: Immunogenicity model (b)




## DISCUSSION AND CONCLUSIONS

- For the simulated datasets with rich sampling, the proposed methods identified subjects with immunogenic increase of clearance, provided unbiased individual estimates of onset time and magnitude of immunogenicity, and unbiased estimates of the population parameters;
- The proposed methods offer the approach to evaluate and describe influence of immunogenicity on the population PK parameters of monoclonal antibodies;
- This work should be viewed as proof-of-concept investigation as it was applied in nearly perfect simulated conditions, with rich sampling before and after onset of immunogenic reaction;
- Application to the real data will likely face more difficulties. However, the proposed methods provide useful tools for detection and evaluation of changes in the PK parameters related to immunogenicity.

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