Shrinkage in Population PK/PKPD Analysis

Sonoko Kawakatsu, PharmD
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RESEARCH GROUP

Sonoko Kawakatsu, PharmD

- Received PharmD from UC San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences in 2019
- Developed an interest in Clinical Pharmacology and Pharmacometrics during pharmacy school, and completed internships/externships at various pharmaceutical companies and the FDA
- Completed a Clinical Pharmacology Fellowship with the Genentech-University of the Pacific Fellowship in Industry program in 2021
- Currently at Metrum Research Group as a Senior Scientist I in the Modeling and Simulation Group

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References

- Savic, RM; Karlsson, MO. Shrinkage in Empirical Bayes Estimates for Diagnostics and Estimation: Problems and Solutions. PAGE 2007.
- Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. AAPS J. 2009 Sep;11(3):558-69.
- Gelman A; Pardoe I. Bayesian Measures of Explained Variance and Pooling in Multilevel (Hierarchical) Models.Technometrics 2006, 48:2, 241-251.

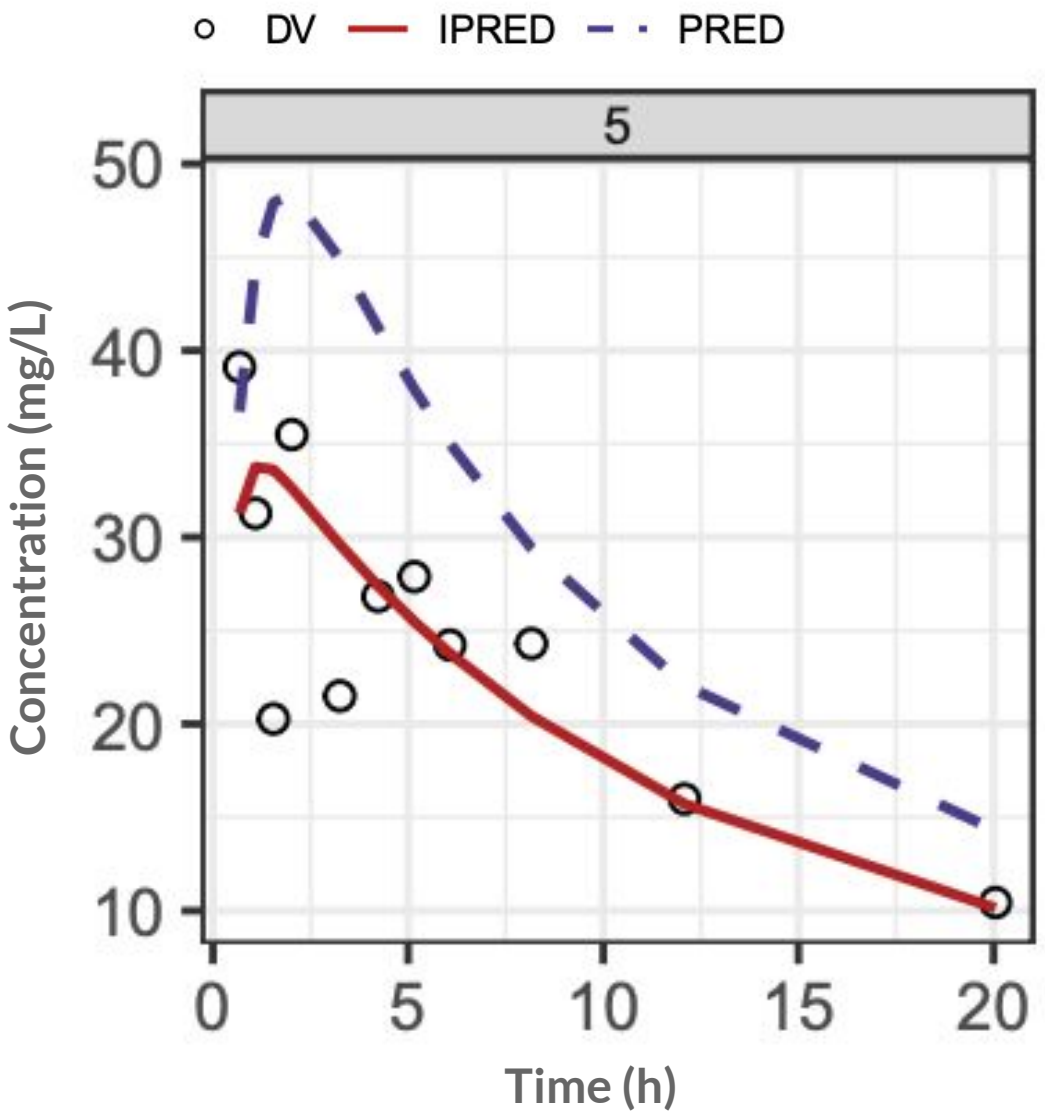
Objectives

This presentation will address the following questions:

- What is shrinkage?
- What causes shrinkage?
- How is it calculated?
- Does high shrinkage indicate a problem with the model?
- What is the impact of shrinkage on model development?

Brief Review: Nonlinear Mixed Effects Modeling (NONMEM)

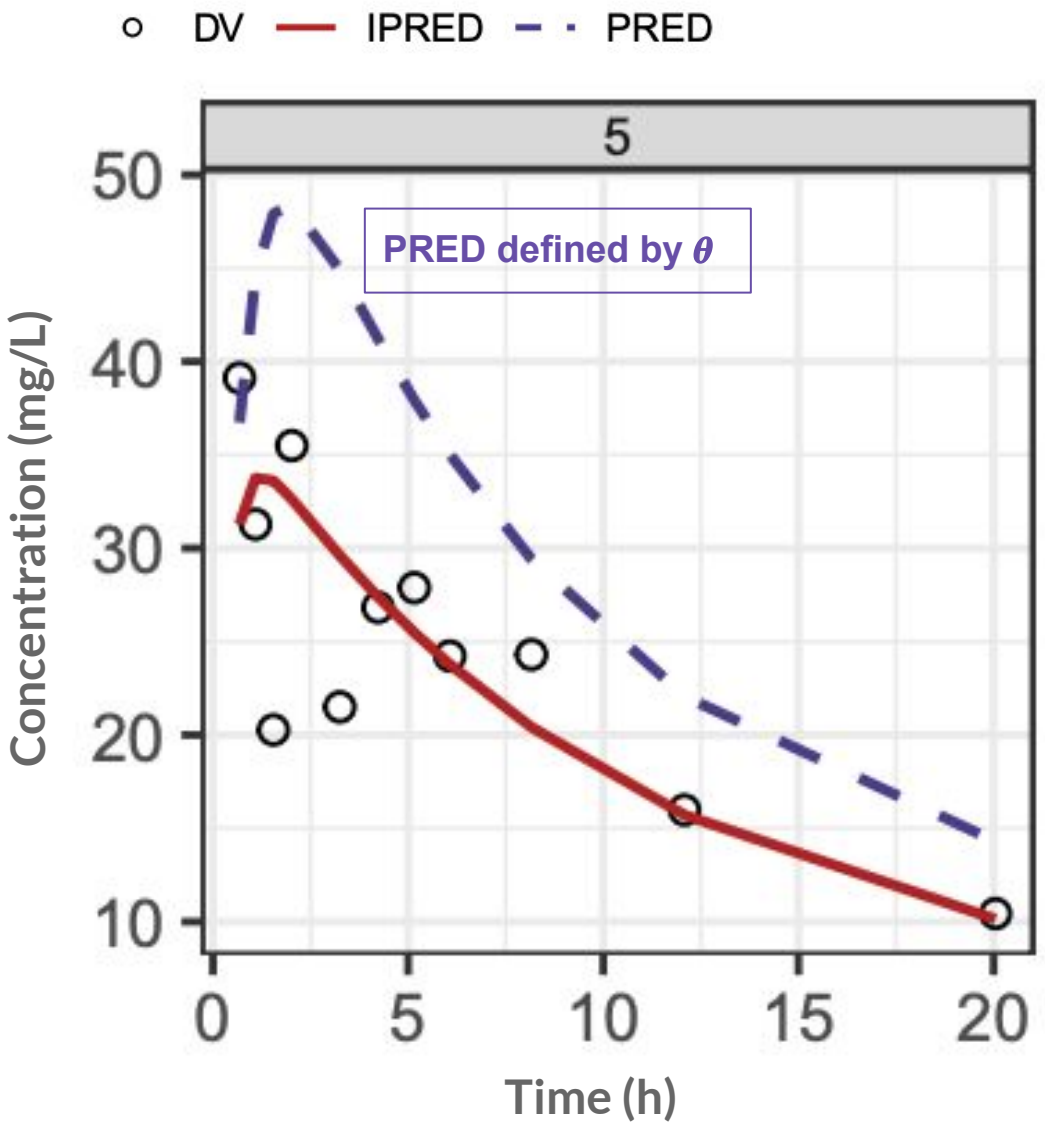
- Fitting a mathematical-statistical representation that defines the relationship between dependent (e.g. concentration) and independent (e.g. time, dose) variables



DV = individual observation; IPRED = individual predictions; PRED = population predictions

Brief Review: Nonlinear Mixed Effects Modeling (NONMEM)

- Fitting a mathematical-statistical representation that defines the relationship between dependent (e.g. concentration) and independent (e.g. time, dose) variables
- Mixed effects
  - Fixed effects - characterize persistent, structural elements of the model ($\boldsymbol{\theta}$)



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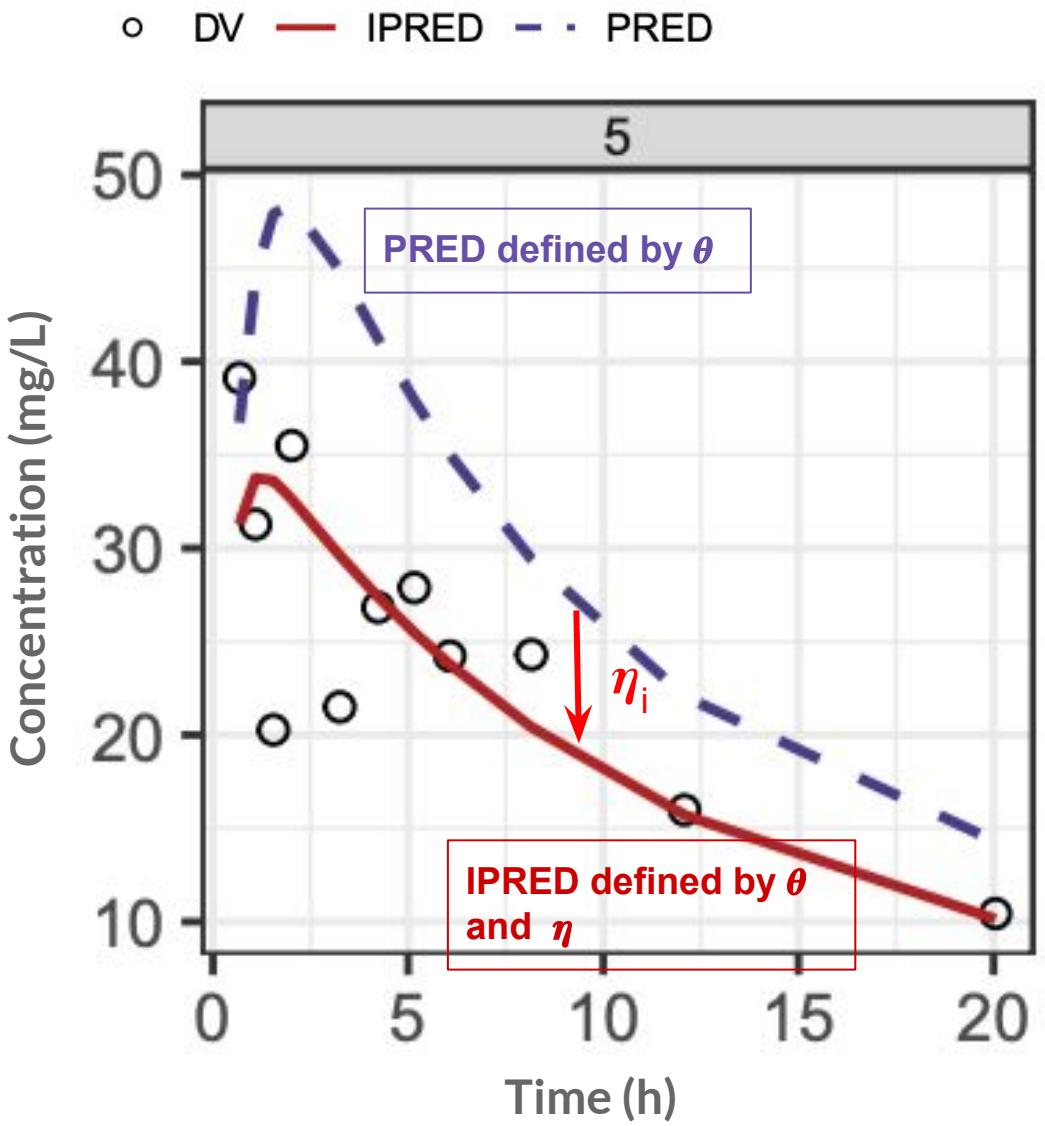
    - Between subjects ($\boldsymbol{\eta}$)



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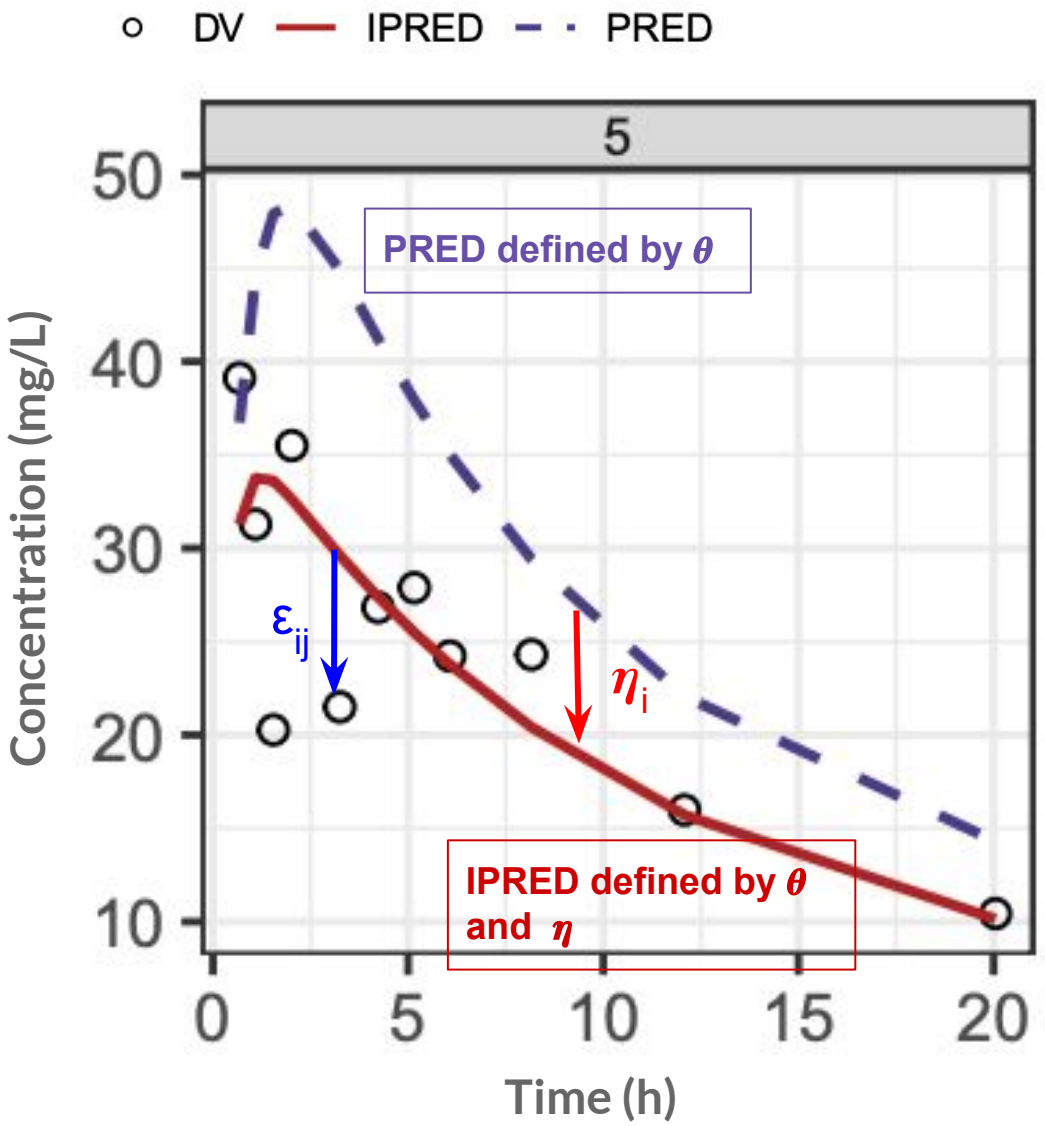
    - Between subjects ($\boldsymbol{\eta}$)
    - Residual variability ($\boldsymbol{\varepsilon}$)



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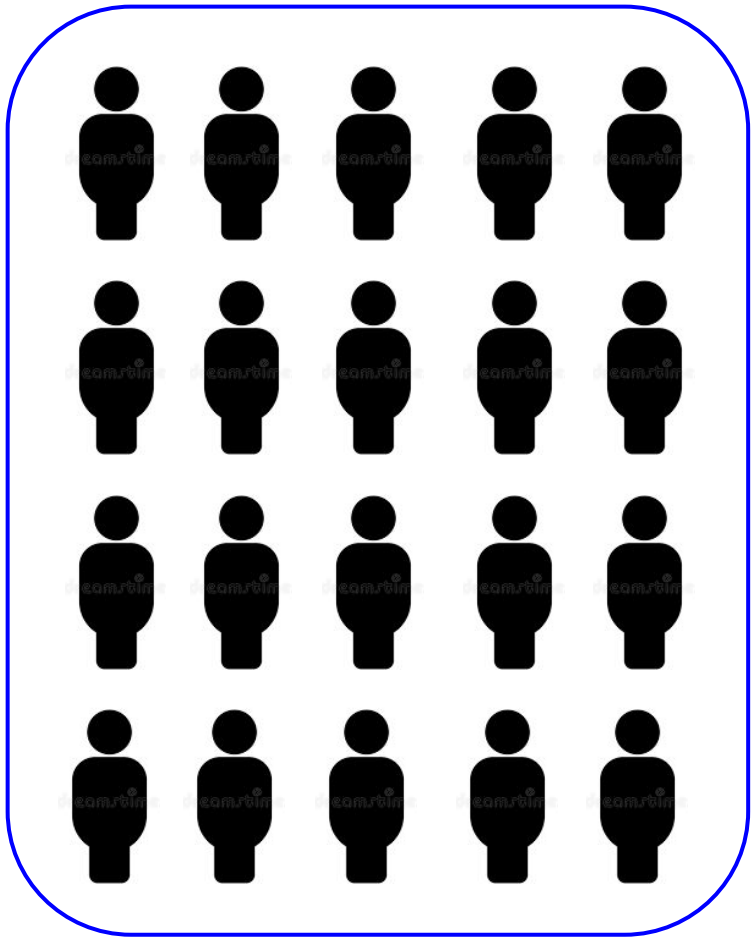
Brief Review: Population vs individual parameters

Population parameters ($\theta, \omega^2, \sigma^2$)



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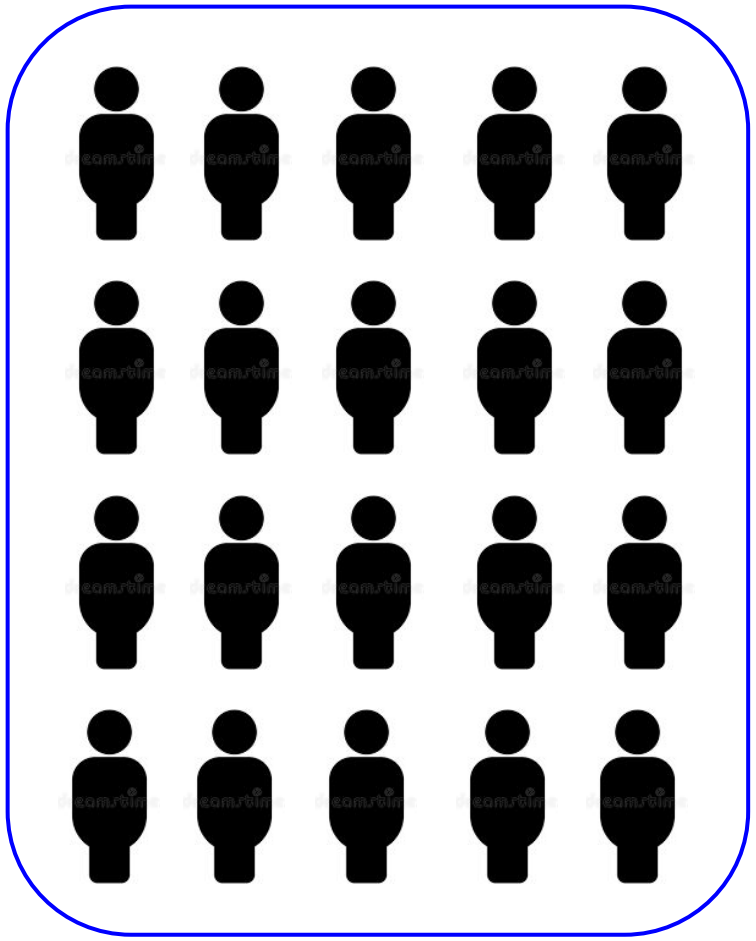

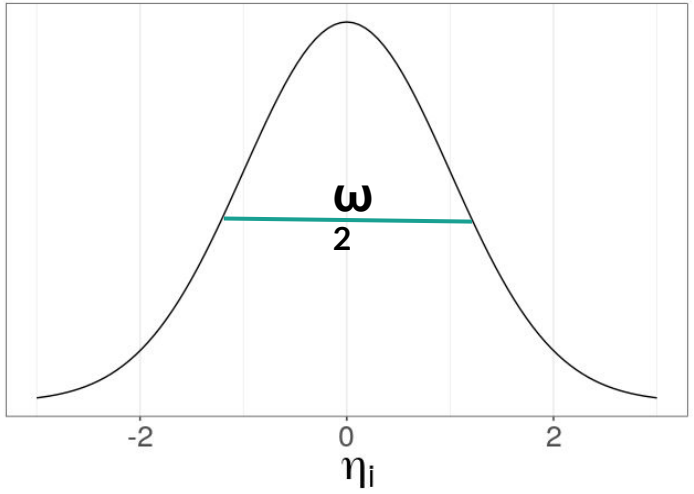

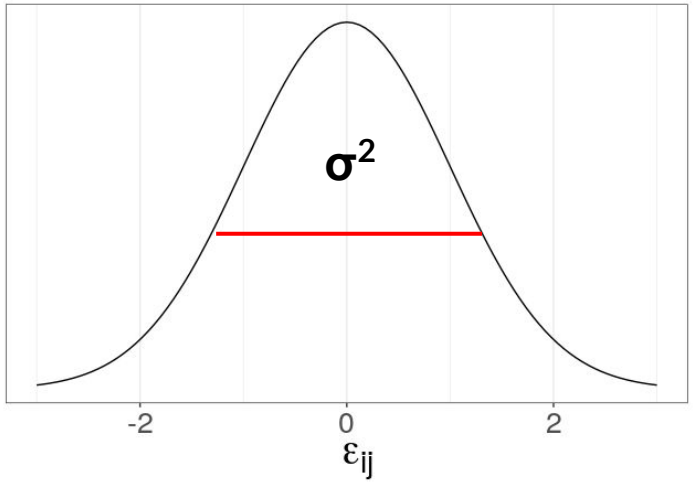

Note: ω^2 and σ^2 are the variances of theoretical distributions of η_i and ε_{ij} (not the actual distribution of η_i and ε_{ij})

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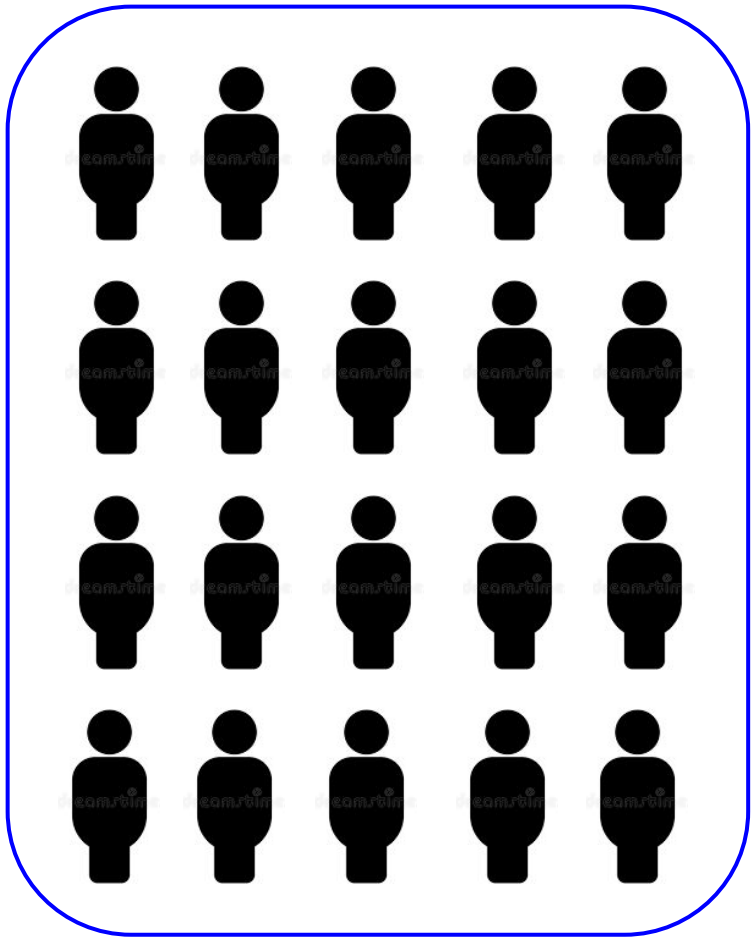
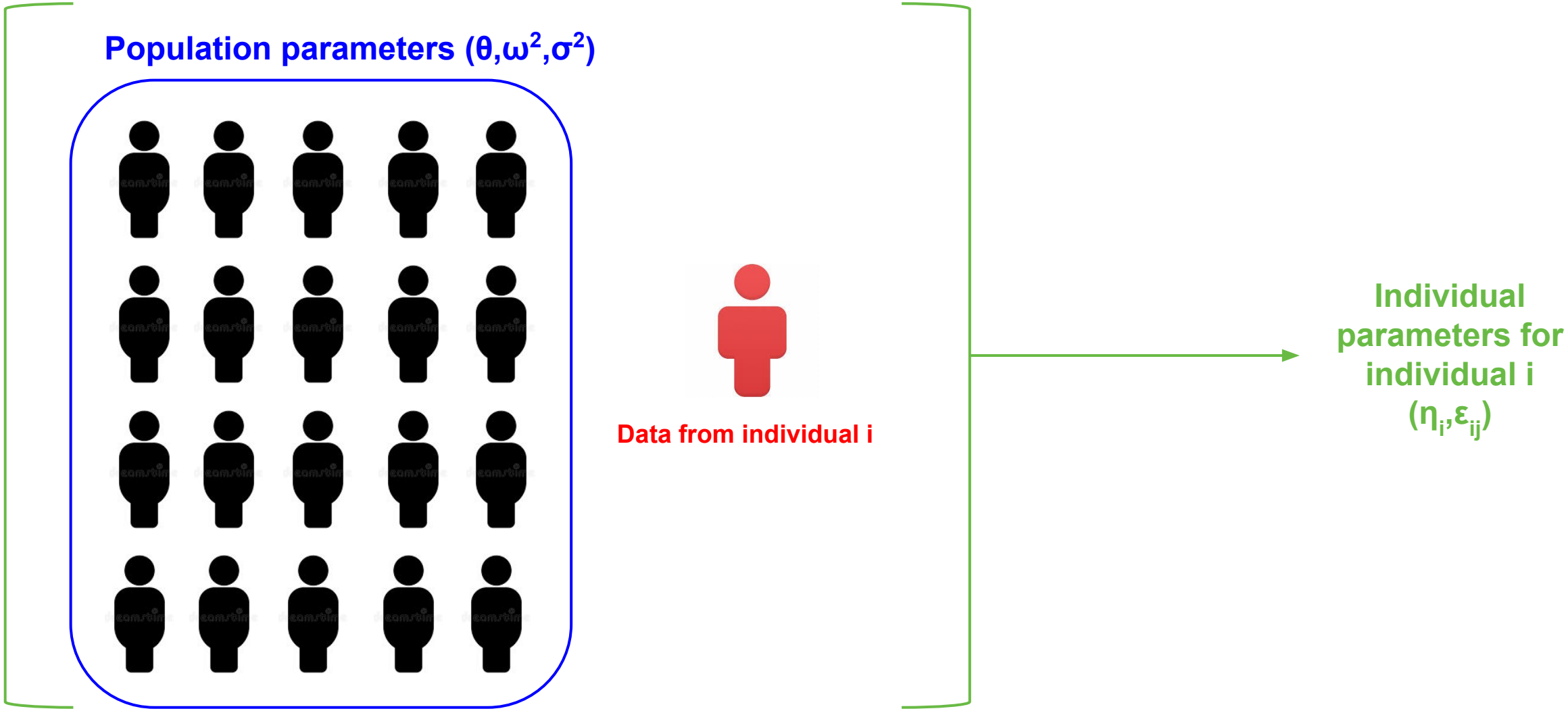
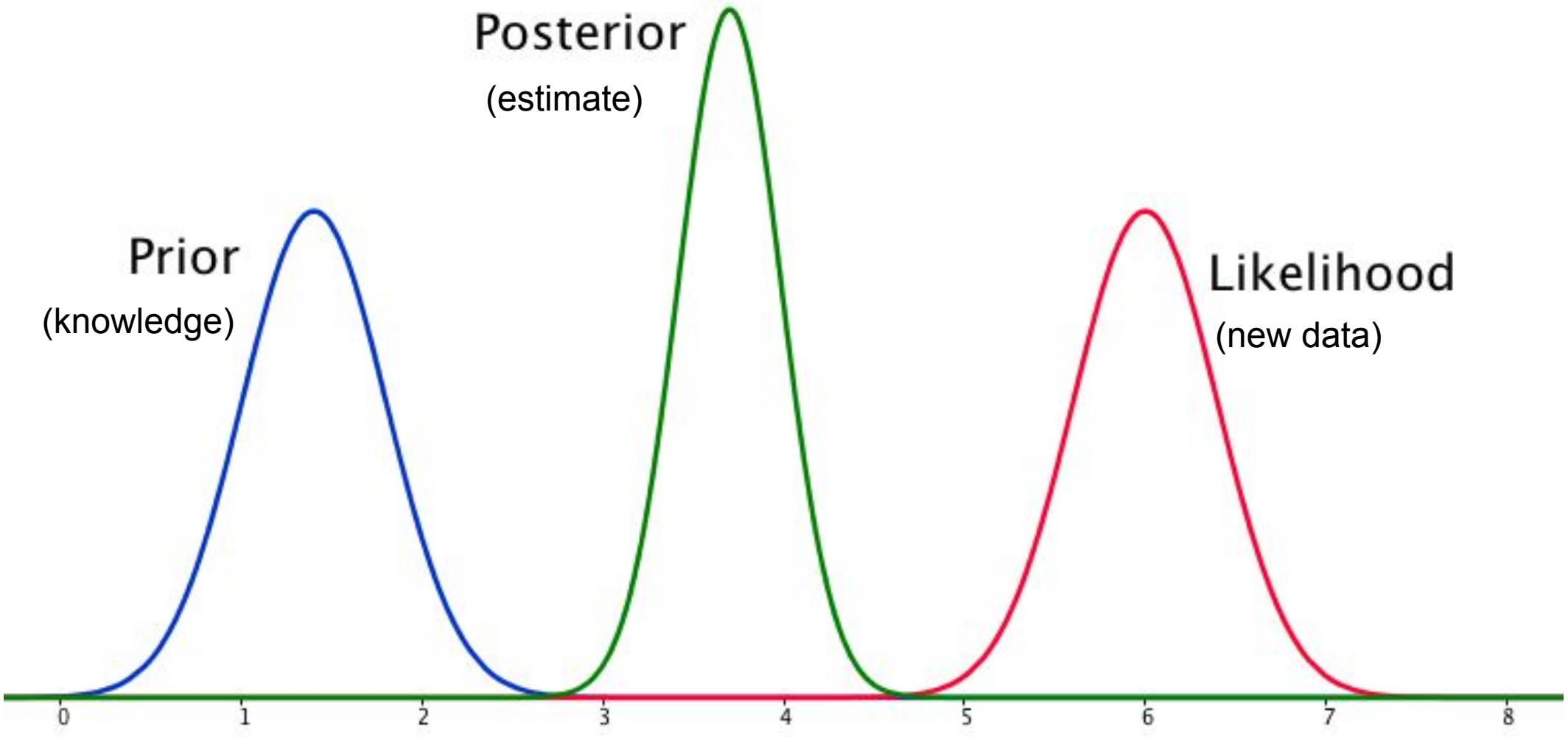


Data from individual i

Brief Review: Population vs individual parameters



Brief Review: Bayesian estimation concepts



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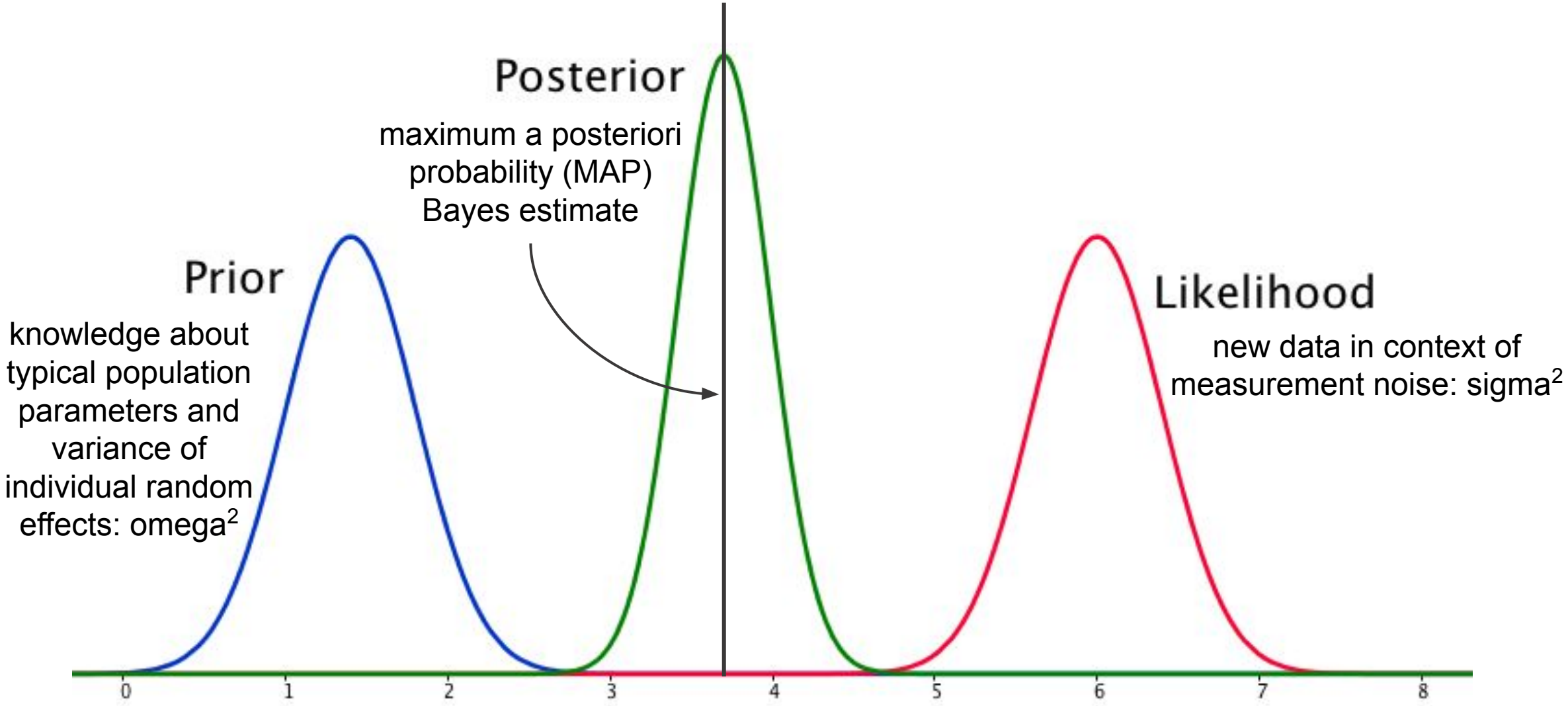

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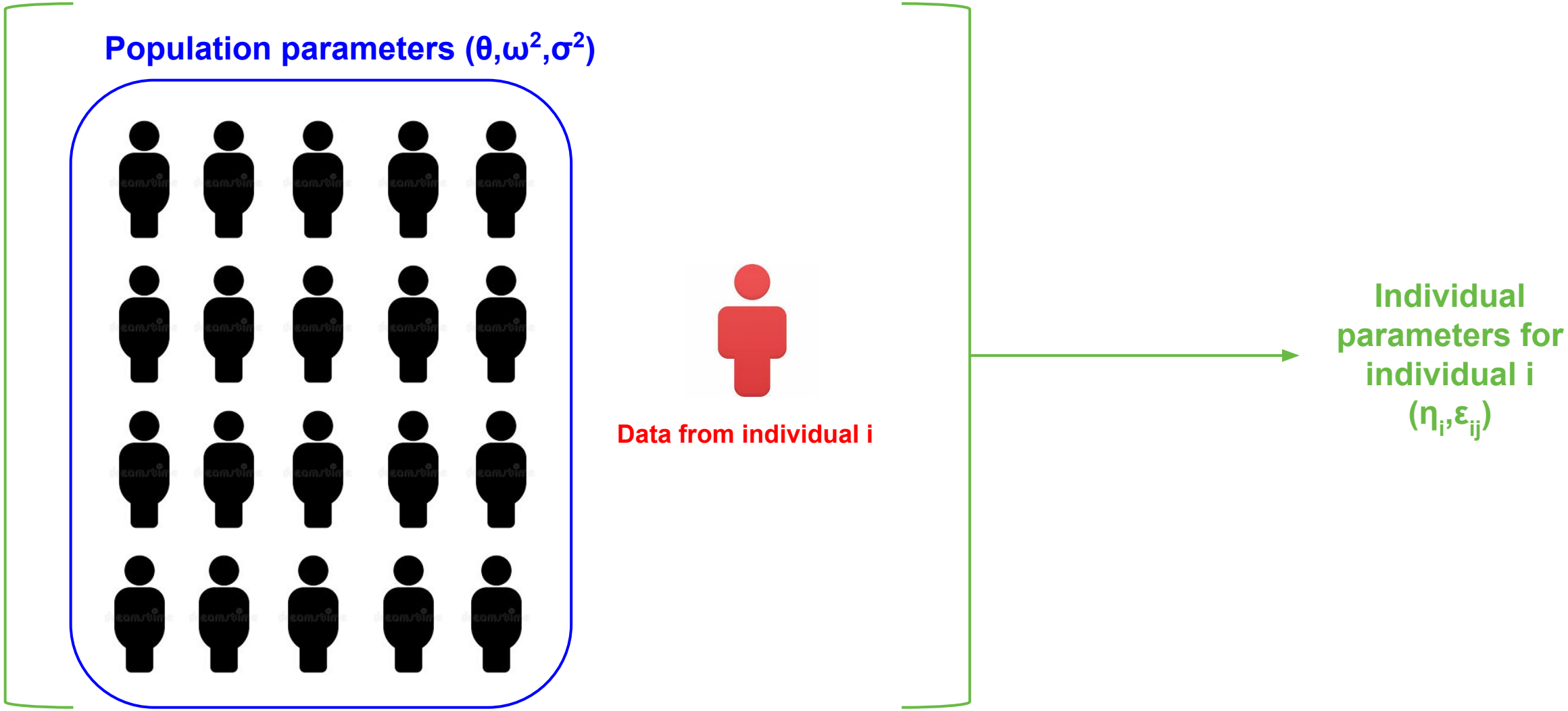
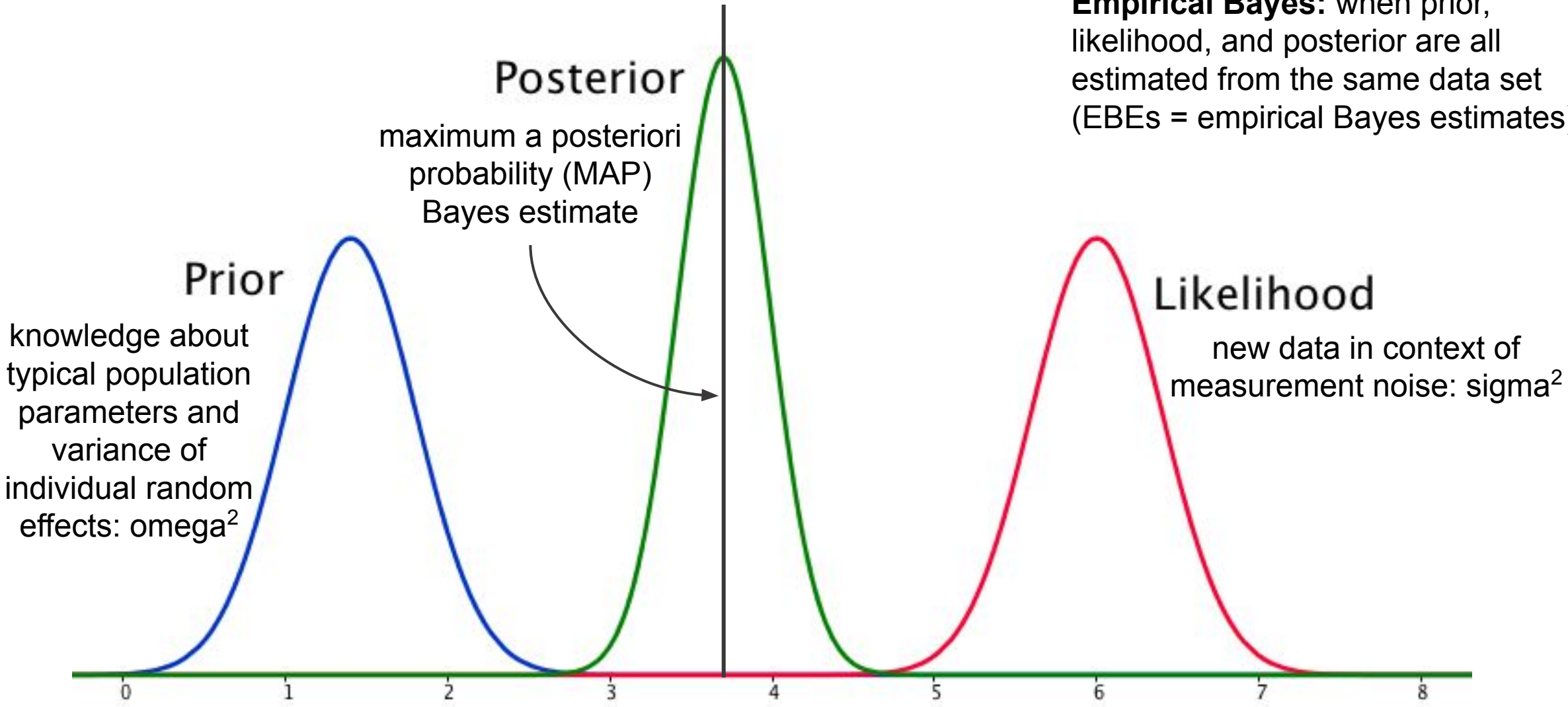


Brief Review: Bayesian estimation concepts

Empirical Bayes: when prior, likelihood, and posterior are all estimated from the same data set (EBEs = empirical Bayes estimates)



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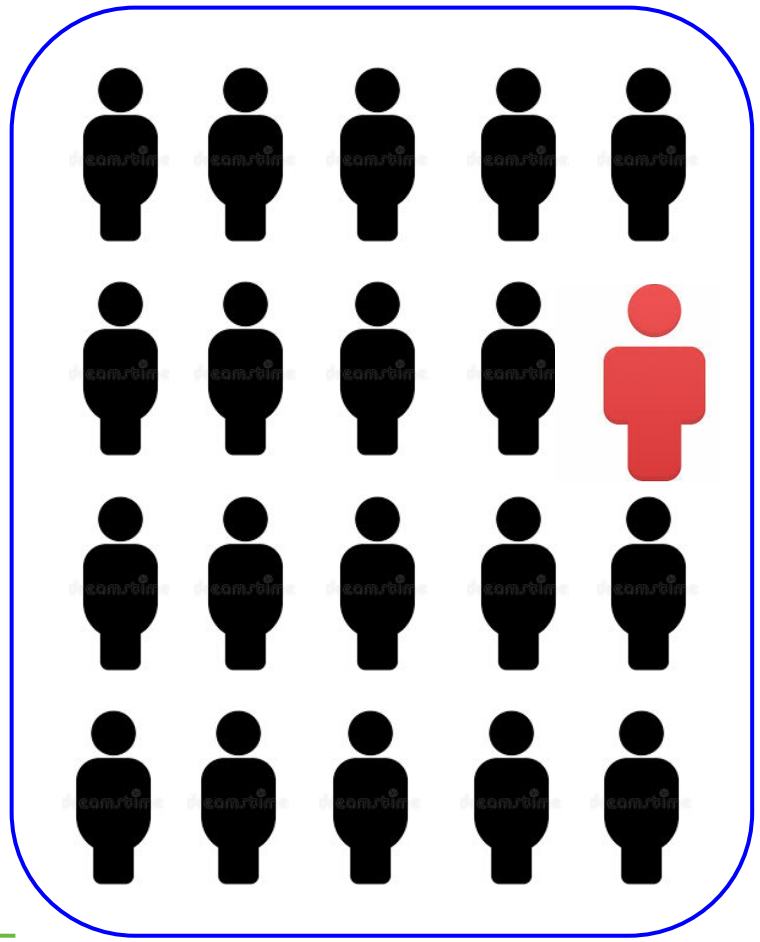
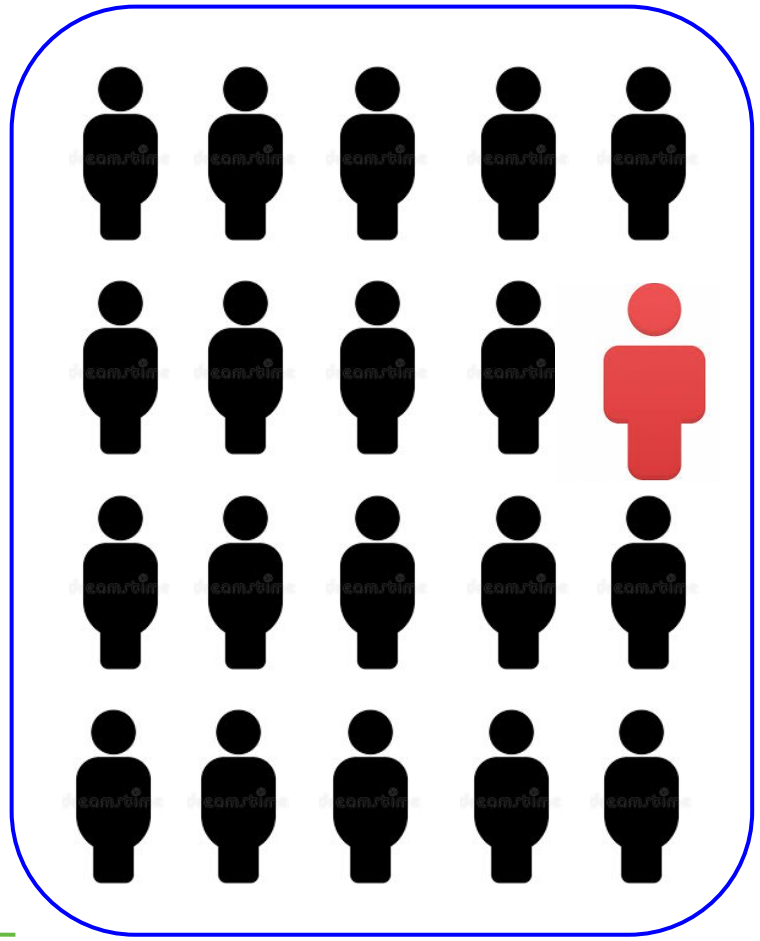


Individual parameters for individual i (η_i, ε_{ij})

Brief Review: Population vs individual parameters

Population parameters (θ,ω,σ)



Individual parameters for individual i (η_i,ε_{ij})

Shrinkage tells us:

Are these individual parameters informed more by the population parameters? or by the individual data?

Objectives

This presentation will address the following questions:

- What is shrinkage?
- What causes shrinkage?
- How is it calculated?
- Does high shrinkage indicate a problem with the model?
- What is the impact of shrinkage on model development?

Shrinkage of Random Effects

- Shrinkage: when the magnitude of individual/residual estimated random effects shrinks towards the prior expectation (=0)
  - η shrinkage (shk_{η})
    - $(\eta_i)_{variance} \rightarrow 0$
    - Individual estimates → population mean
  - ε shrinkage (shk_{ε})
    - IWRES → 0
    - IPRED → DV
    - "Overfitting"

DV = individual observation; IPRED = individual predictions; IWRES = individual weighted residuals = $(DV-IPRED)/SD_{\varepsilon}$

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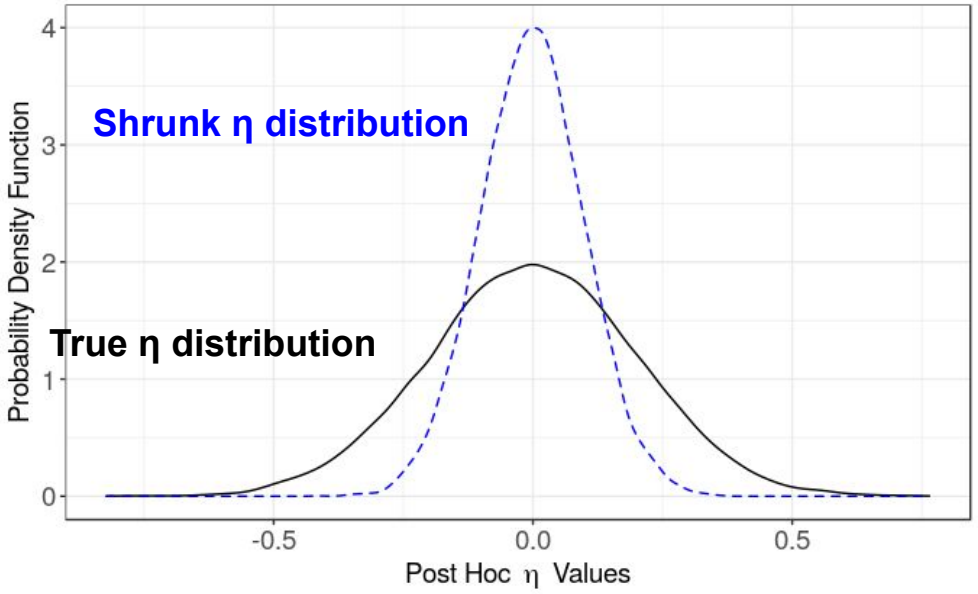

DV = individual observation; IPRED = individual predictions; IWRES = individual weighted residuals = $(DV-IPRED)/SD_{\varepsilon}$

η shrinkage example: ETA = true ETA

https://metrumrg.shinyapps.io/tdmdosing/

mAb TDM

Patient ID

bar1188

Weight (kg)

35

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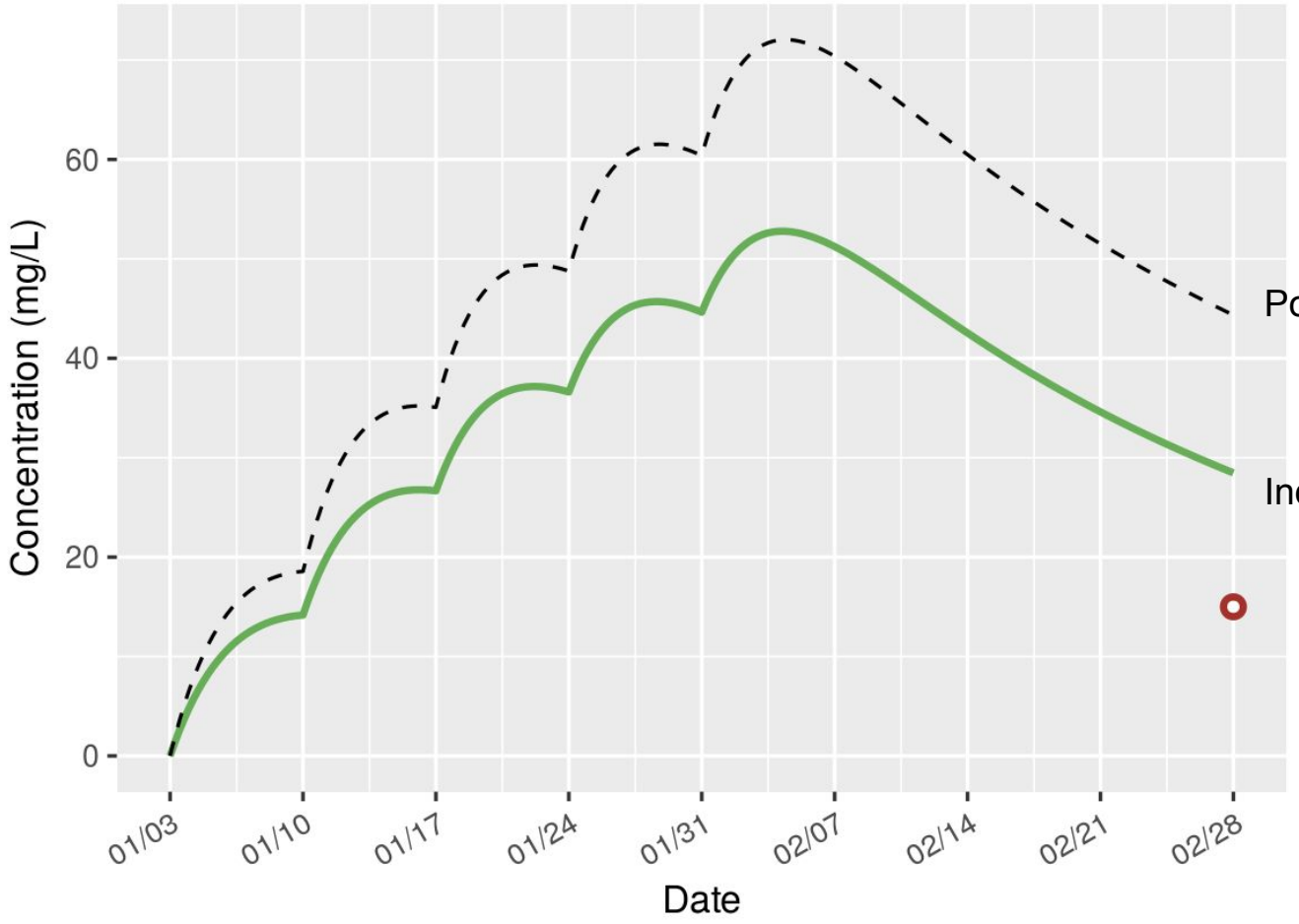
PK Parameters

	Value	ETA
CL	0.12	0.48
Vc	2.33	0.33
Vp	1.79	0.05

CL in L/day, Vc and Vp in L. ETA is the estimated individual random effect.

Dosing history



η shrinkage example: ETA = shrunken estimated ETA

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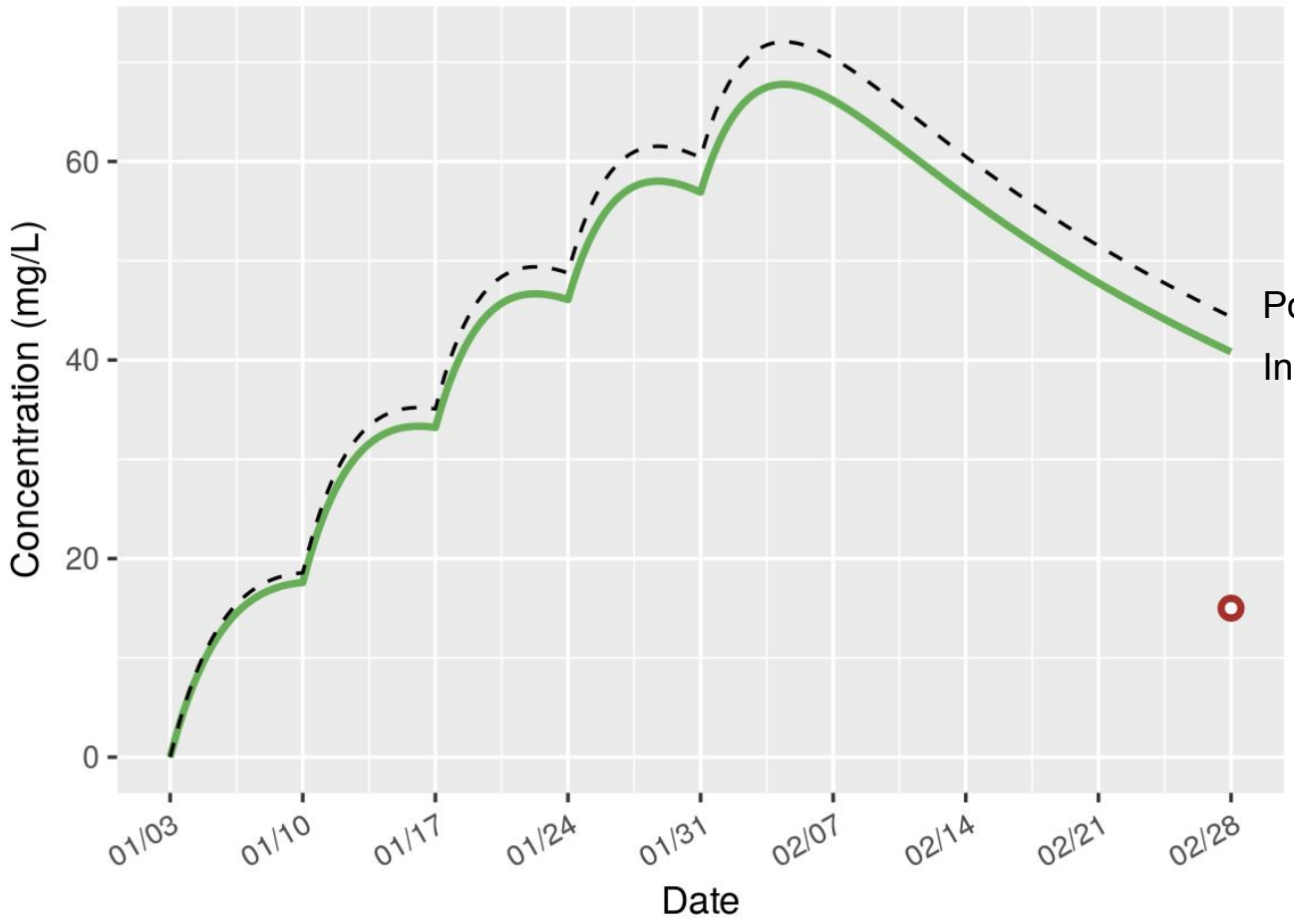
PK Parameters

	Value	ETA
CL	0.08	0.09
Vc	1.80	0.07
Vp	1.72	0.02

CL in L/day, Vc and Vp in L. ETA is the estimated individual random effect.

Dosing history



Pop (eta=0)

Ind_{est} (eta=$eta_{i,est}$)

Shrinkage of Random Effects

- ε shrinkage (shk_{ε})
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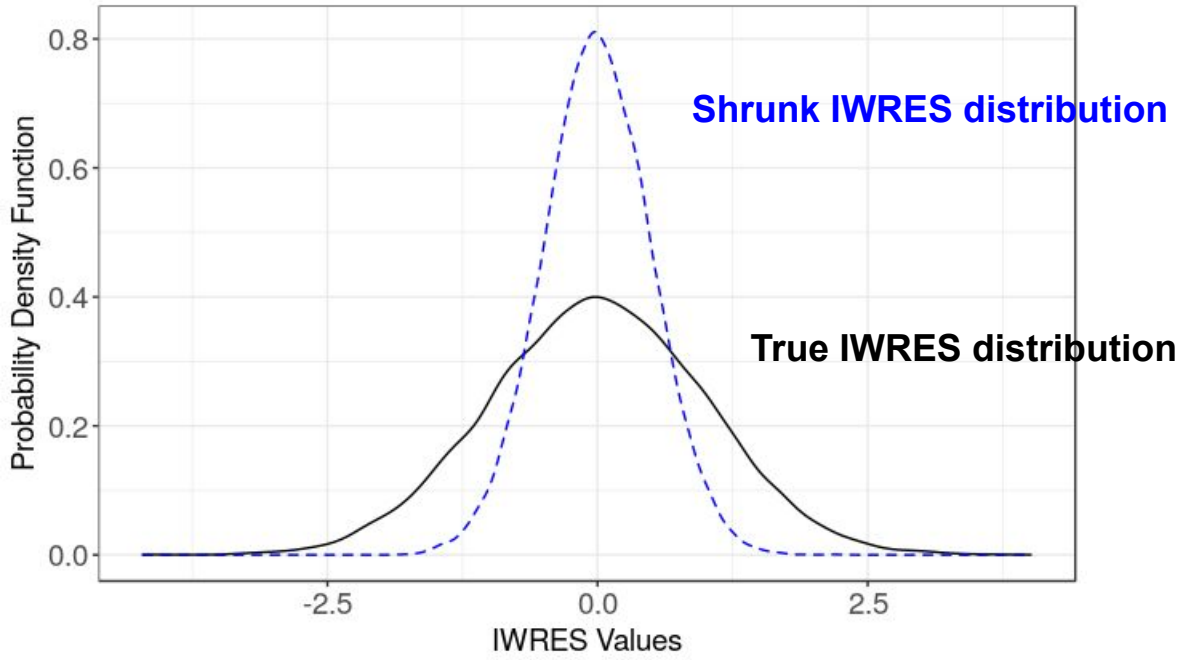

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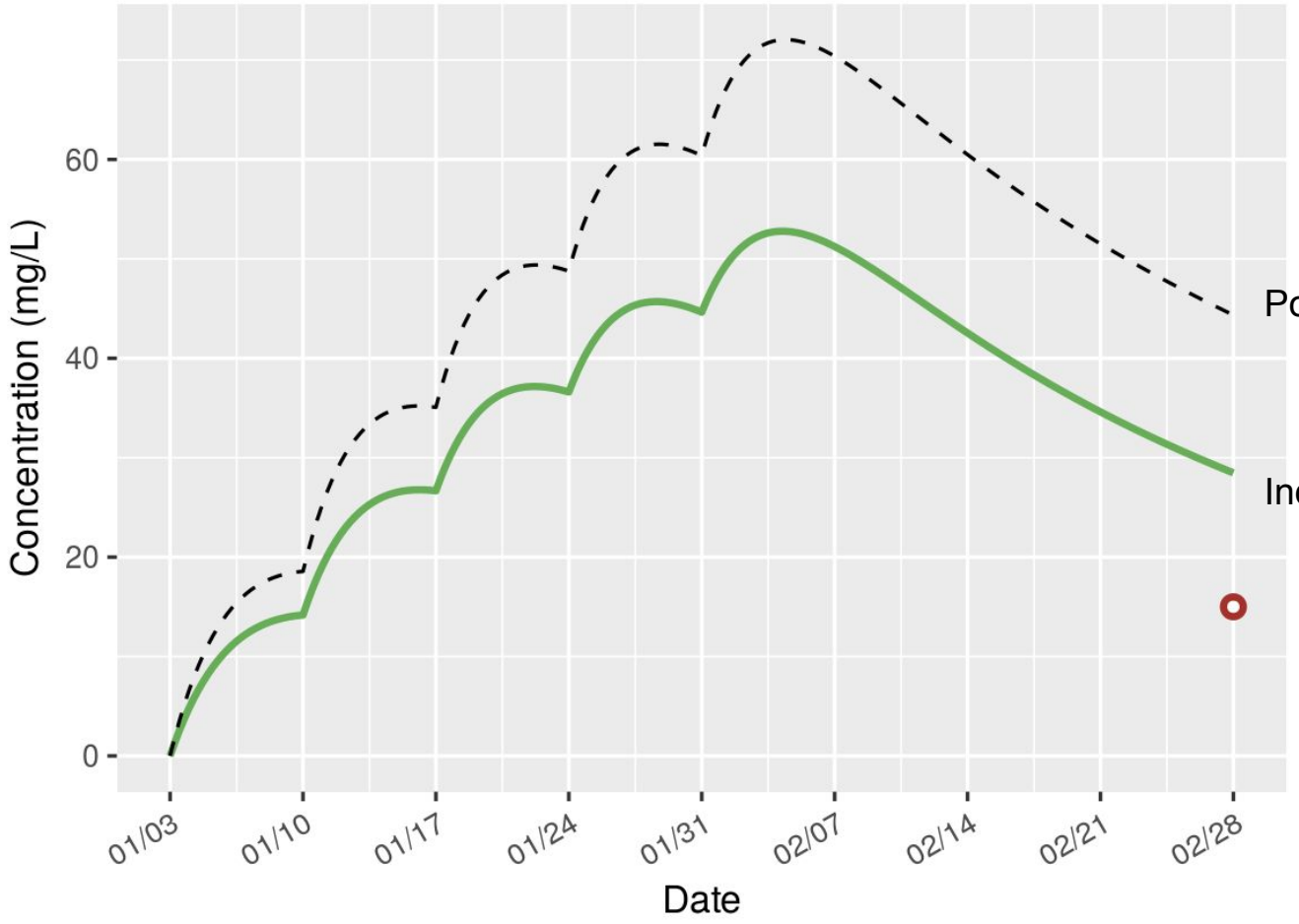

ε shrinkage example: ETA = ETA with epsilon shrinkage

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	Value	ETA
CL	0.17	0.82
Vc	2.78	0.50
Vp	1.77	0.04

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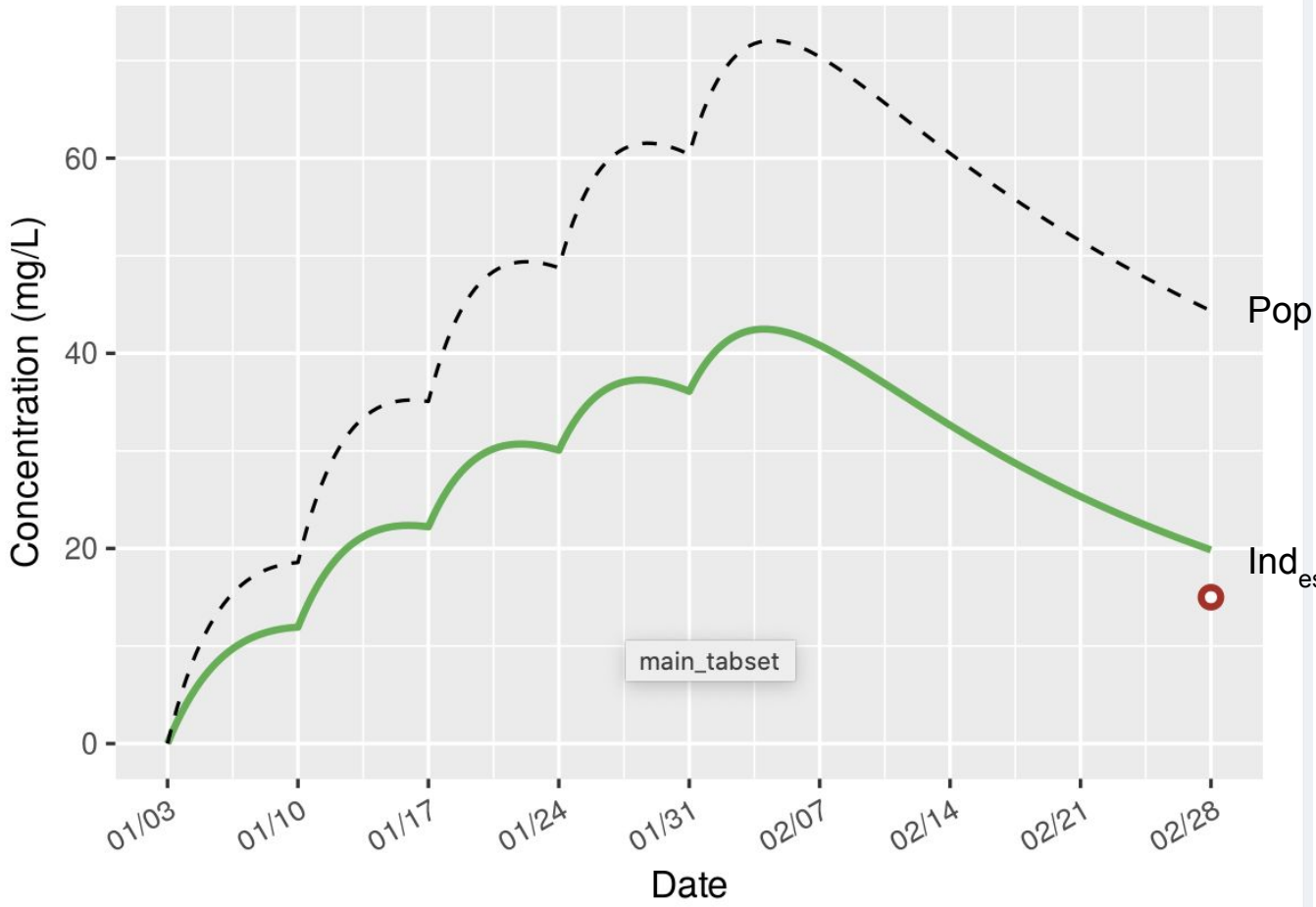
Dosing history



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$$OBJ = \sum_{i=1}^{p} \frac{(\theta_i - \hat{\theta}_i)^2}{\hat{\omega}^2} + \sum_{j=1}^{n} \left(\frac{(C_j - \hat{C}_j)^2}{\hat{\sigma}^2} + ln(\hat{\sigma}^2) \right)$$

Post Hoc Objective Function in NONMEM

θ_i is the parameter estimate for individual i

$\hat{\theta}_i$ is the population fixed effect estimate for individual i

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$\theta_i - \hat{\theta}_i$ **approaches 0 → η shrinkage**

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$\theta_i - \hat{\theta}_i$ **approaches 0 → η shrinkage**

$C_j - \hat{C}_j$ **approaches 0 → ε shrinkage**

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$\hat{\omega}^2$ and $\hat{\sigma}^2$ are the variances of the random effects (individual, residual, respectively) in the population model

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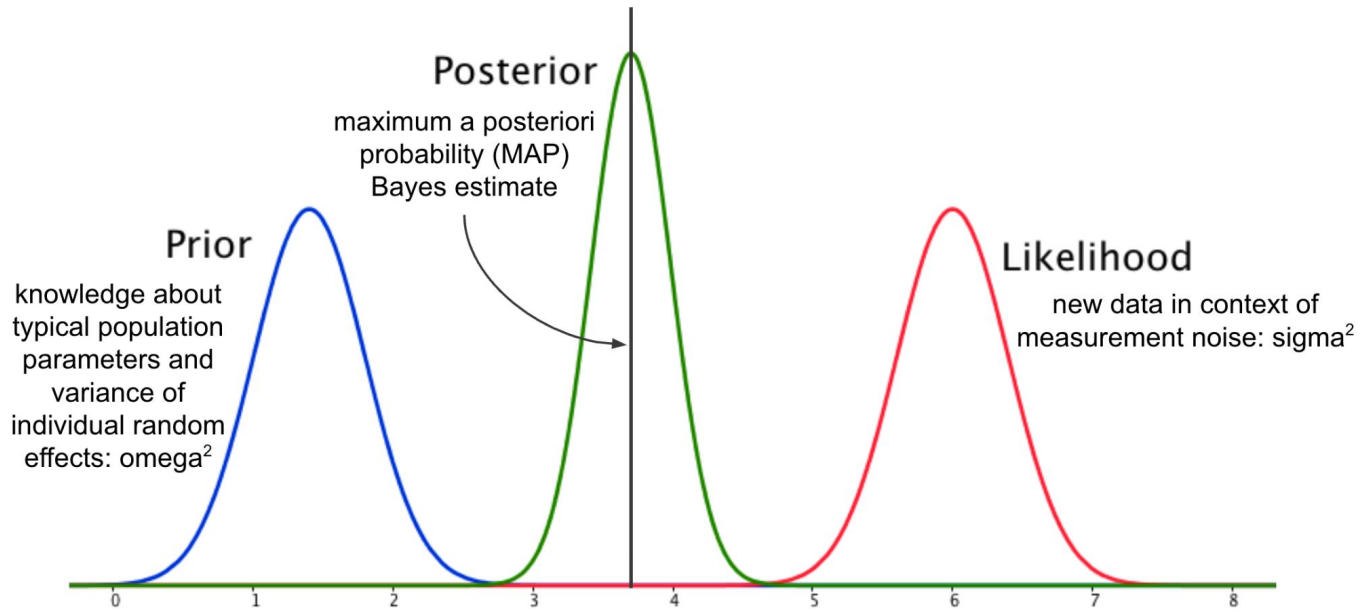

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Given the goal to minimize the objective function value (OBJ), we want to minimize $\theta_i - \hat{\theta}_i$ and $C_j - \hat{C}_j$:

- Moving individual parameters away from the mean (increasing $\theta_i - \hat{\theta}_i$) is discouraged unless there is an improvement in model fit (decreasing $C_j - \hat{C}_j$) to offset the increase in OBJ
- If an individual has more observations, there is more opportunity to support moving a parameter away from the typical value to improve the fit of the model → less η shrinkage

Post Hoc Objective Function in NONMEM

$$OBJ = \sum_{i=1}^{p} \frac{(\theta_i - \hat{\theta}_i)^2}{\hat{\omega}^2} + \sum_{j=1}^{n} \left(\frac{(C_j - \hat{C}_j)^2}{\hat{\sigma}^2} + ln(\hat{\sigma}^2) \right)$$

Also consider $\hat{\omega}^2$ and $\hat{\sigma}^2$:

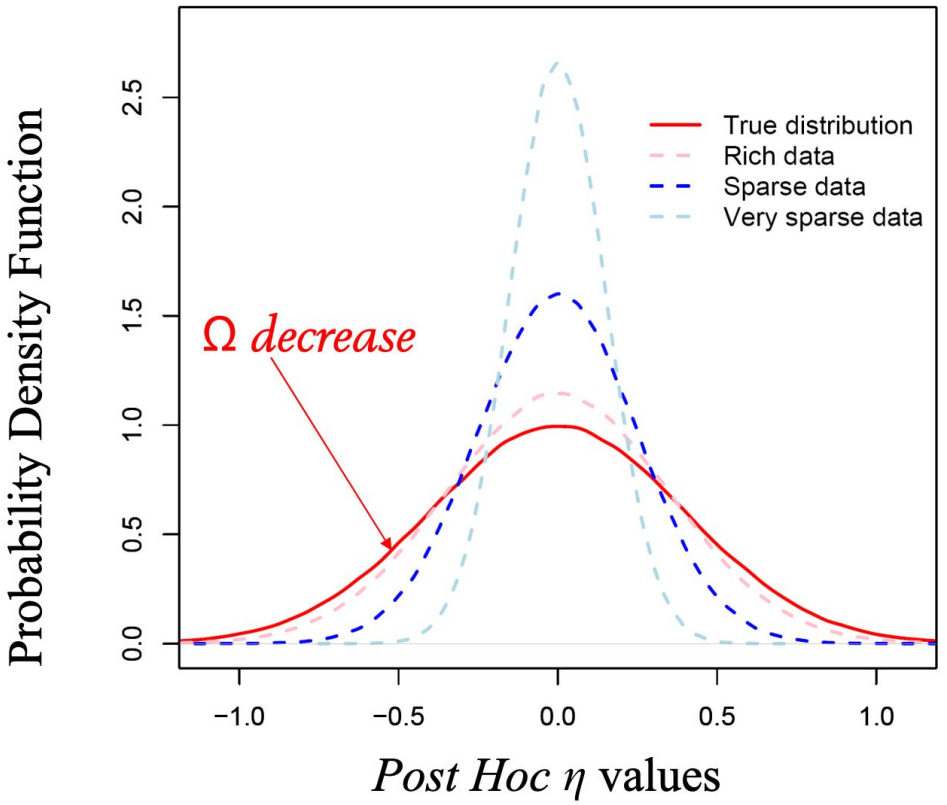
- If $\hat{\omega}^2$ is large, the change in OBJ caused by moving an individual parameter way from the typical value (increasing $\theta_i - \hat{\theta}_i$) will be small
  - Higher IIV → more flexibility in the individual model to approach observed values → ε shrinkage
- If $\hat{\sigma}^2$ is large, the change in OBJ caused by improving model fit to an observation (decreasing $C_j - \hat{C}_j$) will be small
  - Higher RUV → observations are less informative and can not support increasing $\theta_i - \hat{\theta}_i$ → η shrinkage

What causes high shrinkage?

High shrinkage may result from contributions of the following:

- Uninformative data
  - Sparse data
  - Inadequate timing of sample collection (e.g. no samples collected during absorption phase when trying to estimate η_{ka})
- RUV ($\widehat{\sigma}^2$)>> IIV ($\widehat{\omega}^2$) $\rightarrow \eta$ shrinkage

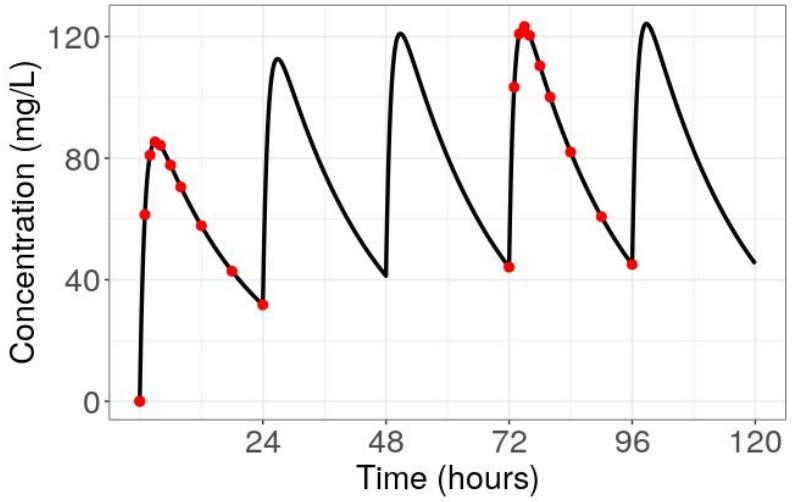
  IIV ($\widehat{\omega}^2$) >> RUV ($\widehat{\sigma}^2$) $\rightarrow \varepsilon$ shrinkage



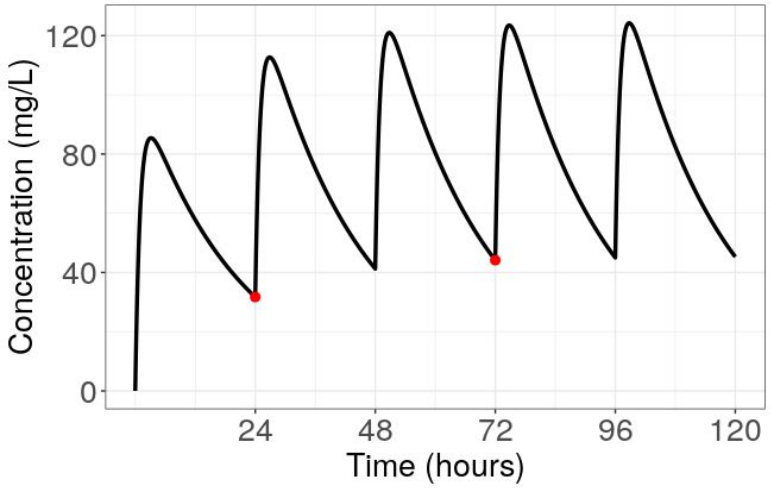
Savic, RM; Karlsson, MO. Shrinkage in Empirical Bayes Estimates for Diagnostics and Estimation: Problems and Solutions. PAGE 2007.

IIV = inter-individual variability; RUV = residual unexplained variability

Example: Uninformative data in Phase 3



Population PK Model (k_a,CL,V)



Phase 1

Rich sampling: predose, 1, 2, 3, 4, 6, 8, 12, 18, 24 hours at Day 1 and steady state

Phase 3

Sparse sampling: predose at Day 2 and steady state only

Individual data from Phase 3 is sparse and uninformative for k_a → Individual estimates informed more by the population estimates → high η_{ka} shrinkage

Example: Impact of residual error ($\hat{\sigma}^2$) in TDM

mAb TDM

Patient ID

bar1188

Weight (kg)

35

Download Report

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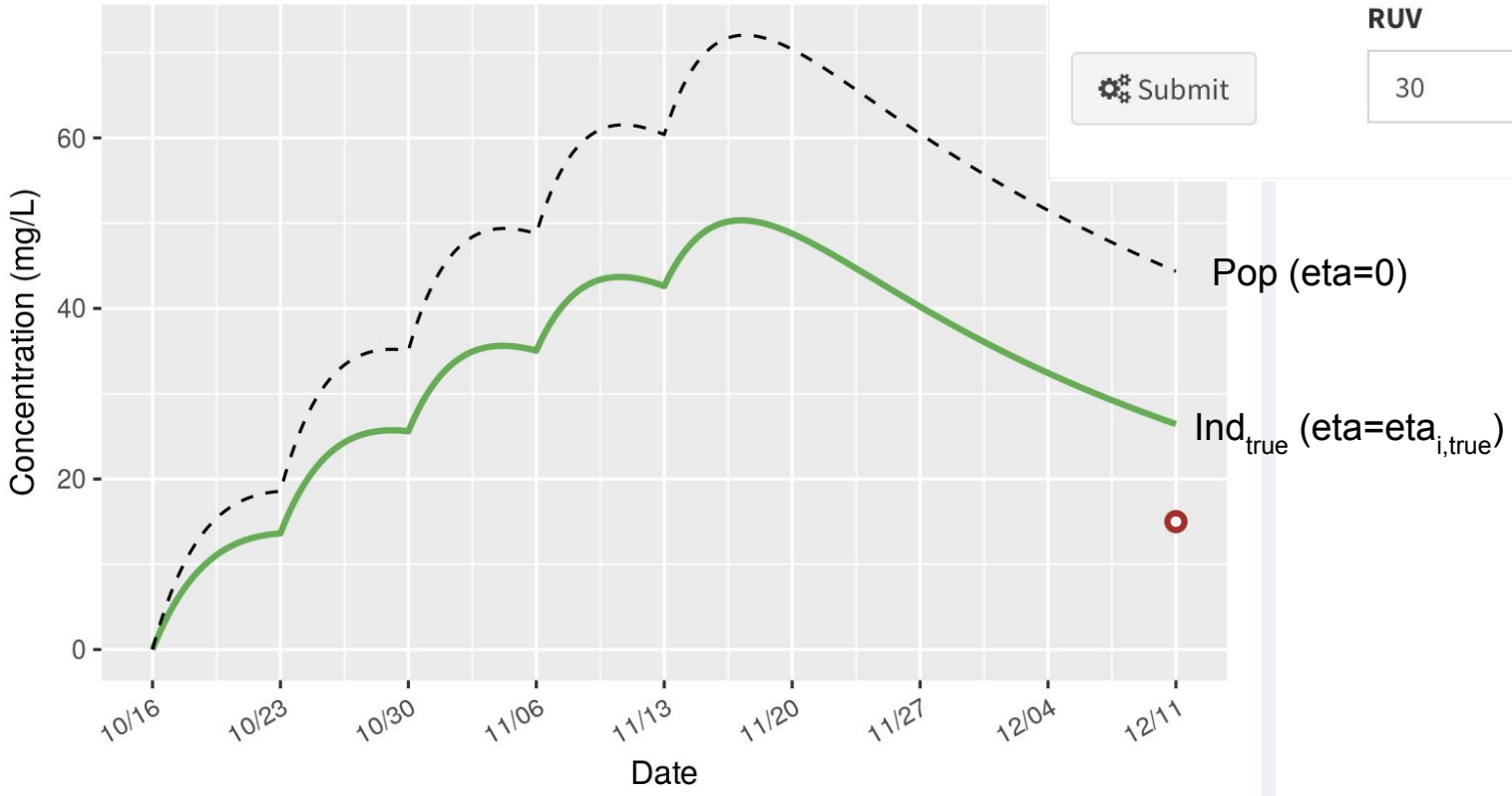
CL	0.13	0.55
Vc	2.43	0.37
Vp	1.79	0.06

CL in L/day, Vc and Vp in L. ETA is the estimated individual random effect.

Dosing history



Controls

Submit

RUV

30

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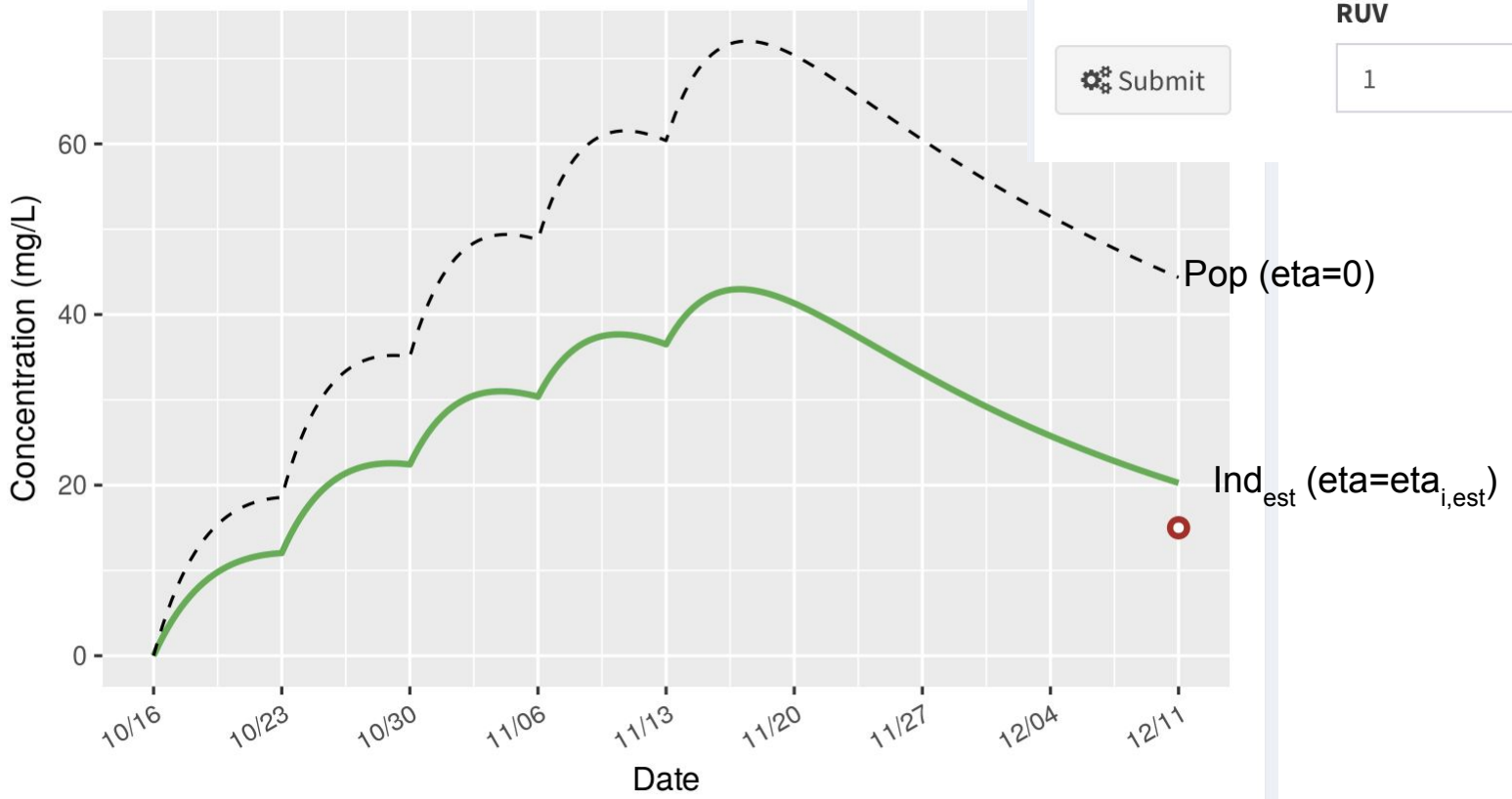
Submit

RUV

1



Low RUV (<< IIV) → Individual observations are more informative and support moving individual parameters away from population estimates → ε shrinkage

Example: Impact of residual error ($\hat{\sigma}^2$) in TDM

mAb TDM

Patient ID

bar1188

Weight (kg)

35

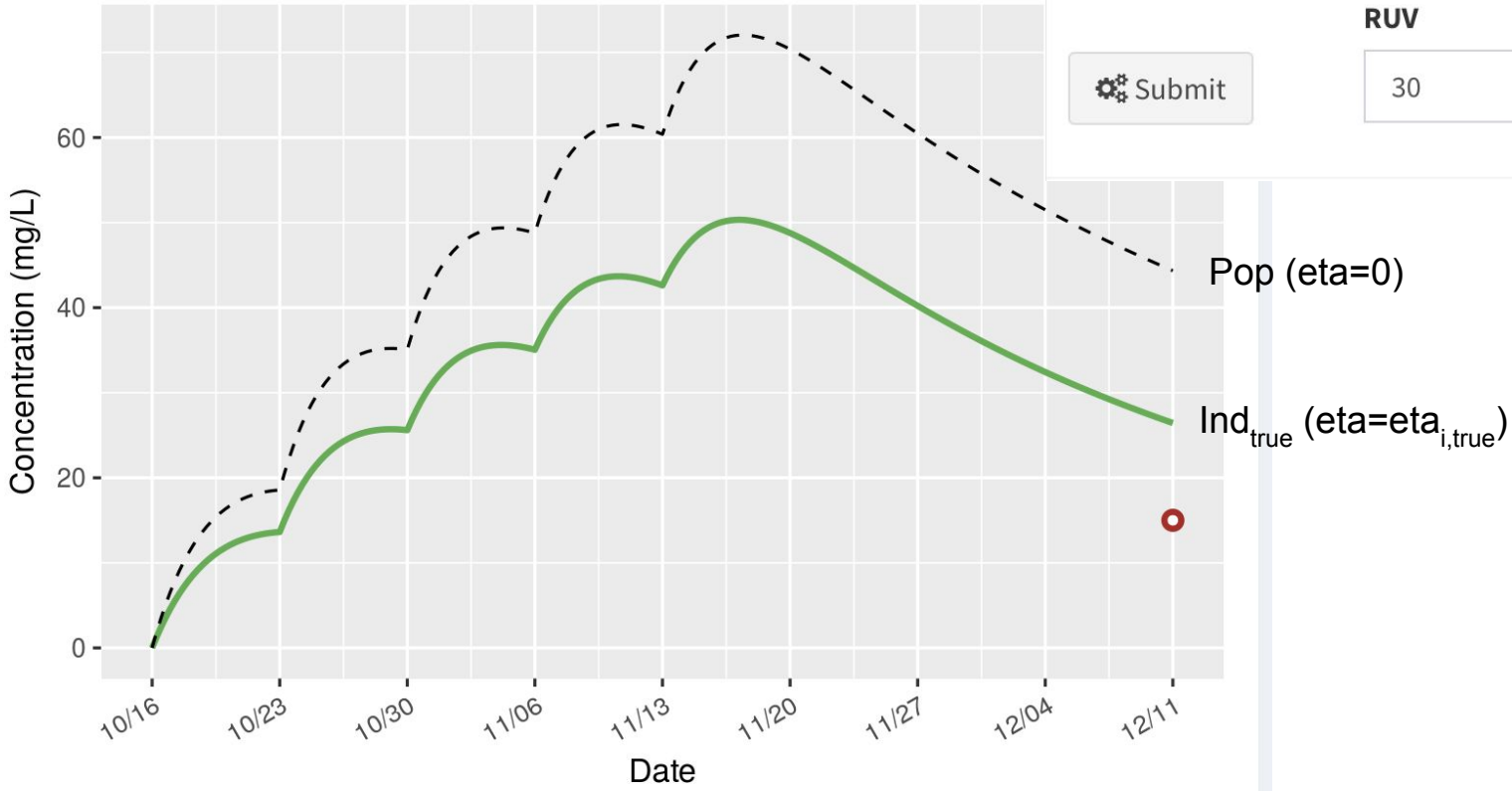
Download Report

PK Parameters

	Value	ETA
CL	0.13	0.55
Vc	2.43	0.37
Vp	1.79	0.06

CL in L/day, Vc and Vp in L. ETA is the estimated individual random effect.

Dosing history



Controls

Submit

RUV

30

Example: Impact of residual error ($\hat{\sigma}^2$) in TDM

mAb TDM

Patient ID

bar1188

Weight (kg)

35

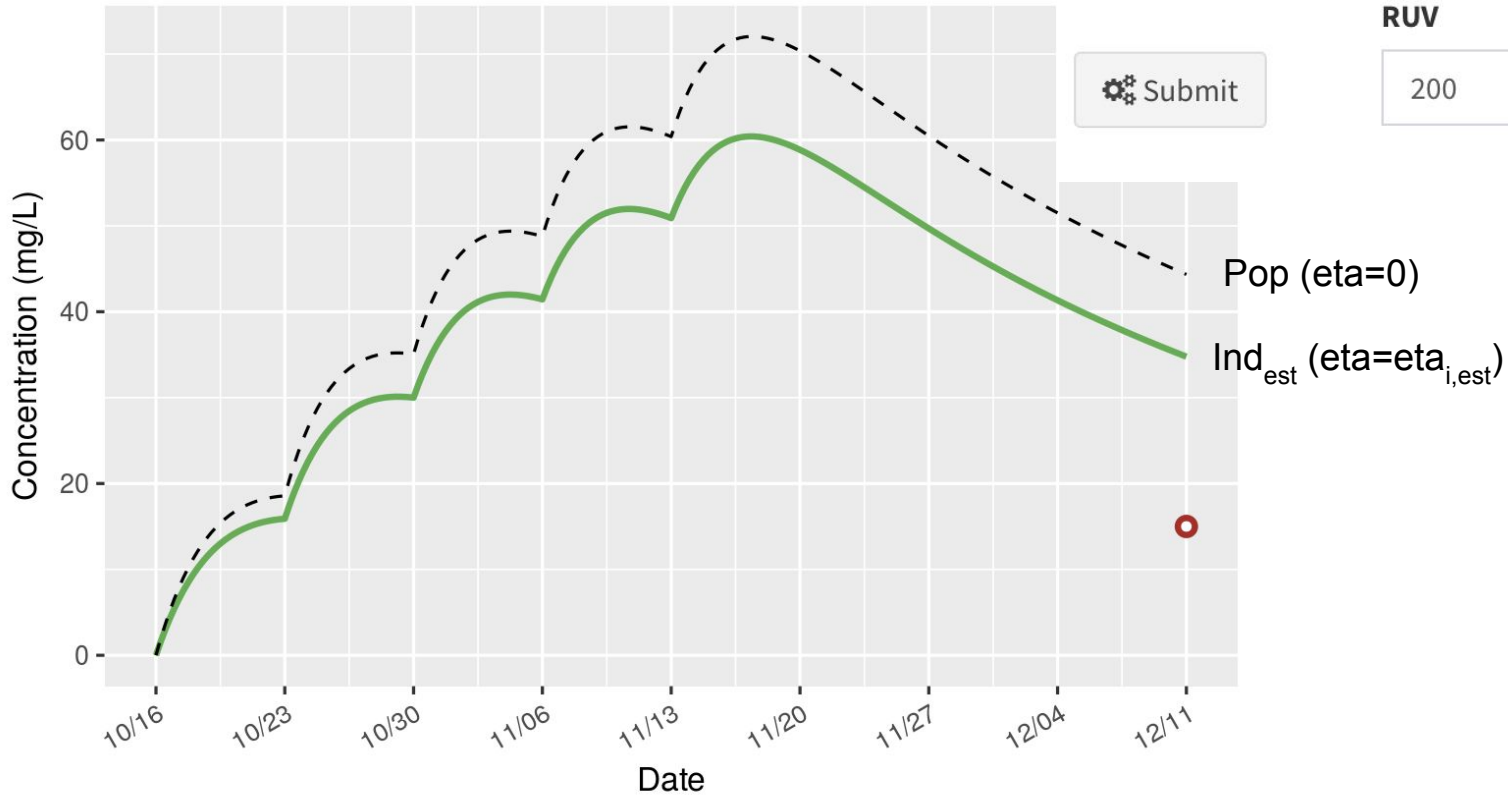
Download Report

PK Parameters

	Value	ETA
CL	0.10	0.27
Vc	2.04	0.19
Vp	1.76	0.04

CL in L/day, Vc and Vp in L. ETA is the estimated individual random effect.

Dosing history



Controls

Submit

RUV

200

High RUV (>>IIV) → Individual observations are less informative and individual parameters become more informed by population estimates → η shrinkage

Objectives

This presentation will address the following questions:

- What is shrinkage?
- What causes shrinkage?
- How is it calculated?
- Does high shrinkage indicate a problem with the model?
- What is the impact of shrinkage on model development?

Shrinkage of Random Effects: How is it calculated?

- Pharmacometrics convention: the "SD parameterization" (Savic and Karlsson, 2009)

$$shk_{\eta, SD} = 1 - SD(\eta_i) / \omega$$

$$shk_{\varepsilon, SD} = 1 - SD(IWRES)$$

  - Rule of thumb associated with that paper is that you probably shouldn't trust ETA-based diagnostics when shk_{η} or $shk_{\varepsilon} > 0.3$

    [Note: this is a general rule of thumb, but there are exceptions]

DV = individual observation; IPRED = individual predictions; IWRES = individual weighted residuals = (DV-IPRED)/σ

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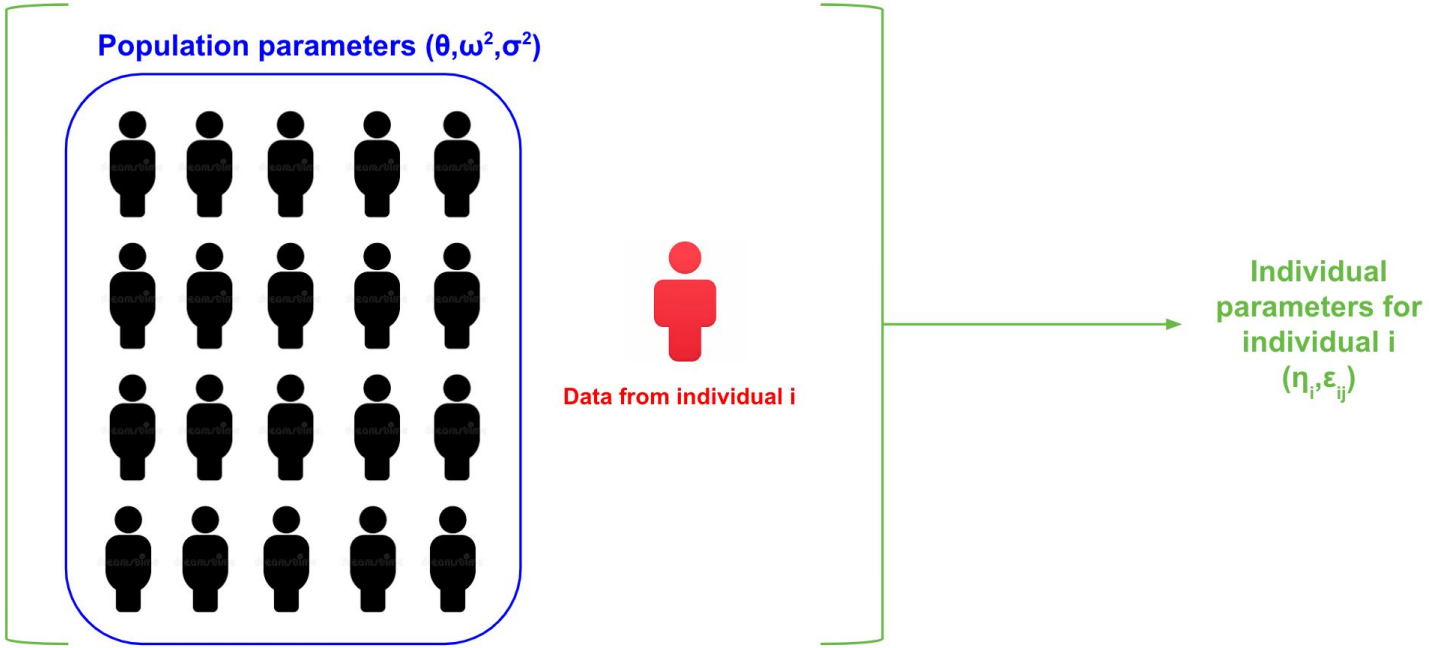

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DV = individual observation; IPRED = individual predictions; IWRES = individual weighted residuals = (DV-IPRED)/σ

Shrinkage of Random Effects: How is it calculated?

- Gelman and Pardoe (2006) present a "pooling factor" based on the proportion of variances

$$shk_{\eta, var} = 1 - var(\eta_i) / \omega^2 \qquad \text{(they called "pooling factor")}$$

$$shk_{\varepsilon, var} = 1 - var(IWRES)$$

  - The $shk_{\eta, SD} > 0.3$ rule of thumb translates to $shk_{\eta, var} > 0.5$

    ($shk_{\eta, SD} = 0.30 \rightarrow shk_{\eta, var} = 1 - 0.7^2 = 0.51$)

DV = individual observation; IPRED = individual predictions; IWRES = individual weighted residuals = (DV-IPRED)/σ

Shrinkage of Random Effects: How is it calculated?

- Savic and Karlsson, 2009: $shk_{\eta, SD} = 1 - SD(\eta_i) / \omega$ $shk_{\varepsilon, SD} = 1 - SD(IWRES)$
- Gelman and Pardoe (2006) : $shk_{\eta, var} = 1 - var(\eta_i) / \omega^2$ $shk_{\varepsilon, var} = 1 - var(IWRES)$

Note that in both equations, shrinkage calculation is an estimate of the shrinkage, conditional on the estimates of the variance terms. We never know the true shrinkage in an estimation problem.

DV = individual observation; IPRED = individual predictions; IWRES = individual weighted residuals = (DV-IPRED)/σ

#TERM from example NONMEM lst file


```
 #TERM:
0MINIMIZATION SUCCESSFUL
 NO. OF FUNCTION EVALUATIONS USED:      321
 NO. OF SIG. DIGITS IN FINAL EST.:  3.5

 ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
 AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.

 ETABAR:         -1.8987E-02 -2.3805E-03  1.3363E-03
 SE:              3.0653E-02  2.9896E-02  3.4365E-02
 N:                      160         160         160

 P VAL.:          5.3565E-01  9.3653E-01  9.6898E-01

 ETASHRINKSD(%)   1.8010E+01  3.1730E+00  4.8142E-01
 ETASHRINKVR(%)   3.2777E+01  6.2453E+00  9.6052E-01
 EBVSHRINKSD(%)   1.8120E+01  3.4639E+00  7.9179E-01
 EBVSHRINKVR(%)   3.2957E+01  6.8078E+00  1.5773E+00
 EPSSHRINKSD(%)   5.3432E+00
 EPSSHRINKVR(%)   1.0401E+01
```

As of NM74, calculations based on SD and variance are both outputted

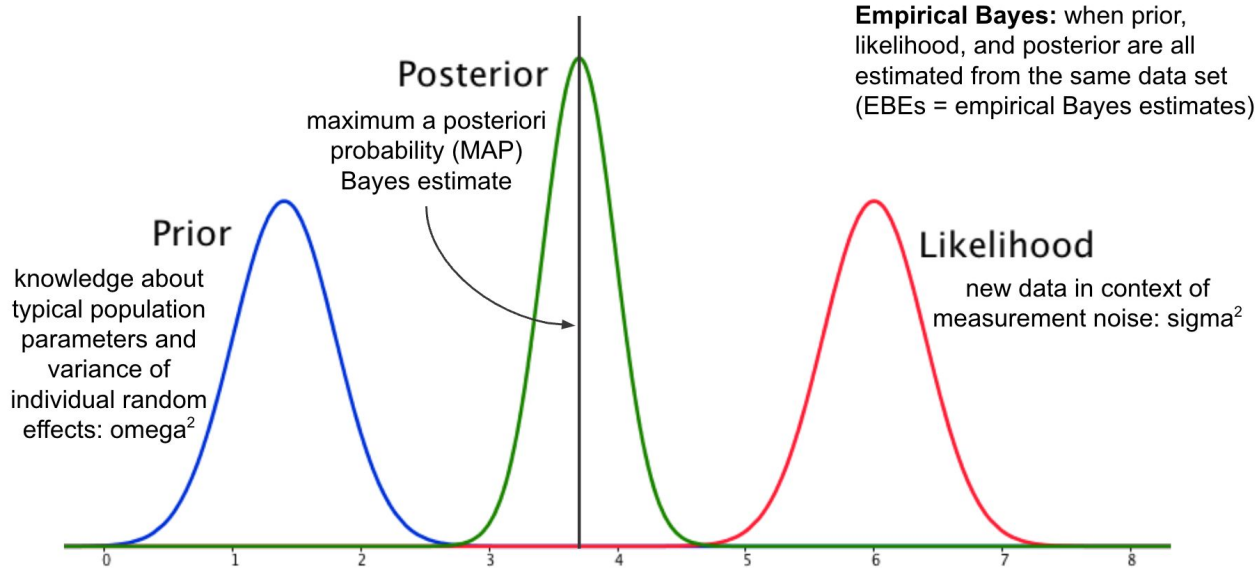
Objectives

This presentation will address the following questions:

- What is shrinkage?
- What causes shrinkage?
- How is it calculated?
- Does high shrinkage indicate a problem with the model?
- What is the impact of shrinkage on model development?

Does high shrinkage mean you have a bad model?

- High shrinkage isn't indicative of a problem with the model per se.
  - It is a reflection of the information content of *individual* model parameter estimates
  - Is it informed more by the population mean/prior? → high η shrinkage
  - Is it informed more by the individual observations? → high ε shrinkage



https://stats.stackexchange.com/questions/86472/posterior-very-different-to-prior-and-likelihood

Does high shrinkage mean you have a bad model?

- Shrinkage only impacts the random effects (random unexplained variability)
- Could have high estimated shrinkage but small impact .
  (e.g. when fixed covariate effects explain most of the variability)
  - Base model: $CL = \theta_{CL} * \exp(\eta)$

    $\eta = 0.7$ and $\exp(\eta) = 2.01 \rightarrow$ relatively large, shrinkage impacts estimation of individual CL
  - Final model with covariate: $CL = \theta_{CL} * \theta_{COV}^{cov} * \exp(\eta)$

    $\eta = 0.05$ and $\exp(\eta) = 1.05 \rightarrow$ relatively small, shrinkage probably has a small impact on the estimation of individual CL

Does high shrinkage mean you have a bad model?

- It may indicate that you can't trust certain ETA-based diagnostics and/or that you should be cautious about using individual parameter estimates in second-stage analyses (e.g. exposure-response modeling)

Objectives

This presentation will address the following questions:

- What is shrinkage?
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- What is the impact of shrinkage on model development?

Impact #1: Model diagnostics involving individual ETA, IPRED, IWRES may be misleading

- ETA based diagnostics affected by η shrinkage
  - ETA vs ETA
- Diagnostics affected by ε shrinkage
  - IPRED vs DV
  - IWRES vs IPRED
- OFV, PRED, NPDEs, and simulation-based diagnostics (e.g. VPCs) are unaffected by shrinkage

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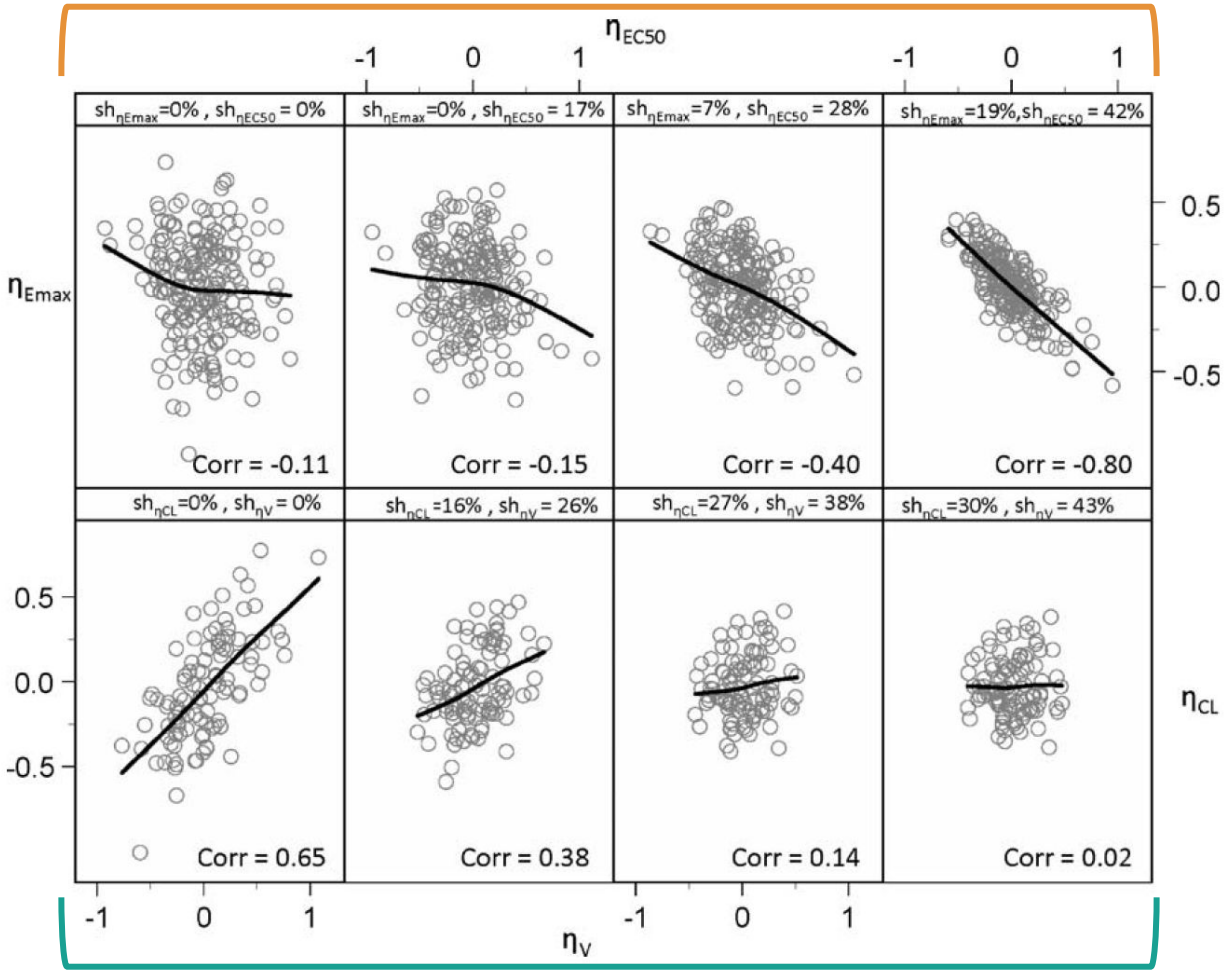
Increasing shk_{η} is falsely indicating parameter correlation



Increasing shk_{η} is hiding parameter correlation

Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. AAPS J. 2009 Sep;11(3):558-69.

Impact #1: Model diagnostics involving individual ETA, IPRED, IWRES may be misleading

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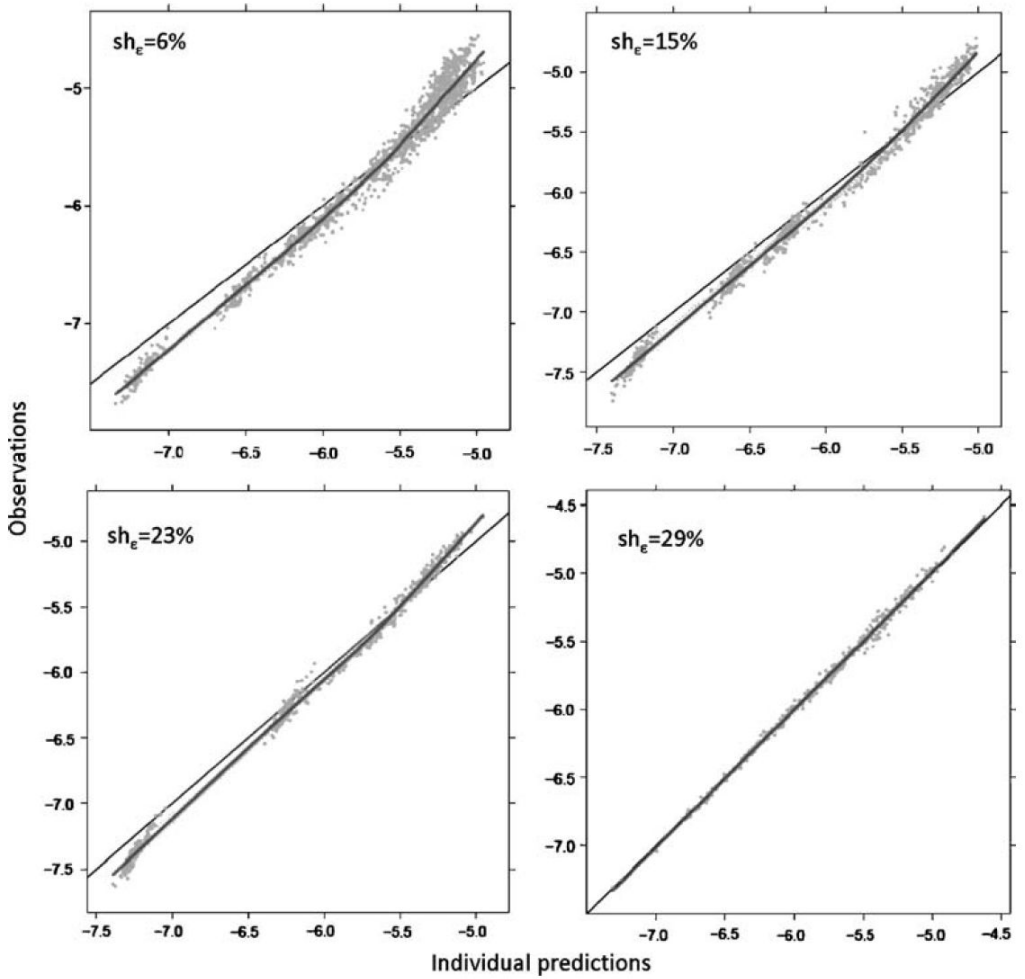

Model misspecification is absent when shk$_\varepsilon$ is high and falsely indicates a perfect fit

Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. AAPS J. 2009 Sep;11(3):558-69.

Impact #1: Model diagnostics involving individual ETA, IPRED, IWRES may be misleading

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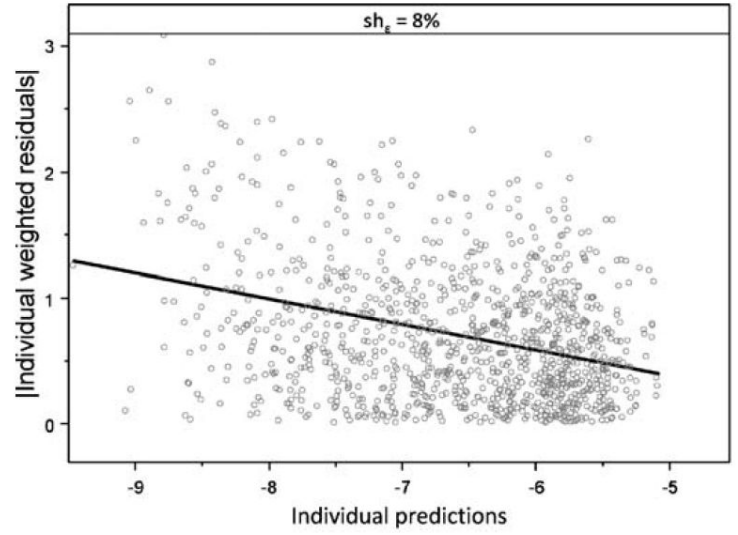
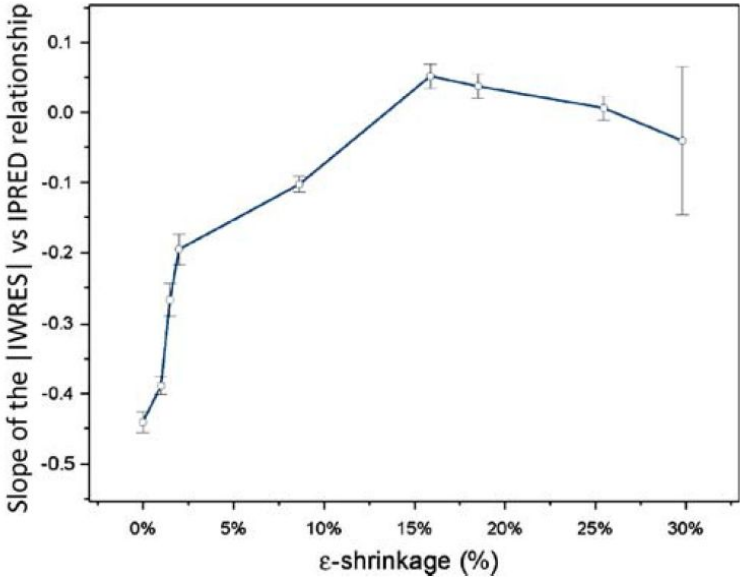
Negative slope when there is relatively small shk_{ε}



Slope diminishes with increasing shk_{ε}



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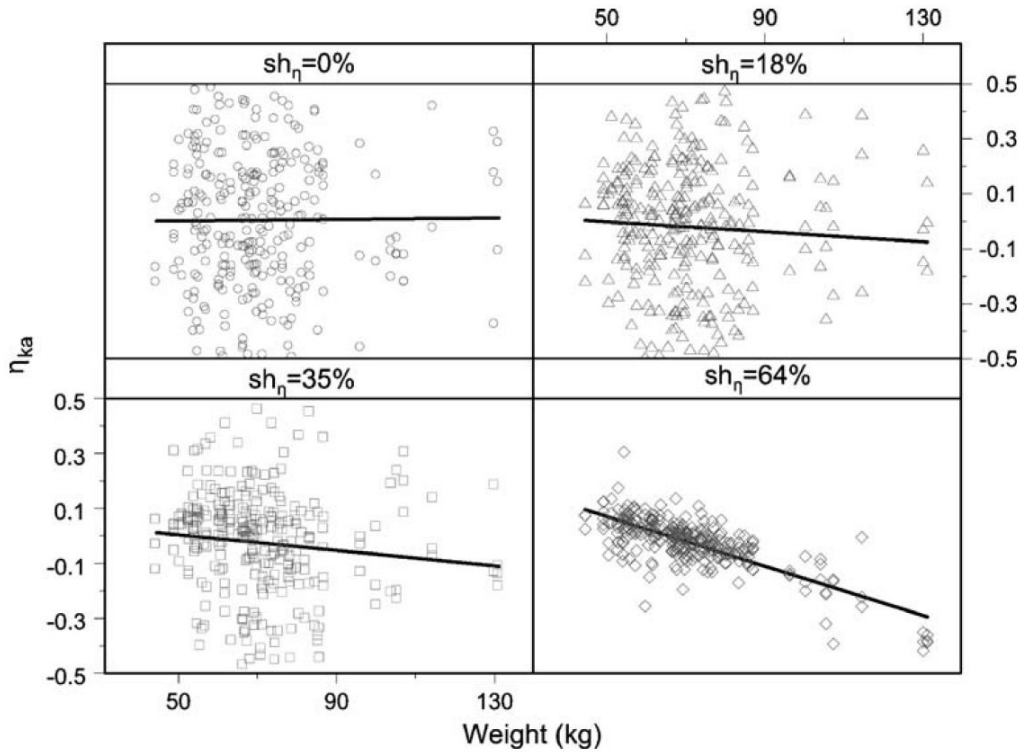
  - ETA vs ETA
- Diagnostics affected by ε shrinkage
  - IPRED vs DV
  - IWRES vs IPRED
- OFV, PRED, NPDEs, and simulation-based diagnostics (e.g. VPCs) are unaffected by shrinkage

OFV = objective function value; PRED = population prediction; NPDE = normalized prediction distribution error; CWRES = conditional weighted residuals

Impact #2: Individual ETAs not reliable for evaluating parameter covariate-relationships



Increasing shrinkage is falsely indicating correlation between parameter and covariate

- Simulations can be used instead to evaluate the impact of covariates

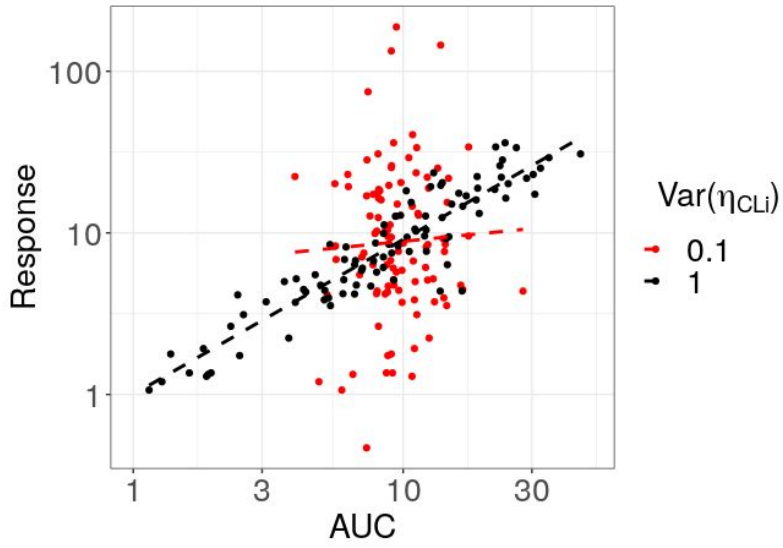
Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. AAPS J. 2009 Sep;11(3):558-69.

Impact #3: Derived individual parameters may not be reliable for use in second stage modeling

PK Model (θ,η,ε)

Individual PK parameters (e.g. CL_i , Vc_i)

Individual exposure metrics (e.g. AUC_i, $Ctrough_i$)



Increasing shrinkage can distort and/or conceal apparent ER relationships

- Should be cautious about using individual parameter estimates and exposure metrics in second stage modeling (e.g. ER modeling) when there is high shrinkage
- Could explore the impact of shrinkage by simulation

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Objectives

This presentation will address the following questions:

- What is shrinkage?
- What causes shrinkage?
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Conclusions/Takeaways (part 1/2)

- **What is shrinkage?**

  η shrinkage is when the magnitude of *individual estimated random effects shrinks towards the prior expectation (=0)*

  ε shrinkage is when the magnitude of *residual estimated random effects shrinks towards the prior expectation (=0)*

- ***What causes shrinkage?***

  Uninformative data, high inter-individual variability, and/or high residual variability

- **How is it calculated?**

  Pharmacometrics convention: $shk_{\eta, SD} = 1 - SD(\eta_i) / \omega$ $shk_{\varepsilon, SD} = 1 - SD(IWRES)$

Conclusions/Takeaways (part 2/2)

- **Does high shrinkage indicate a problem with the model?**

  High shrinkage does not indicate any problem with the dataset or with the model; it is a reflection of the information content of the model parameters at the individual level.

- **What is the impact of shrinkage on model development?**

  Shrinkage only affects graphical diagnostics based on individual parameter estimates, and potentially second-stage modeling

  To address the impact of shrinkage:

  - *Report shrinkage of random effects*
  - *Use holistics assessments of model performance (e.g. OFV, DV vs PRED, NPDE, VPCs)*
  - *Simulations can provide insight on covariate effects and impact on second-stage modeling*

Questions?

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