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A comparison of performance between parametric and nonparametric estimation for nonlinear mixed-effects models

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Questions

- For real data examples with models developed based on parametric methods, can nonparametric estimation offer
  - better description of data?
  - better prediction of new data?

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Estimation methods

- Parametric (P): FOCE(I)/Laplace in NONMEM
  - –But models also evaluated with Importance sampling
- Nonparametric (NP): $NONP in NONMEM
  - –But models also estimated with the extended grid method

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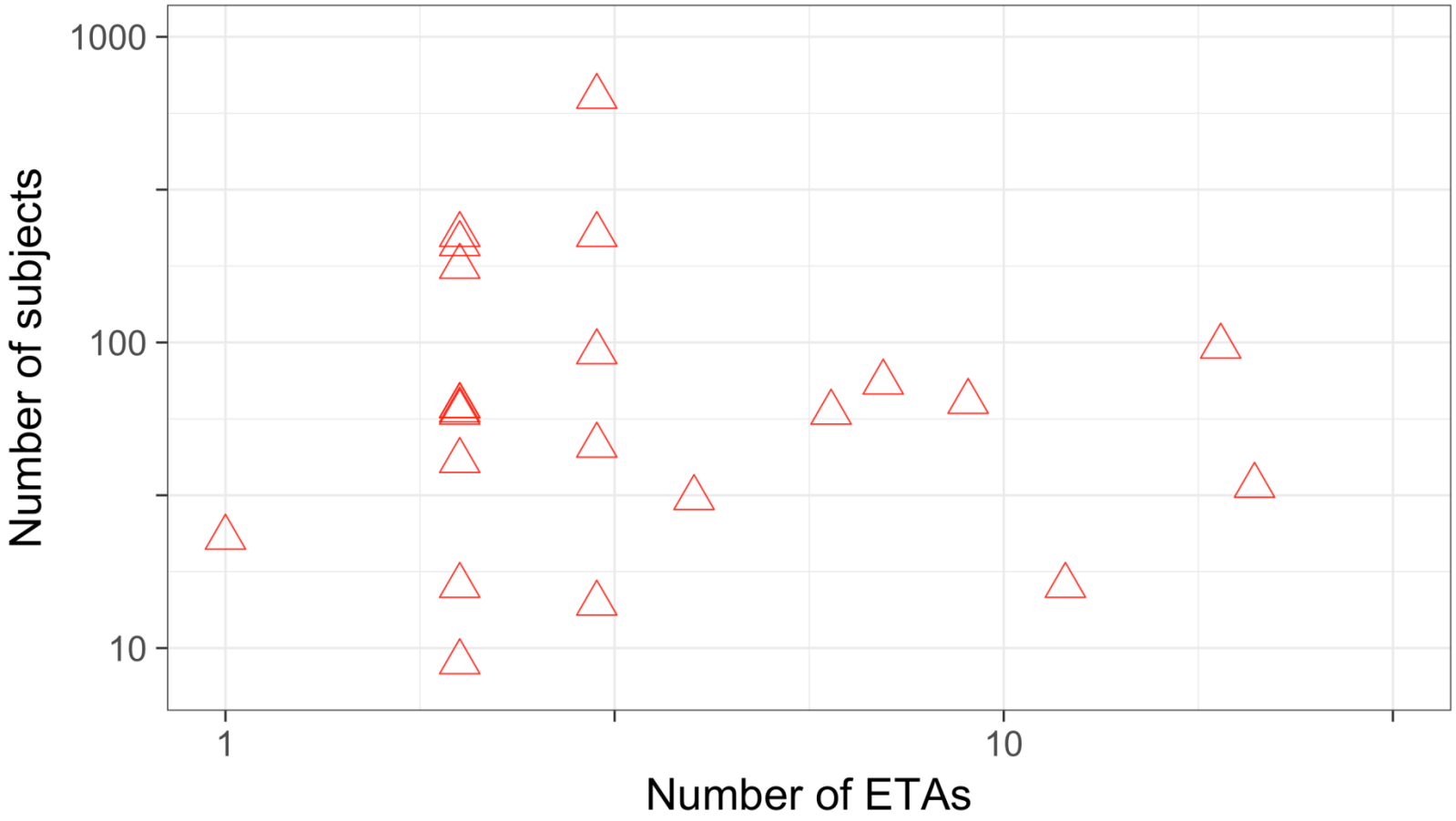
Models and data

- PK (n=16) and PD (n=7) model based on real data



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Comparisons – description of data

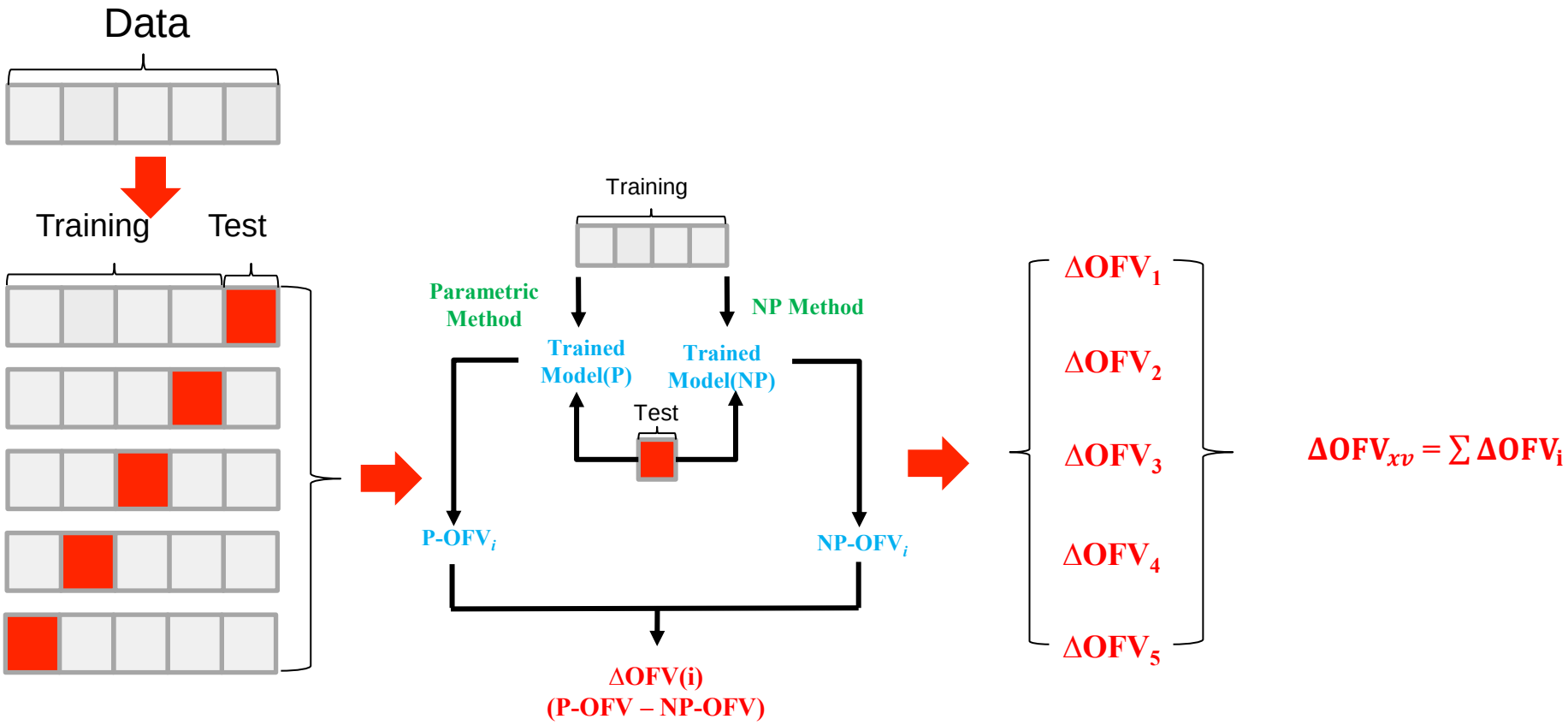
- **ΔOFV(P-NP)**

- **ΔAIC** = ΔOFV(P-NP) + 2·Δ#parameters(P-NP)
  - #parameters(P) = 2·#etas + #covariance terms
  - #parameters(NP) = (#support points)·(#etas+1)-1

- ΔOFV(P-NP) vs reference distribution for ΔOFV(P-NP) when simulating from parametric models and refit with P & NP

Comparisons – prediction of new data

- ΔXVOFV (Cross-validated OFV)
  - –2-fold & 5-fold cross-validation



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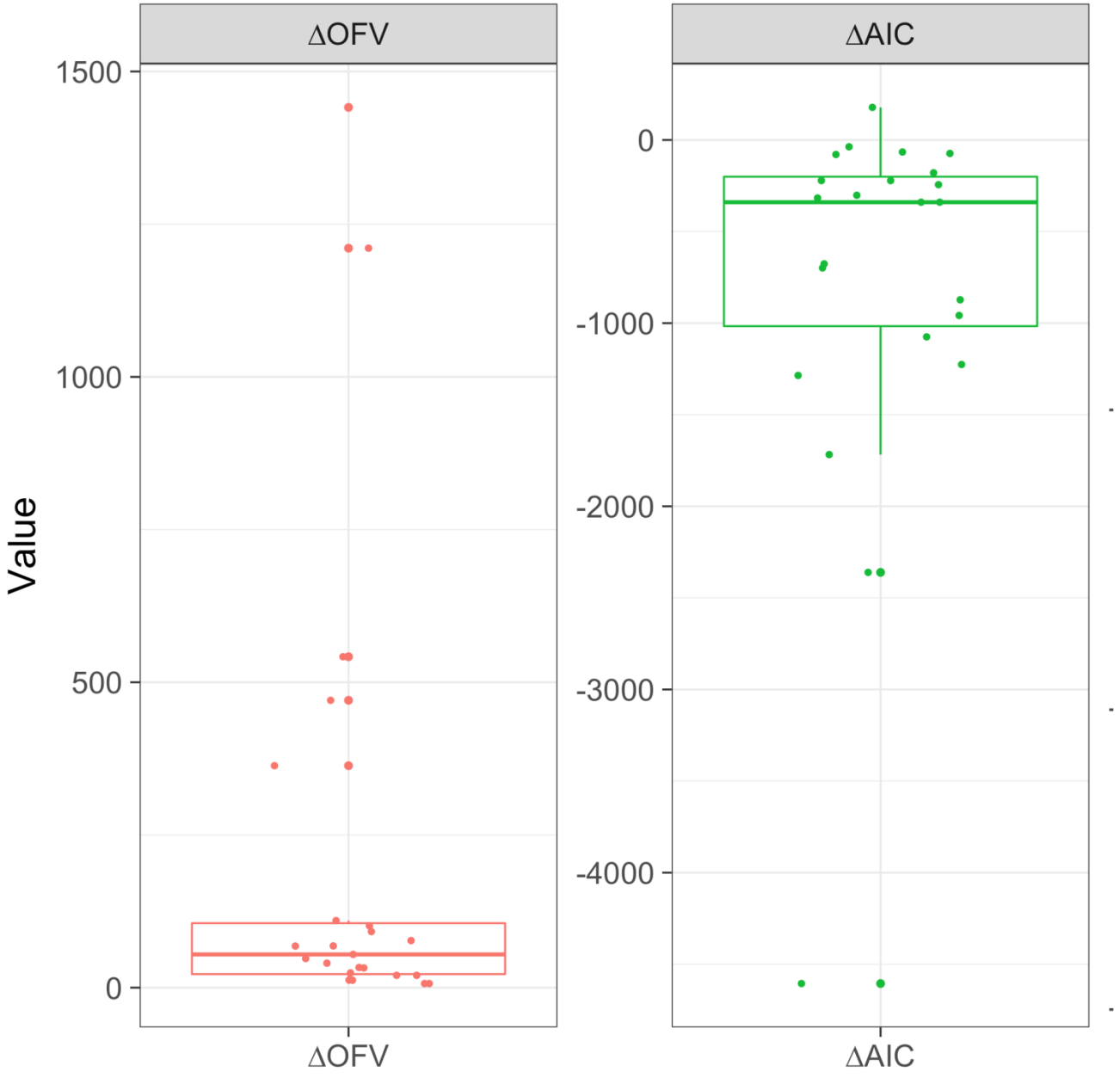
Why compare based on OFV?

- Why not compare prediction error of concentrations/effects?
  - –OFV incorporates this, but also accounts for:
    - Heteroscedasticity in residual error magnitude
    - Correlation among observations within individuals
  - –Not unambigous what ”a” prediction is with NP distribution, OFV is calculated taking the full NP distribution into account


ΔOFV
ΔAIC
Value
1500
1000
500
0
0
-1000
-2000
-3000
-4000
ΔOFV
ΔAIC

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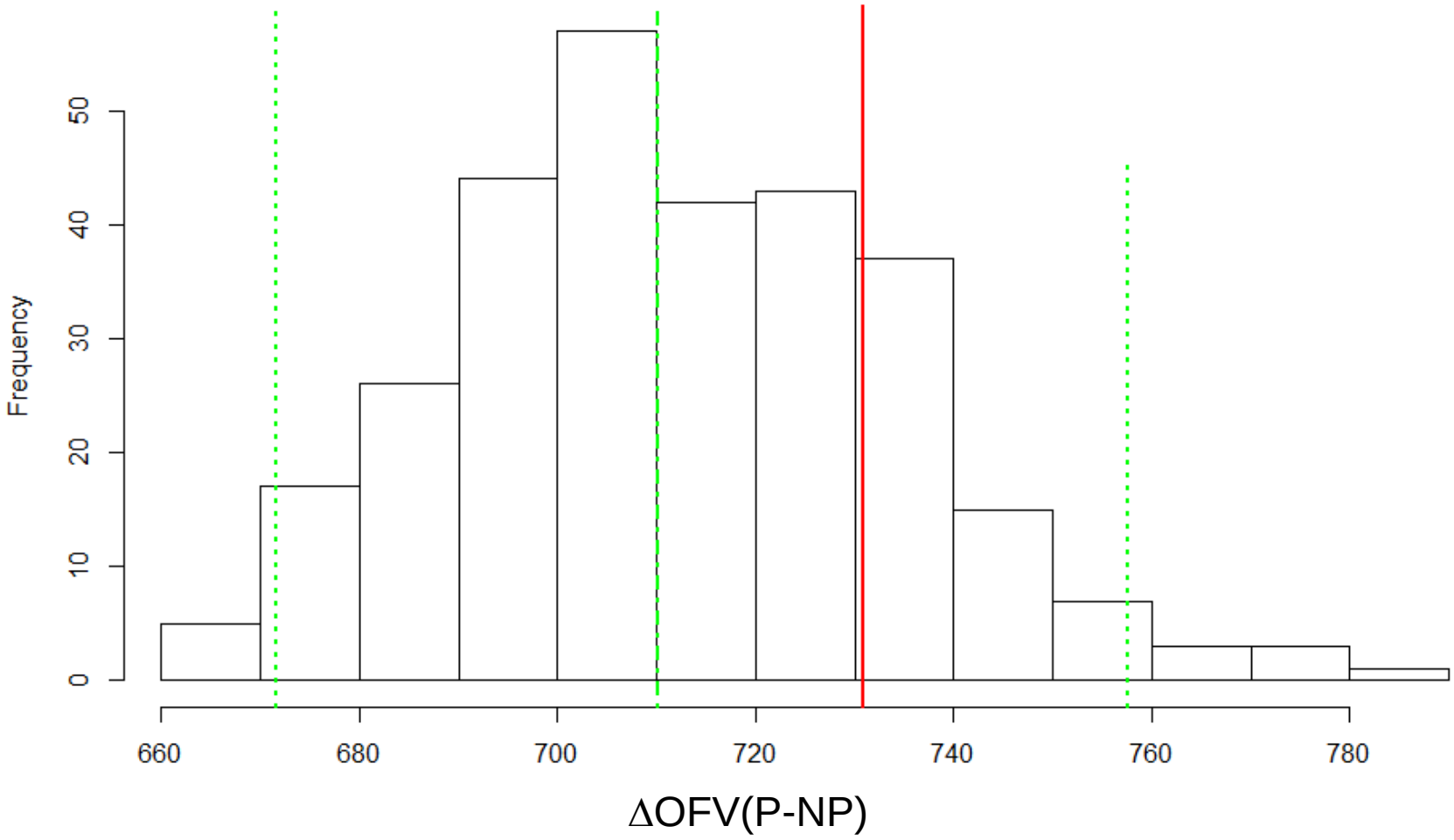
ΔOFV(P-NP) reference distribution



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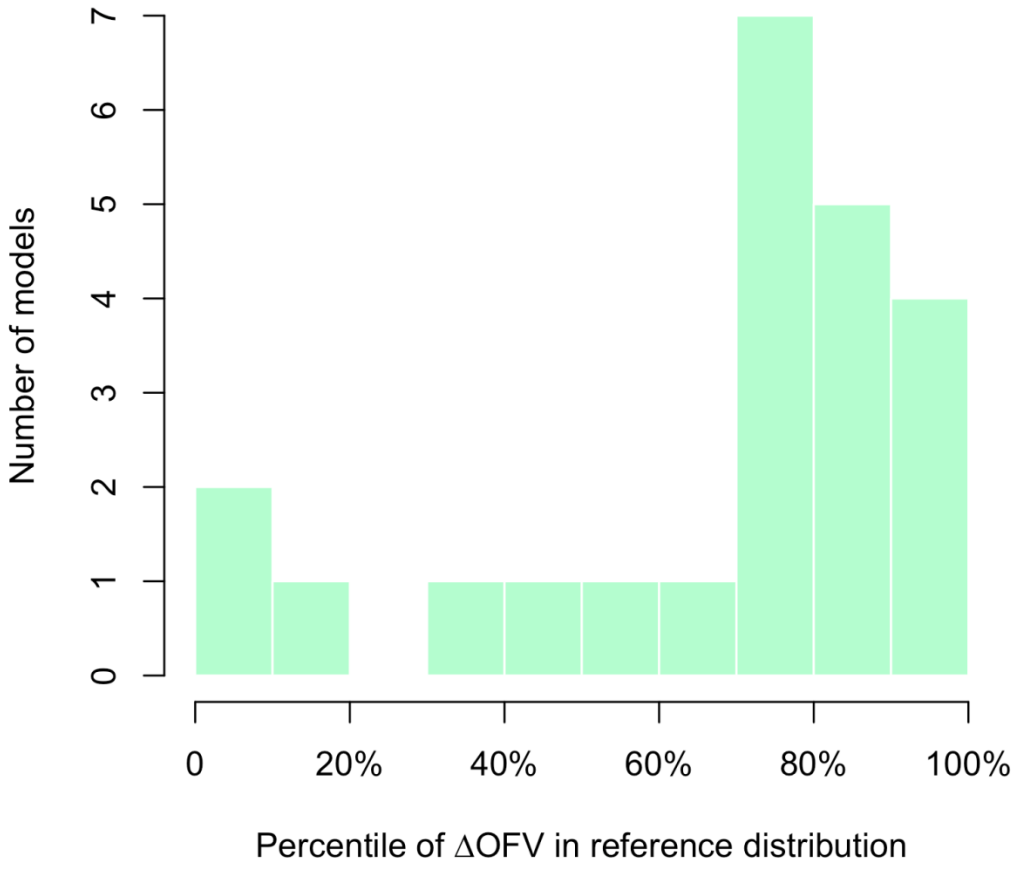
Observed ΔOFV(P-NP) vs reference distribution for ΔOFV(P-NP)



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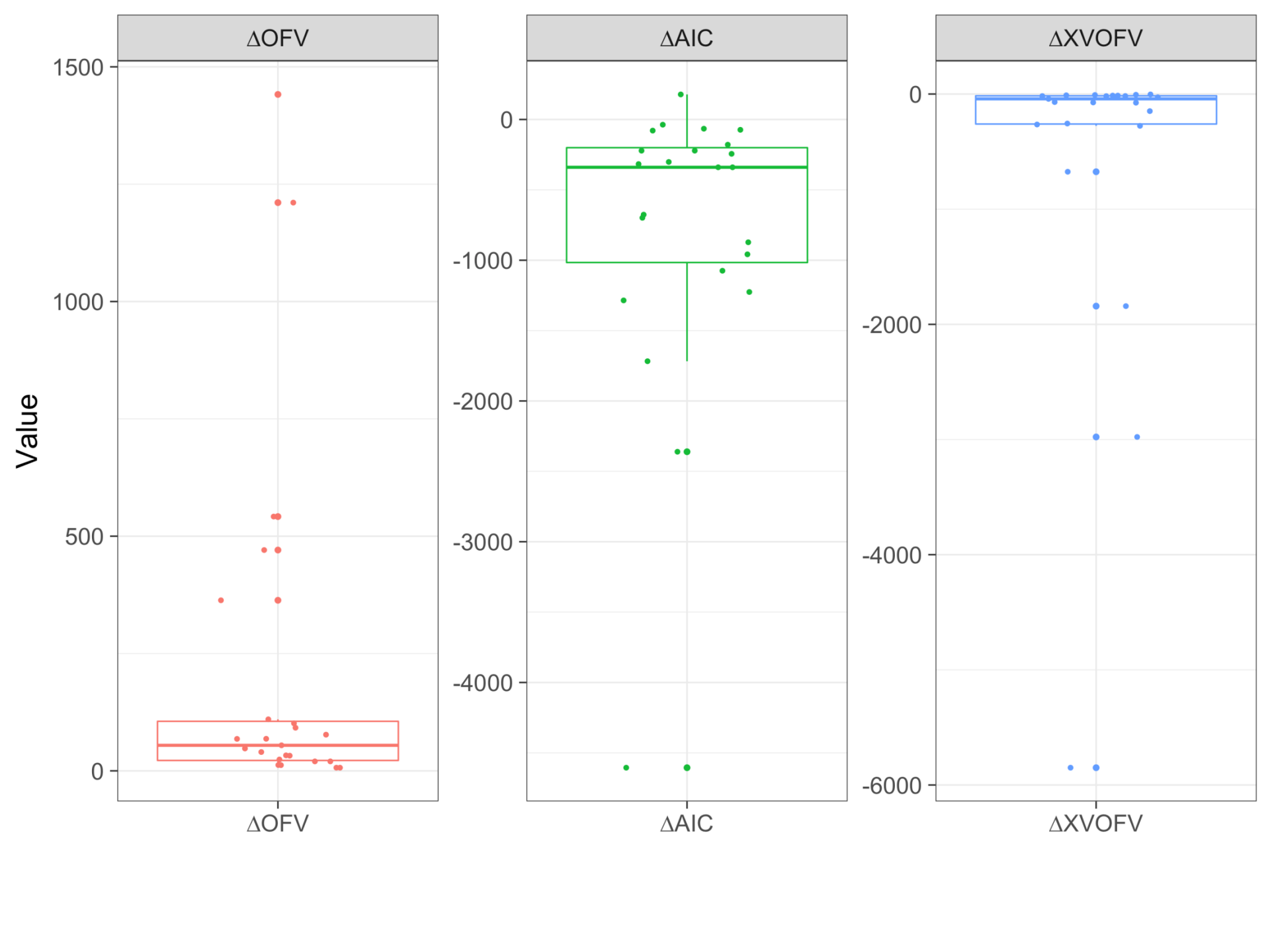
Use of NP information to improve parametric model

- Covariance terms
  - When NP indicates correlations unaccounted for in P
- Mixture models
  - When NP indicates multimodality
- Semi-parametric models with estimated shape parameter(s)
  - When NP indicate skewed or heavy-tailed distributions


ΔOFV
ΔAIC
ΔXVOFV
Value
1500
1000
500
0
0
-1000
-2000
-3000
-4000
0
-2000
-4000
-6000
ΔOFV
ΔAIC
ΔXVOFV

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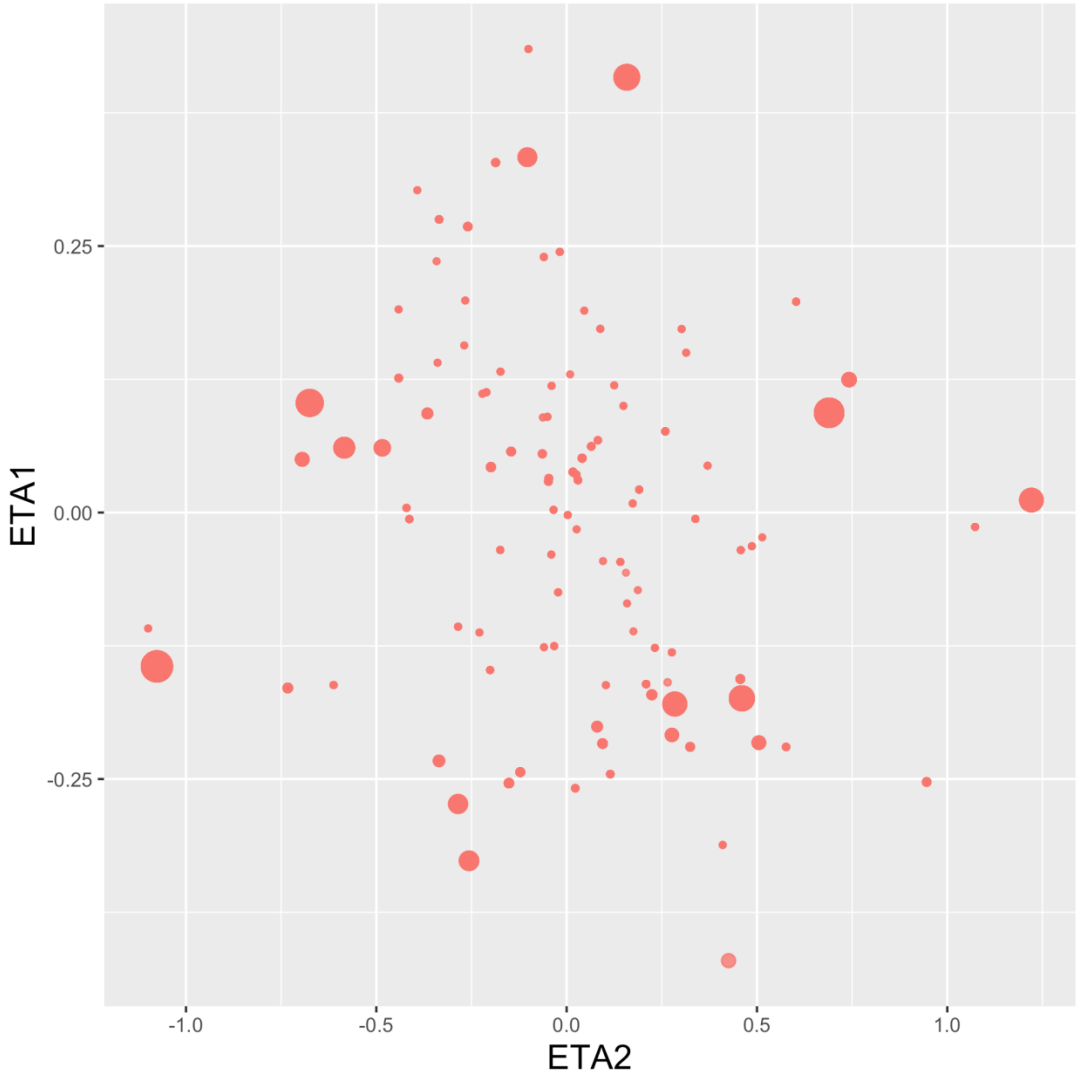
Estimated NP distribution - gentamicin PK model (Nsubj=210)



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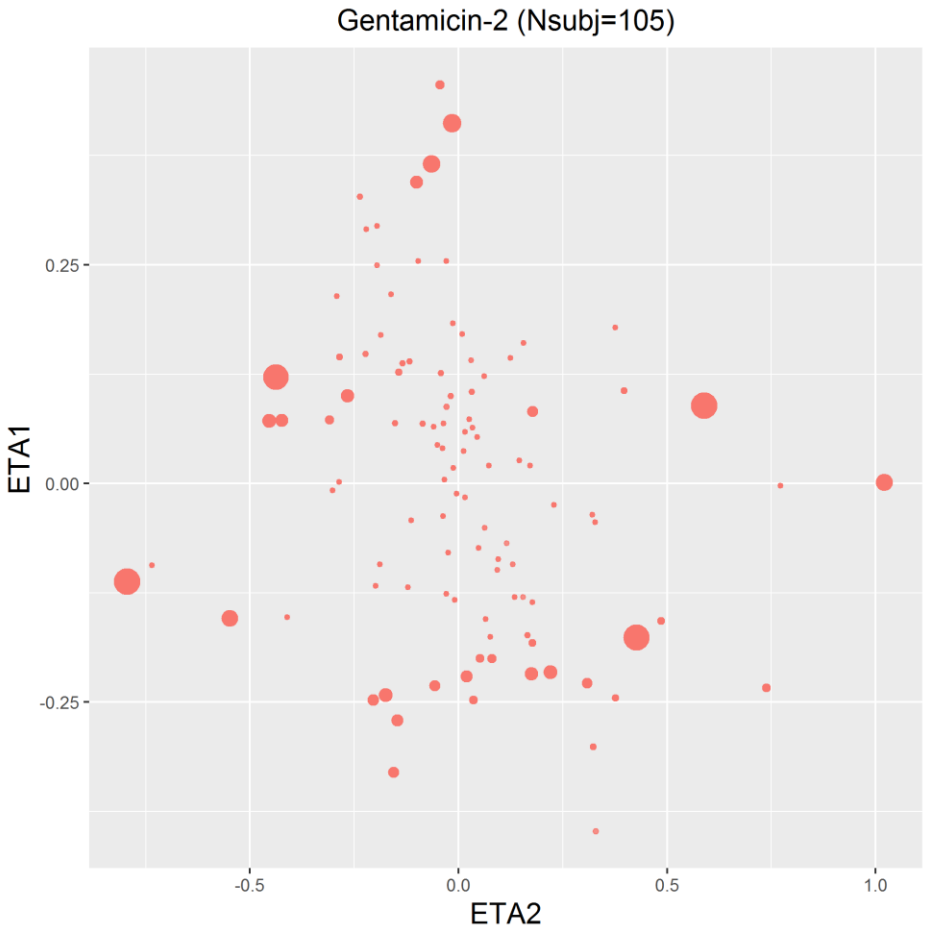
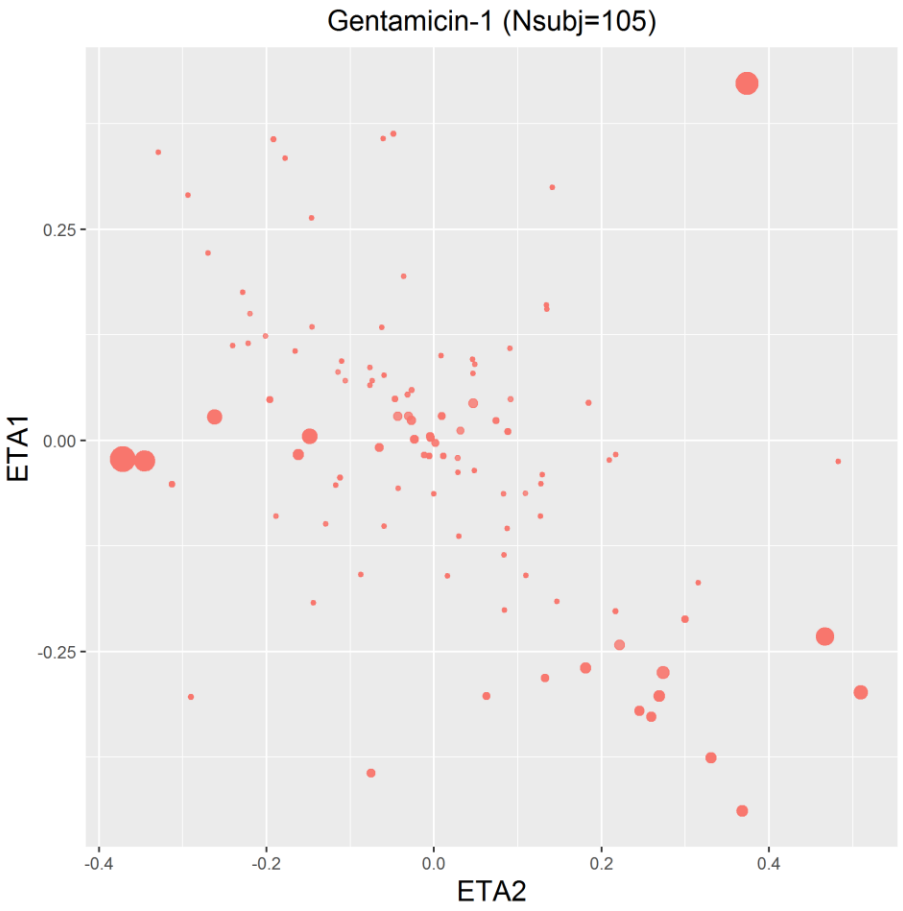
Estimated NP distribution - gentamicin PK models on split data set





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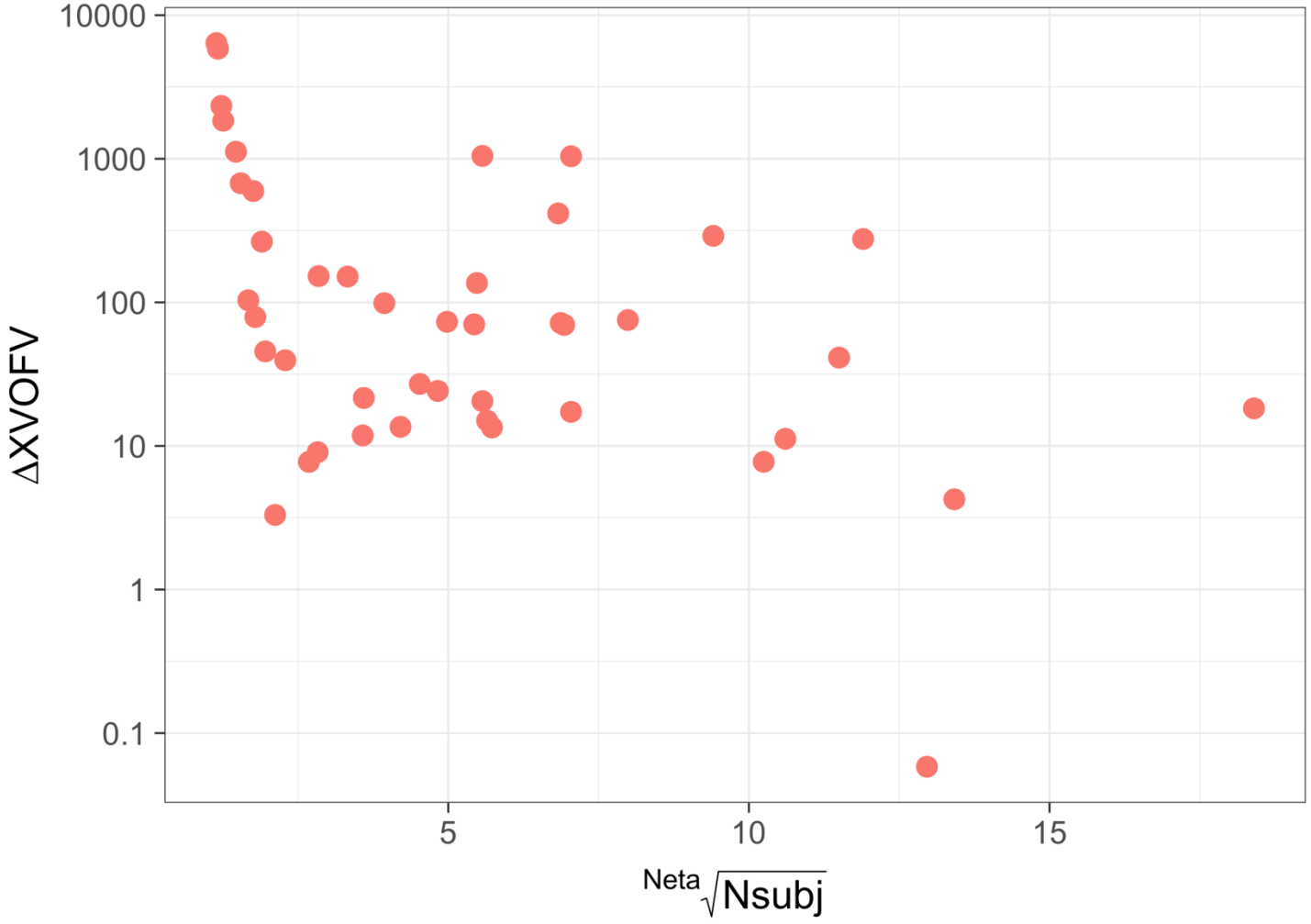
ΔxvOFV versus density metric



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Conclusions

- For the studied models, data and methods:
  - **NP fit is better than fit of P**
  - **Accounting for parsimony, P fit typically better than NP fit**
  - **P better than NP for predicting new data**

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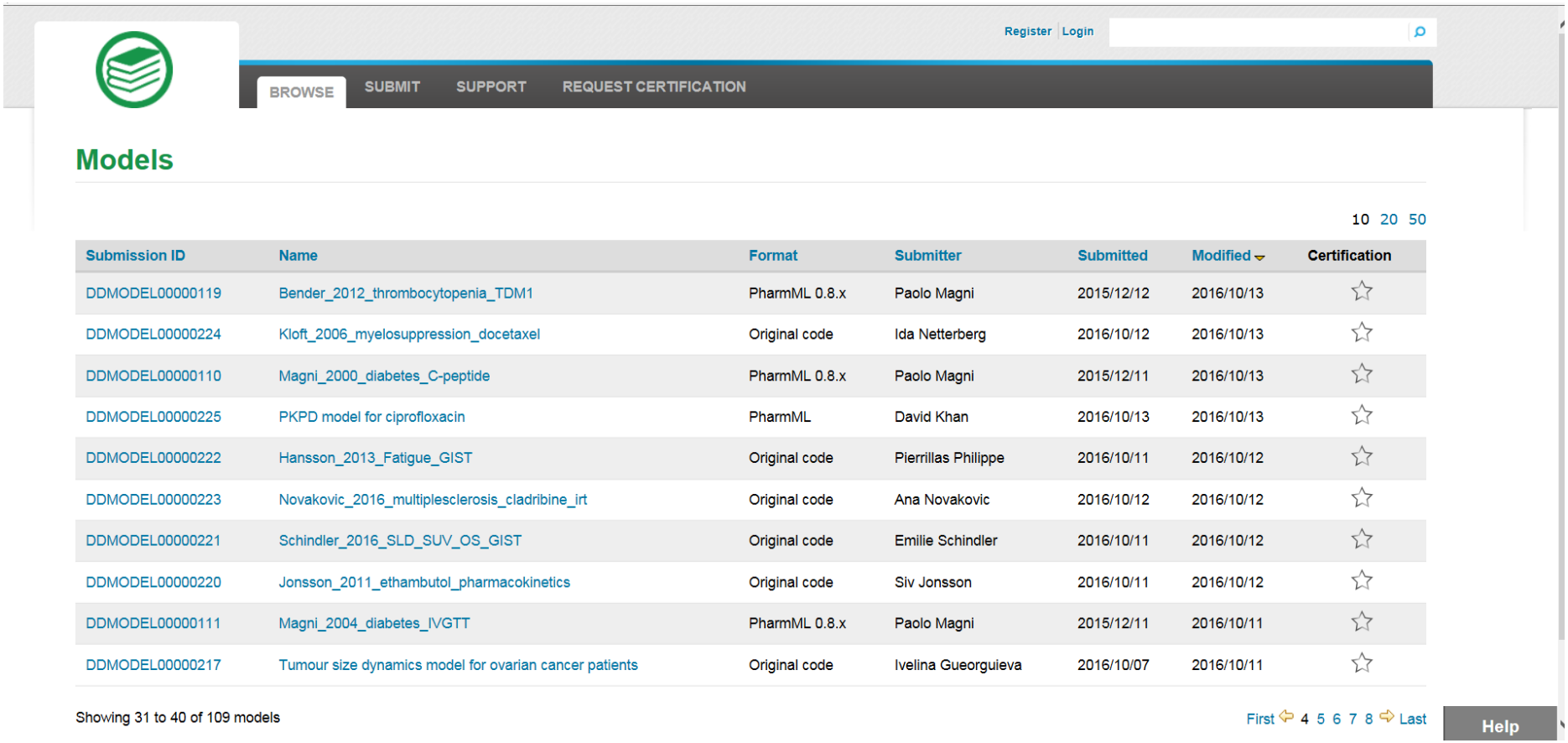
What if we had used NPAG?

- ΔOFV
  - NPAG likely to be better than $NONP
  - NPAG 1-step estimation
  - $NONP 2-step estimation (location, probability)
- ΔAIC
  - NPAG likely to be better than $NONP
  - #parameters(NPAG) < #parameters($NONP)
- ΔxvOFV
  - Not clear (fewer Nsupp of NPAG unlikely an advantage)

DDMoRe Model Repository

repository.ddmore.eu

ddmore FOUNDATION



Submission ID	Name	Format	Submitter	Submitted	Modified	Certification
DDMODEL00000119	Bender_2012_thrombocytopenia_TDM1	PharmML 0.8.x	Paolo Magni	2015/12/12	2016/10/13	☆
DDMODEL00000224	Kloft_2006_myelosuppression_docetaxel	Original code	Ida Netterberg	2016/10/12	2016/10/13	☆
DDMODEL00000110	Magni_2000_diabetes_C-peptide	PharmML 0.8.x	Paolo Magni	2015/12/11	2016/10/13	☆
DDMODEL00000225	PKPD model for ciprofloxacin	PharmML	David Khan	2016/10/13	2016/10/13	☆
DDMODEL00000222	Hansson_2013_Fatigue_GIST	Original code	Pierrillas Philippe	2016/10/11	2016/10/12	☆
DDMODEL00000223	Novakovic_2016_multiplesclerosis_cladribine_irt	Original code	Ana Novakovic	2016/10/12	2016/10/12	☆
DDMODEL00000221	Schindler_2016_SLD_SUV_OS_GIST	Original code	Emilie Schindler	2016/10/11	2016/10/12	☆
DDMODEL00000220	Jonsson_2011_ethambutol_pharmacokinetics	Original code	Siv Jonsson	2016/10/11	2016/10/12	☆
DDMODEL00000111	Magni_2004_diabetes_IVGTT	PharmML 0.8.x	Paolo Magni	2015/12/11	2016/10/11	☆
DDMODEL00000217	Tumour size dynamics model for ovarian cancer patients	Original code	Ivelina Gueorguieva	2016/10/07	2016/10/11	☆

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Thank you!