# Simulation Concepts

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ECP8506 Clinical Trial Simulation

10/18/2024

# Outline

- Simulation Nomenclature
- Types of Simulations
- General Modeling Process
- General Simulation Process

# Simulation Nomenclature

- Population parameter
  - Fixed effects ($\theta_n$): parameters describing structural/covariate model
  - Random effects: parameters describing variability
    - Inter-individual/occasion variability (IIV/IOV, $\omega_n^2$): $\Omega$ matrix ($\omega_1^2 \ldots \omega_n^2$)
    - Residual variability (RV, $\sigma_n^2$): $\Sigma$ matrix ($\sigma_1^2 \ldots \sigma_n^2$)
- Individual IIV/IOV
  - Empirical Bayes estimates (EBEs): $\eta_{n,i} \sim N(0, \omega_n^2)$
- Individual RV: $\varepsilon_{n,ij} \sim N(0, \sigma_n^2)$
- Parameter uncertainty/precision
  - How confident/precise in estimating the population parameters
  - Relevant to both fixed effects & random effects
- Covariate: Patient characteristics (e.g., $\mathbf{weight}_i$, $\mathbf{height}_i$, $\mathbf{age}_i$, etc)
- Replicate: A single set of simulation incorporate all trial components

*Annotations:*
*n: index of a parameter (e.g., the $n^{th}$ parameter).*
*i: index of an individual (e.g., the $i^{th}$ individual).*
*j: index of an observation (e.g., the observation collected at $j^{th}$ time point).*

# Types of Simulations

- Deterministic vs. Stochastic
- Patient-level vs Population-level
- Drug Property vs Clinical Trial

# Deterministic vs. Stochastic Simulation

- Deterministic
  - Produce a typical response for a patient/population.
  - Do not need random number generator for Monte Carlo sampling.
- Stochastic (Monte Carlo)
  - Produce a distribution of response for a patient/population.
  - Require random number generator for Monte Carlo sampling in single or multiple levels:
    - Inter-individual / occasion variability
    - Parameter uncertainty

*Mike Heathman, Simulation Concepts, ACoP 2019*

# Patient-level vs Population-level

- Patient-level
  - Each simulation replicate correspond to a (typical) patient
- Population-level
  - Each simulation replicate correspond to a population (e.g., a trial patient population, a study arm, etc)

# Drug Property vs Clinical Trial

- Drug Property
  - To understand the property of a drug
  - Independent of study design
  - Example: what is the probability to achieve X response in a typical patient given Y dosing regimen of drug Z?
- Clinical Trial
  - To understand the performance of a trial design
  - Dependent on trial design (e.g., number or characteristics of subjects, duration of study, study arms/doses)
  - Example: what is the power of the X trial given Y design?

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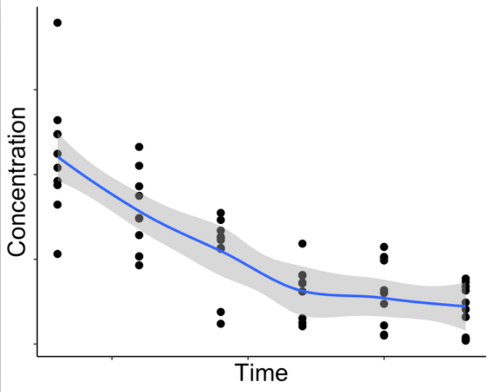
- **General Modeling Process**
- General Simulation Process

# Model Development

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|---|---|---|---|
| 65 | 31 | F | ... |
| 77 | 25 | M | ... |
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| ... | ... | ... | ... |

| ID | TIME | DV | AMT | CMT | EVID | WT | AGE |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 100 | 1 | 1 | 65 | 31 |
| 1 | 0.69 | 48.1 | 0 | 2 | 0 | 65 | 31 |
| 1 | 1.98 | 12.5 | 0 | 2 | 0 | 65 | 31 |
| 2 | 0 | 0 | 100 | 1 | 1 | 77 | 25 |
| 2 | 0.52 | 69.7 | 0 | 2 | 0 | 77 | 25 |
| 2 | 2.56 | 15.3 | 0 | 2 | 0 | 77 | 25 |

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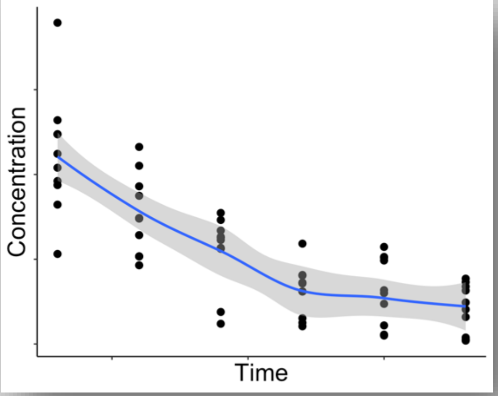


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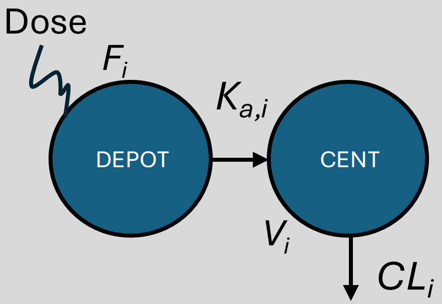

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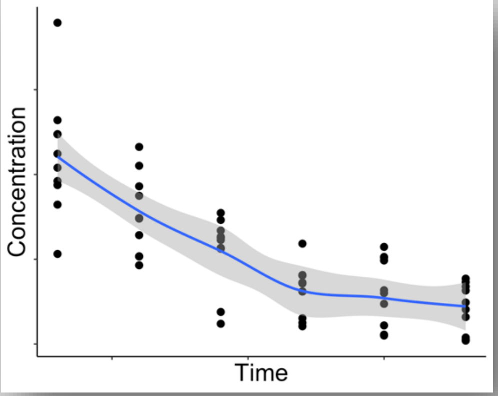


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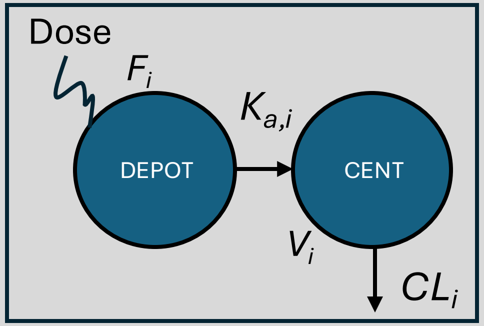


$$CL_i = \theta_1 \times \frac{WT_i}{70kg}^{\theta_2} \times e^{\eta_{1,i}}$$

$$\eta_{1,i} \sim N(0, \omega^2_{1,1})$$

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$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$$

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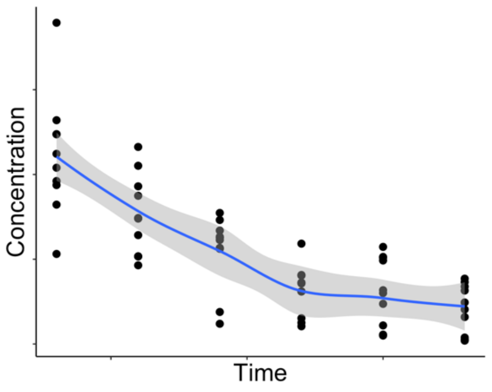


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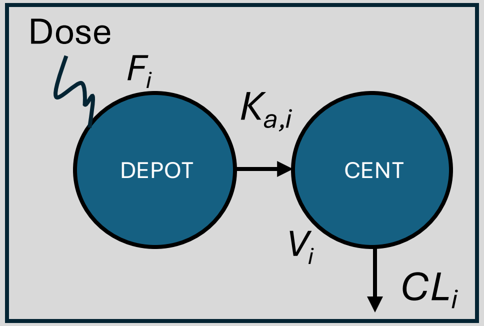


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Population parameters (`.ext`)

1. Fixed-effect

   $\theta_1, \theta_2$ ...

2. Random-effect

   2.1 $\Omega$ matrix

$$\begin{pmatrix} \omega_{1,1}^2 & \cdots & \omega_{n,1}^2 \\ \vdots & \ddots & \vdots \\ \omega_{1,n}^2 & \cdots & \omega_{n,n}^2 \end{pmatrix}$$

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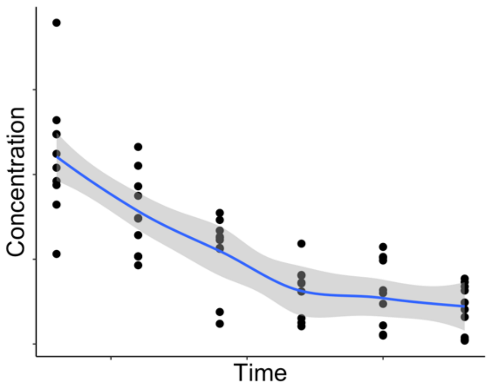


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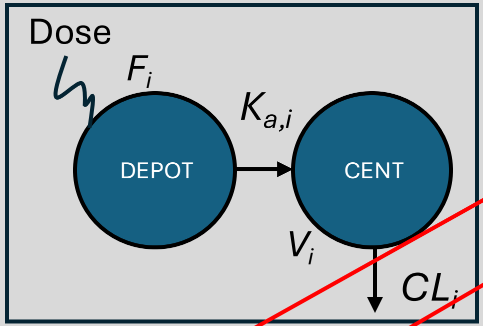


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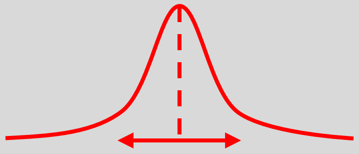
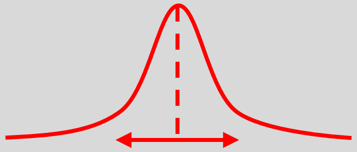


$\omega_{1,1}^2$

2.2 Σ matrix



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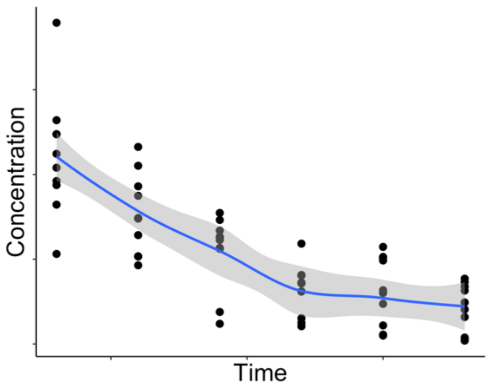


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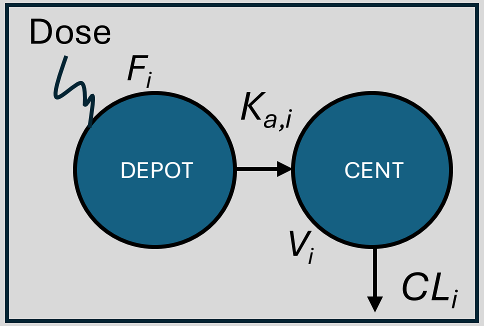


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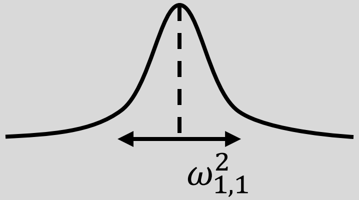


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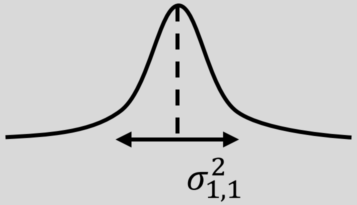


Individual random effects (`.phi`)
(Empirical-bayes estimates, EBE)
For each individual *i*:
$\boldsymbol{\eta_{1,i}, \eta_{2,i}}$....

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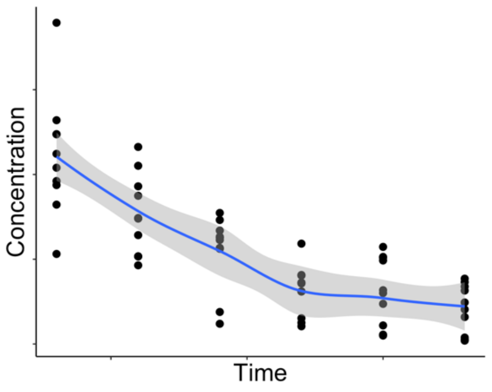


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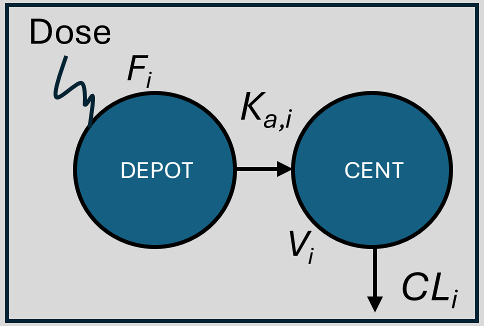


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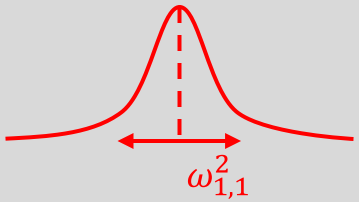


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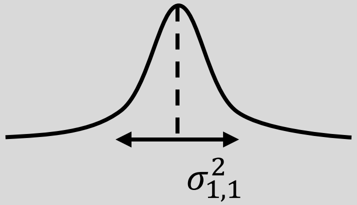


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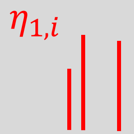

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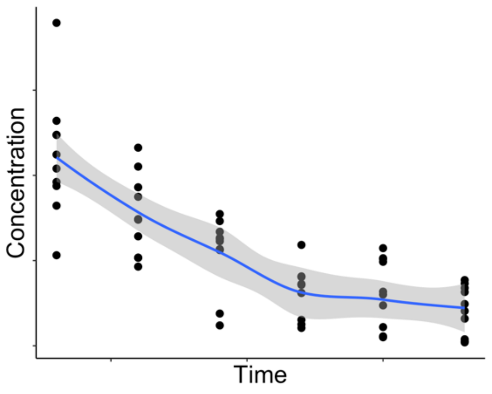


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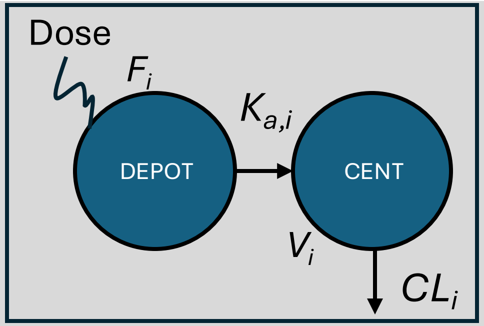
Parameter precision (.cov)
(Variance-Covariance Matrix)

$$\begin{pmatrix} VAR(\theta_1) & \cdots & COV(\sigma^2_{n,n}, \theta_1) \\ \vdots & \ddots & \vdots \\ COV(\theta_1, \sigma^2_{n,n}) & \cdots & VAR(\sigma^2_{n,n}) \end{pmatrix}$$

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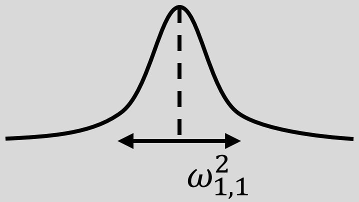


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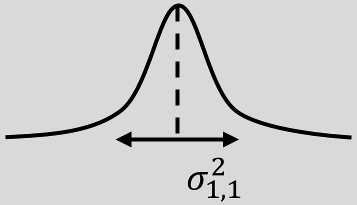


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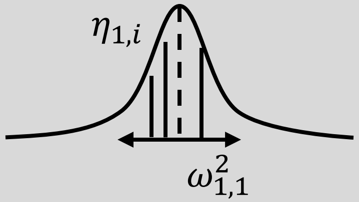

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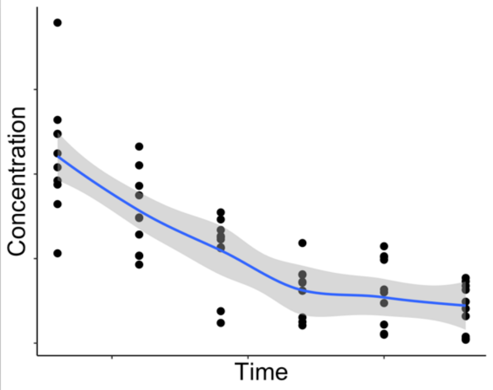


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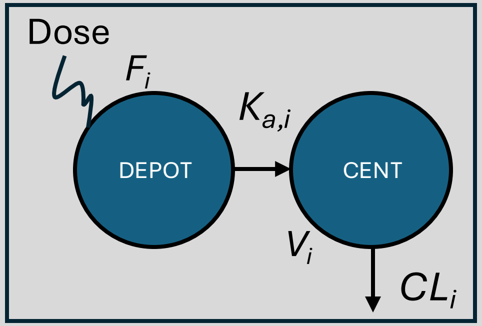


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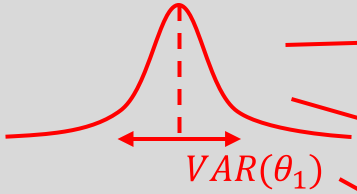


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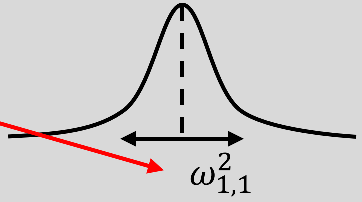


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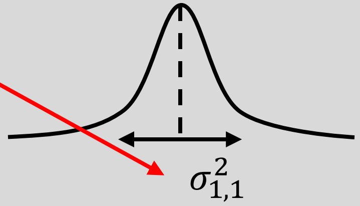


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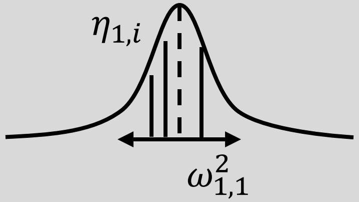

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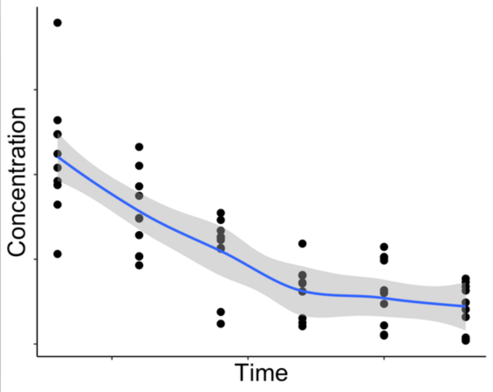


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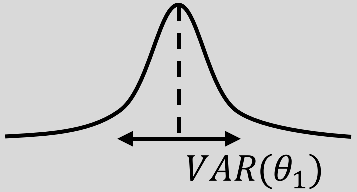


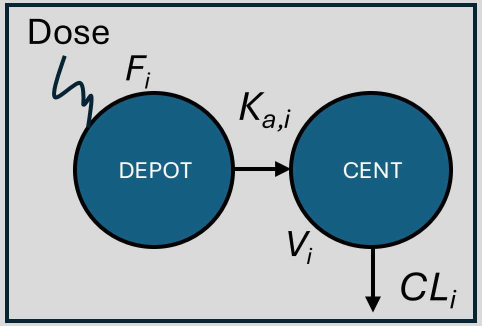


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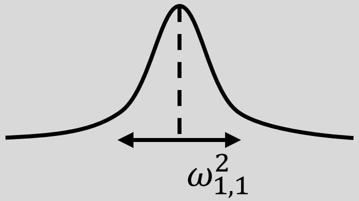


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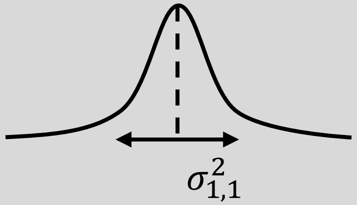


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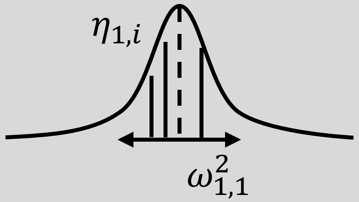

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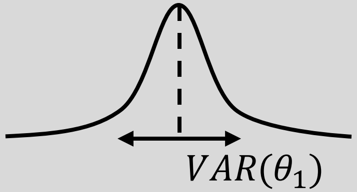
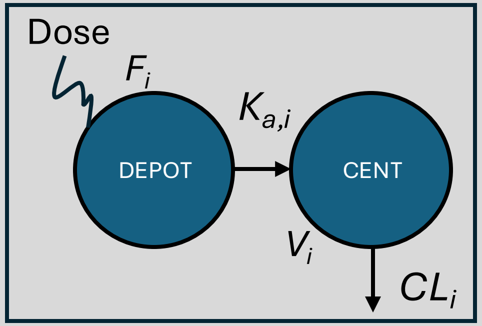
(Variance-Covariance Matrix)




$$CL_i = \theta_1 \times {\frac{WT_i}{70kg}}^{\theta_2} \times e^{\eta_{1,i}}$$

$$\eta_{1,i} \sim N(0, \omega_{1,1}^2)$$

...

$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$$

$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

$$\epsilon_{1,ij} \sim N(0, \sigma_{1,1}^2)$$

...

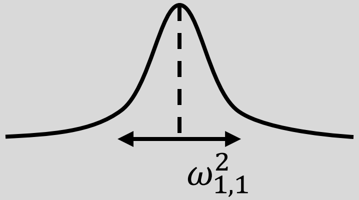
Population parameters (`.ext`)

1. Fixed-effect

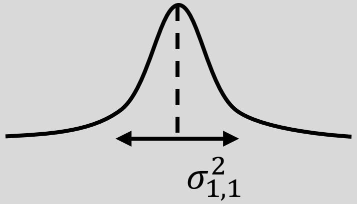
   $\boldsymbol{\theta_1}, \boldsymbol{\theta_2}$ ...

2. Random-effect

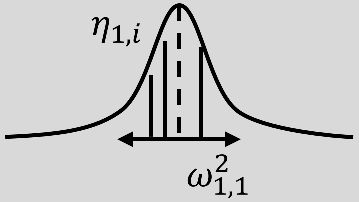
   2.1 Ω matrix




   2.2 Σ matrix



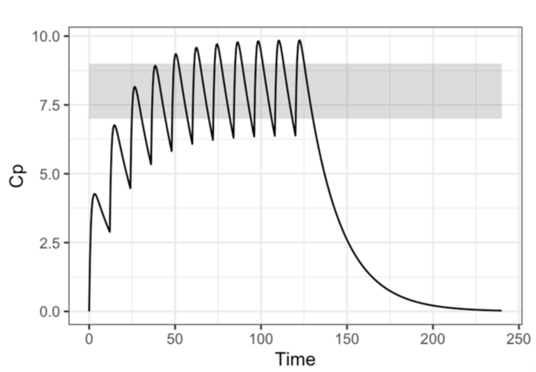

Individual random effects (`.phi`)
(Empirical-bayes estimates, EBE)




| WT | AGE | SEX | ... |
|---|---|---|---|
| 65 | 31 | F | ... |
| 77 | 25 | M | ... |
| 102 | 36 | M | ... |
| ... | ... | ... | ... |

# Simulation

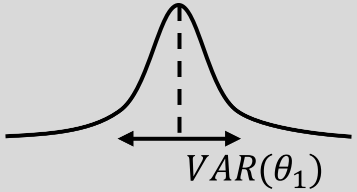
Simulation design:
- Treatment regimen
- Study duration
- Sampling schedule




| WT | AGE | SEX | ... |
|---|---|---|---|
| 65 | 31 | F | ... |
| 77 | 25 | M | ... |
| 102 | 36 | M | ... |
| ... | ... | ... | ... |

?

Parameter precision (`.cov`)
(Variance-Covariance Matrix)




?

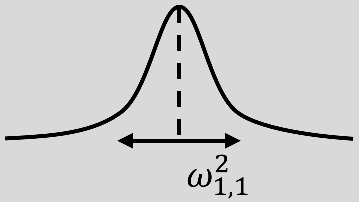
Population parameters (`.ext`)

1. Fixed-effect

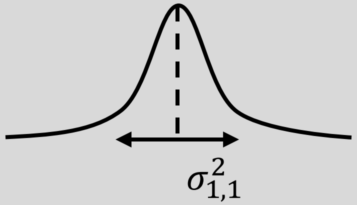
   $\boldsymbol{\theta_1}, \boldsymbol{\theta_2}$ ...

2. Random-effect

   2.1 Ω matrix

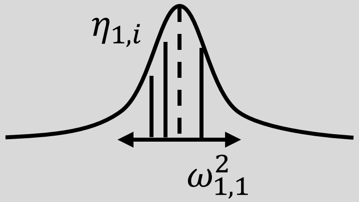


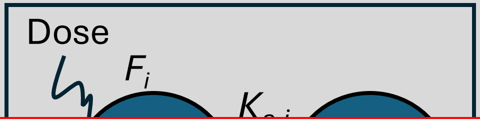

   2.2 Σ matrix




?

Individual random effects (`.phi`)
(Empirical-bayes estimates, EBE)




The incorporation of simulation components depend on the type of simulation and the question to be answered

$$\eta_{1,i} \sim N(0, \omega_{1,1}^2)$$

...

$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$$

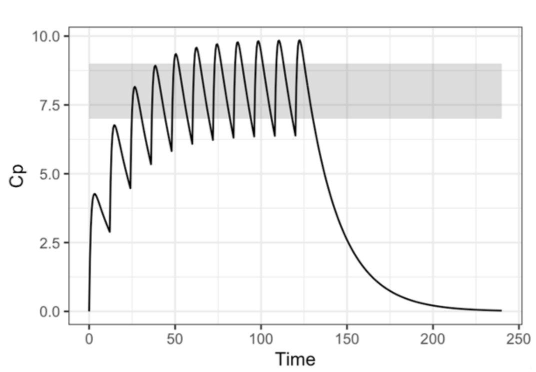
$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

$$\epsilon_{1,ij} \sim N(0, \sigma_{1,1}^2)$$

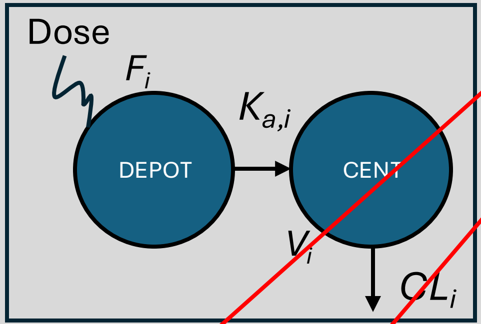
...

# Deterministic Simulation-Typical Value Simulation

Simulation design:
- Treatment regimen
- Study duration
- Sampling schedule




| WT | AGE | SEX | ... |
|---|---|---|---|
| 65 | 31 | F | ... |
| 77 | 25 | M | ... |
| 102 | 36 | M | ... |
| ... | ... | ... | ... |




$$CL_i = \theta_1 \times \left(\frac{WT_i}{70kg}\right)^{\theta_2} \times e^{\eta_{1,i}}$$

$$\boldsymbol{\eta_{1,i} = 0}$$

...

$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$$

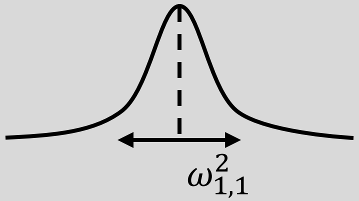
$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

$$\boldsymbol{\epsilon_{1,ij} = 0}$$

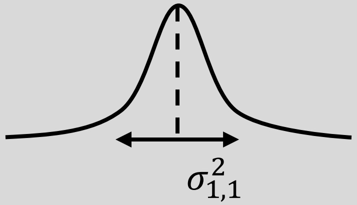
...

Population parameters (`.ext`)

1. Fixed-effect
   $\boldsymbol{\theta_1, \theta_2}$ ...
2. Random-effect
   - 2.1 Ω matrix




   - 2.2 Σ matrix



# Typical Workflow When Perform Typical Value Simulations

For i=1, …, nsub

  Fix $\eta_i$=0 for subject i

  Fix $\varepsilon_{ij}$=0 for subject i at time j

  Derive $\theta_i = f(\theta, cov_i)$ for subject i

  Calculate response $Y_{ij} = f(\theta_i, \eta_i=0, \varepsilon_{ij}=0)$

End

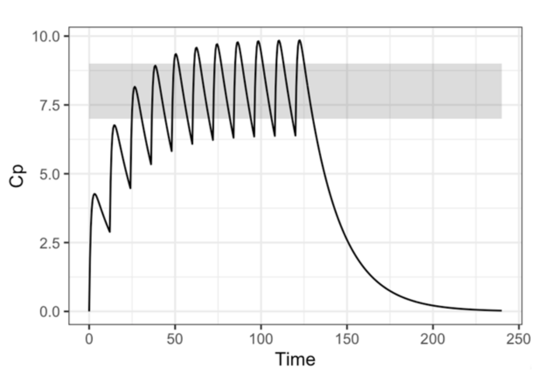
nsub: number of subjects

$cov_i$: covariates (e.g., body weight, age, etc) in subject i

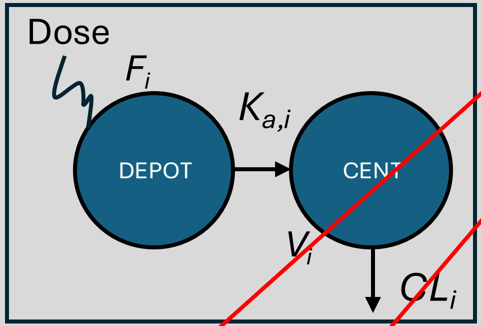
Adapted from Hu C. *J Pharmacokinet Pharmacodyn.* 2022 PMID: 35927373.

# Deterministic Simulation-EBE simulation

Simulation design:
- Treatment regimen
- Study duration
- Sampling schedule




| WT | AGE | SEX | ... |
|---|---|---|---|
| 65 | 31 | F | ... |
| 77 | 25 | M | ... |
| 102 | 36 | M | ... |
| ... | ... | ... | ... |




$$CL_i = \theta_1 \times \frac{WT_i}{70kg}^{\theta_2} \times e^{\eta_{1,i}}$$

$$\eta_{1,i} \sim N(0, \omega_{1,1}^2)$$

...

$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$$

$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

$$\epsilon_{1,ij} \sim N(0, \sigma_{1,1}^2)$$

...

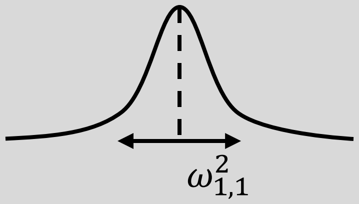
Population parameters (`.ext`)

1. Fixed-effect

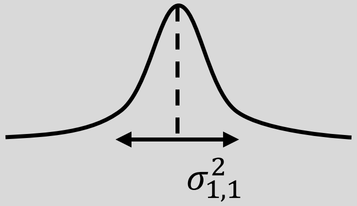
   $\boldsymbol{\theta_1, \theta_2}$ ...

2. Random-effect

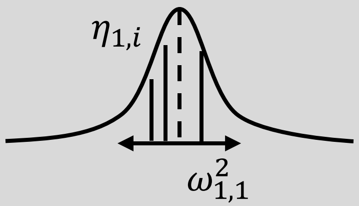
   2.1 Ω matrix




   2.2 Σ matrix




Individual random effects (`.phi`)
(Empirical-bayes estimates, EBE)



# Typical Workflow When Perform EBE Simulations

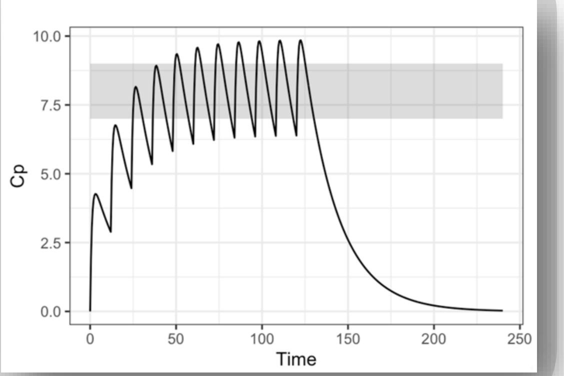
```
For i=1, …, nsub
    Fix ηi=ηi in model output for subject i
    Fix εij=0 for subject i at time j
    Derive EBEi= f(θ, covi, ηi) for subject i
    Calculate response Yij = f(EBEi,εij=0)
End
```

nsub: number of subjects
$cov_{i:}$ covariates (e.g., body weight, age, etc) in subject i
$EBE_i$: empirical Bayes estimates in subject i

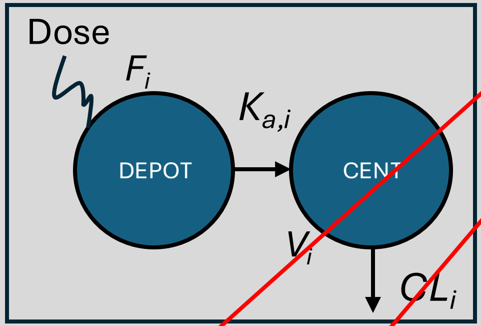
Adapted from Hu C. *J Pharmacokinet Pharmacodyn.* 2022 PMID: 35927373.

# Stochastic Simulation

Simulation design:
- Treatment regimen
- Study duration
- Sampling schedule




| WT | AGE | SEX | ... |
|---|---|---|---|
| 65 | 31 | F | ... |
| 77 | 25 | M | ... |
| 102 | 36 | M | ... |
| ... | ... | ... | ... |




$$CL_i = \theta_1 \times \frac{WT_i}{70kg}^{\theta_2} \times e^{\eta_{1,i}}$$

$$\eta_{1,i} \sim N(0, \omega^2_{1,1})$$

...

$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$$

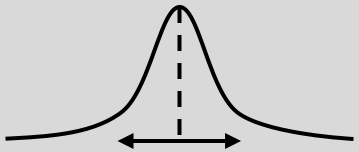
$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

$$\epsilon_{1,ij} \sim N(0, \sigma^2_{1,1})$$

...

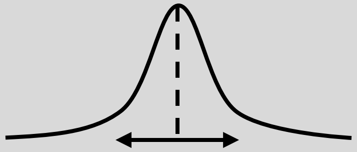
Population parameters (`.ext`)

1. Fixed-effect
   $\boldsymbol{\theta_1, \theta_2}$ ...
2. Random-effect
   - 2.1 Ω matrix



$\omega^2_{1,1}$

   - 2.2 Σ matrix



$\sigma^2_{1,1}$

# Typical Workflow When Perform Stochastic Simulations

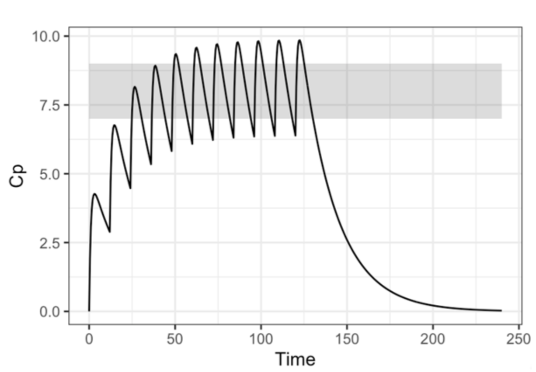
```
For i=1, …, nsub
    Draw sample ηi for subject i using Ω matrix
    *Draw sample εij for subject i at time j using Σ matrix/Fix εij=0
    Derive θi = f(θ,covi)
    Calculate response Yij = f(θi,ηi,εij)
End
```

nsub: number of subjects
$cov_{i:}$ covariates (e.g., body weight, age, etc) in subject i
*: this step may or may not be needed

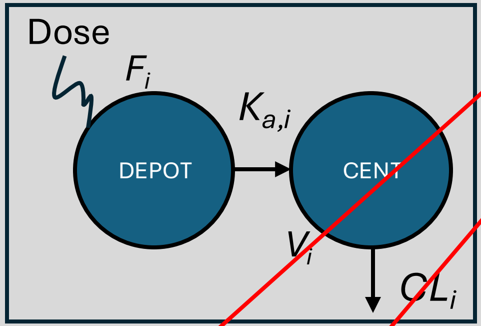
Adapted from Hu C. *J Pharmacokinet Pharmacodyn.* 2022 PMID: 35927373.

# Covariate (Virtual Patient) Simulations

Simulation design:
- Treatment regimen
- Study duration
- Sampling schedule




| WT | AGE | SEX | ... |
|---|---|---|---|
| 45 | 12 | M | ... |
| 57 | 15 | F | ... |
| 33 | 6 | F | ... |
| ... | ... | ... | ... |




$$CL_i = \theta_1 \times \left(\frac{WT_i}{70kg}\right)^{\theta_2} \times e^{\eta_{1,i}}$$

$$\eta_{1,i} \sim N(0, \omega^2_{1,1})$$

...

$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$$

$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

$$\epsilon_{1,ij} \sim N(0, \sigma^2_{1,1})$$

...

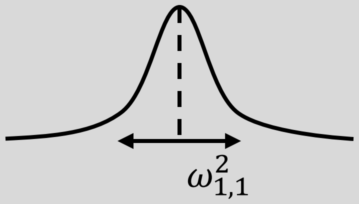
Population parameters (`.ext`)

1. Fixed-effect

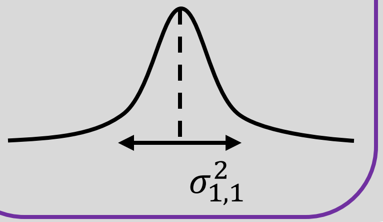
   $\boldsymbol{\theta_1}, \boldsymbol{\theta_2}$ ...

2. Random-effect

   2.1 Ω matrix




   2.2 Σ matrix



# Typical Workflow When Perform Stochastic Simulations

```
For i=1, …, nsub
    Draw sample ηi for subject i using Ω matrix
    *Draw sample εij for subject i at time j using Σ matrix/Fix εij=0
    Derive θi = f(θ,covi)
    Calculate response Yij = f(θi,ηi,εij)
End
```

nsub: number of subjects
$cov_i$: covariates (e.g., body weight, age, etc) in subject i
*: this step may or may not be needed

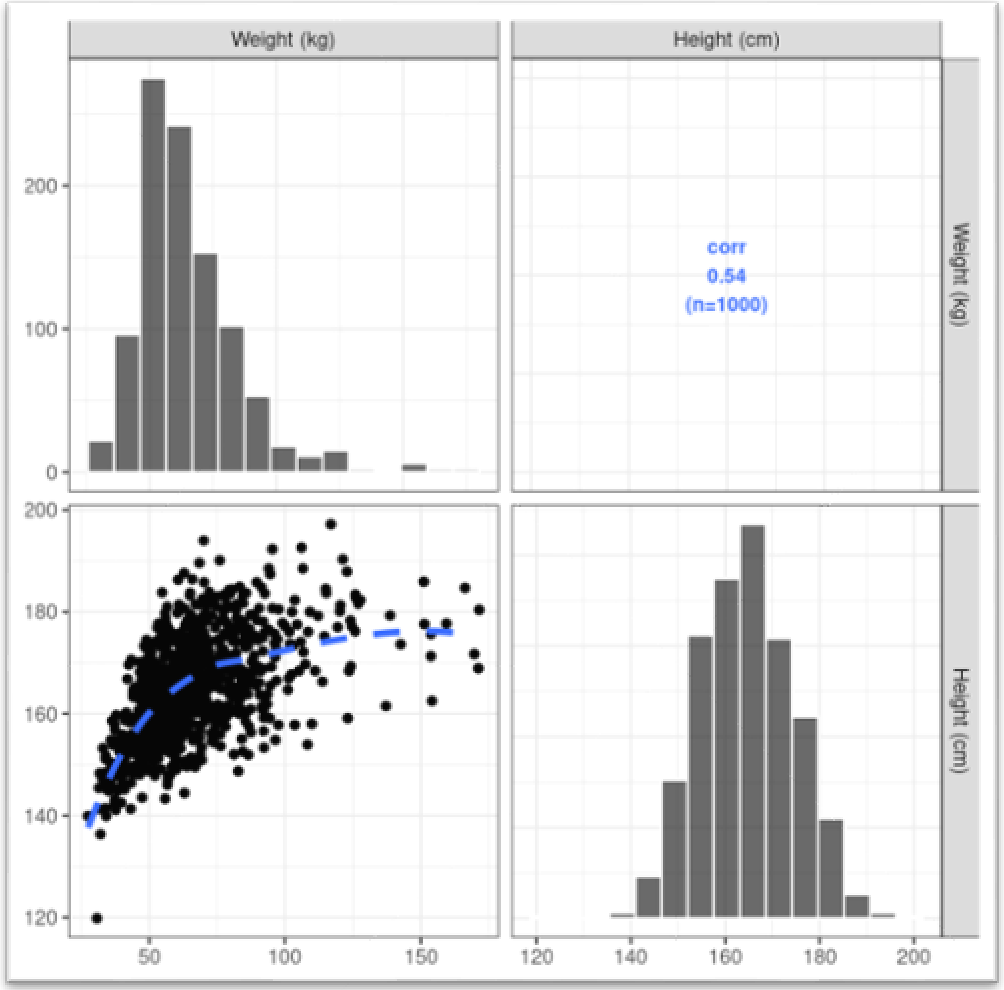
Adapted from Hu C. *J Pharmacokinet Pharmacodyn.* 2022 PMID: 35927373.

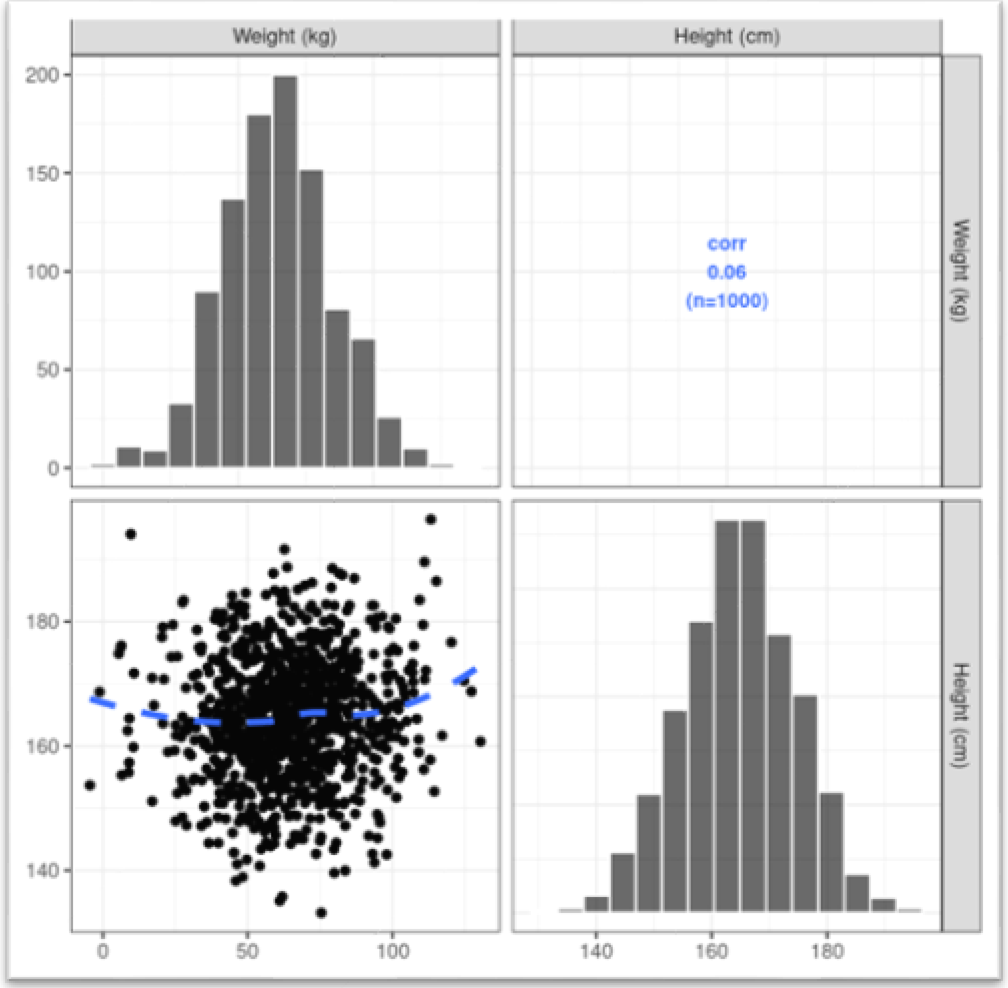
# The Importance of Realistic Covariates/Virtual Patients

```
mean_WT  <- mean(test1$WT)
sd_WT    <- sd(test1$WT)
mean_HT <- mean(test1$HT)
sd_HT   <- sd(test1$HT)

withr::with_seed(1234,
                 test2 <- data.frame(ID=1:1000,
                                     WT=rnorm(1000,mean=mean_WT,sd=sd_WT),
                                     HT=rnorm(1000,mean=mean_HT,sd=sd_HT)
                                     )
                 )
```

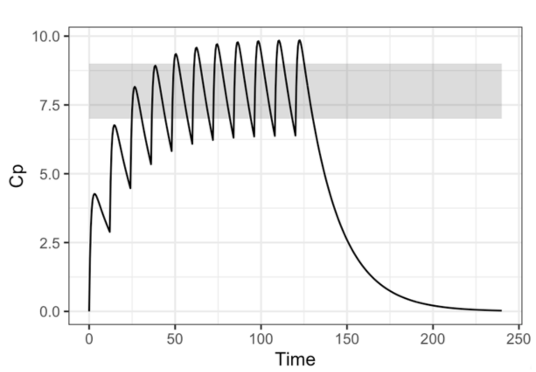
# The Importance of Realistic Covariates/Virtual Patients



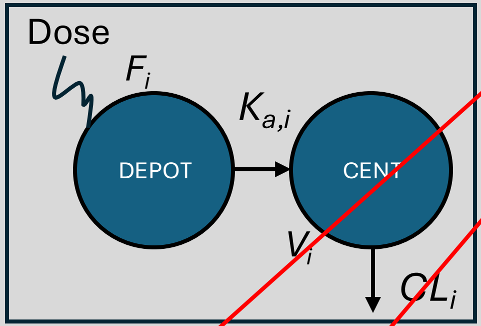



# Stochastic Simulation-Multiple Replicates

Simulation design:
- Treatment regimen
- Study duration
- Sampling schedule




| WT | AGE | SEX | ... |
|---|---|---|---|
| 65 | 31 | F | ... |
| 77 | 25 | M | ... |
| 102 | 36 | M | ... |
| ... | ... | ... | ... |




$$CL_i = \theta_1 \times \frac{WT_i}{70kg}^{\theta_2} \times e^{\eta_{1,i}}$$

$$\eta_{1,i} \sim N(0, \omega_{1,1}^2)$$

...

$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$$

$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

$$\epsilon_{1,ij} \sim N(0, \sigma_{1,1}^2)$$

...

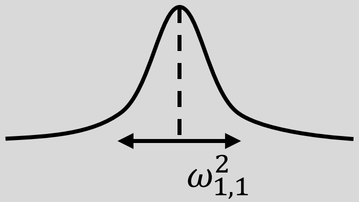
Population parameters (`.ext`)

1. Fixed-effect

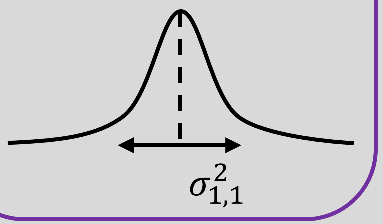
$\theta_1, \theta_2$ ...

2. Random-effect

2.1 Ω matrix




2.2 Σ matrix




n simulation replicates...

e.g., Visual Predictive Check (VPC)

# Typical Workflow When Perform Stochastic Simulations with Replicates

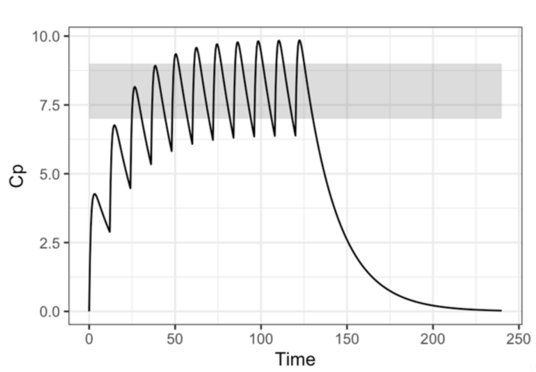
```
For n=1, …, nrep
    Fixed population parameters (θn,Ωn,Σn)
    For i=1, …, nsub
        Draw sample ηni for subject i using Ωn matrix
        *Draw sample εnij for subject i at time j using Σn matrix
        Derive θni = f(θn,covi)
        Calculate response Ynij = f(θni,ηni,εnij)
    End
End
```

Adapted from Hu C. *J Pharmacokinet Pharmacodyn.* 2022 PMID: 35927373.

nrep: number of replicates
nsub: number of subjects
$cov_{i:}$ covariates (e.g., body weight, age, etc) in subject i
*: this step may or may not be needed

# Simulations with Parameter Uncertainty

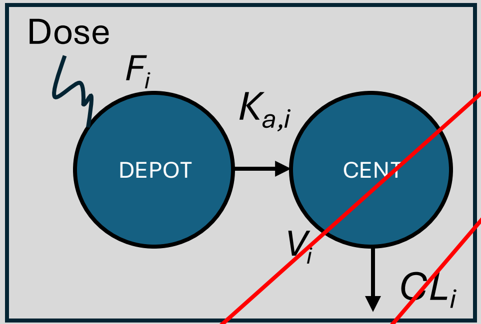
Simulation design:
- Treatment regimen
- Study duration
- Sampling schedule




| WT | AGE | SEX | ... |
| --- | --- | --- | --- |
| 65 | 31 | F | ... |
| 77 | 25 | M | ... |
| 102 | 36 | M | ... |
| ... | ... | ... | ... |

Parameter precision (.cov)
(Variance-Covariance Matrix)

$VAR(\theta_1)$




$$CL_i = \theta_1 \times \frac{WT_i}{70kg}^{\theta_2} \times e^{\eta_{1,i}}$$

$$\eta_{1,i} \sim N(0, \omega^2_{1,1})$$

...

$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$$

$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

$$\epsilon_{1,ij} \sim N(0, \sigma^2_{1,1})$$

...

Population parameters (.ext)

1. Fixed-effect

$\theta_1, \theta_2$ ...

2. Random-effect

2.1 Ω matrix

$\omega^2_{1,1}$

2.2 Σ matrix

$\sigma^2_{1,1}$

n simulation replicates

n = number of (parameter vector) samples from uncertainty/precision distributions

# Parameter uncertainty

- Parametric
  - Variance-Covariance matrix
    - Multivariate normal distribution (MVN) for fixed effects ($\theta$)
    - Inverse wishart distribution for random effects ($\omega^2$, $\sigma^2$)
- Non-parametric
  - Non-parametric bootstrap (BS)
  - Sampling-importance resampling (SIR)
  - Bayesian posterior distribution

# Example-parameter uncertainty distribution

| THETA26 | THETA27 | THETA28 | THETA29 | THETA30 | THETA31 | SIGMA11 | SIGMA21 | SIGMA22 | SIGMA31 | SIGMA32 | SIGMA33 | SIGMA41 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 78.2643 | 173.280 | 4.23748 | 11.29380 | 38.4408 | 0.421612 | 0.1284490 | 0 | 0.231501 | 0 | 0 | 1.42394e-02 | 0 |
| 75.4385 | 187.590 | 6.70469 | 10.08790 | 38.2204 | 0.770196 | 0.1230070 | 0 | 0.169305 | 0 | 0 | 5.43827e-02 | 0 |
| 79.6005 | 199.938 | 8.32571 | 8.66037 | 34.6556 | 0.459137 | 0.1171680 | 0 | 0.225894 | 0 | 0 | 2.33182e-02 | 0 |
| 87.9661 | 175.794 | 8.29748 | 11.13200 | 39.0711 | 0.759876 | 0.1244250 | 0 | 0.220386 | 0 | 0 | 2.17099e-02 | 0 |
| 75.8812 | 191.139 | 6.86712 | 9.22780 | 38.4680 | 0.732315 | 0.1244530 | 0 | 0.175997 | 0 | 0 | 9.39109e-02 | 0 |
| 70.3069 | 173.470 | 4.82680 | 14.95260 | 47.1471 | 0.579151 | 0.1076460 | 0 | 0.210610 | 0 | 0 | 7.75502e-02 | 0 |
| 81.8855 | 188.210 | 7.74528 | 11.30250 | 44.6379 | 0.600335 | 0.1237930 | 0 | 0.179454 | 0 | 0 | 3.97410e-02 | 0 |
| 66.3120 | 168.565 | 4.72414 | 10.55790 | 43.1807 | 0.689960 | 0.1142910 | 0 | 0.202239 | 0 | 0 | 1.01691e-01 | 0 |
| 81.8855 | 188.210 | 7.74528 | 11.30250 | 44.6379 | 0.600335 | 0.1237930 | 0 | 0.179454 | 0 | 0 | 3.97410e-02 | 0 |
| 79.9607 | 175.246 | 6.69603 | 13.90940 | 46.7332 | 0.495290 | 0.1135310 | 0 | 0.148579 | 0 | 0 | 9.13649e-02 | 0 |
| 74.4892 | 193.416 | 7.24374 | 10.24710 | 37.2643 | 0.544433 | 0.1077070 | 0 | 0.238335 | 0 | 0 | 3.82922e-02 | 0 |
| 74.3885 | 152.993 | 3.46359 | 16.16600 | 51.5856 | 0.767976 | 0.1066810 | 0 | 0.173881 | 0 | 0 | 1.10103e-01 | 0 |
| 73.3570 | 172.858 | 7.41016 | 15.44230 | 48.3020 | 0.593316 | 0.1251960 | 0 | 0.227475 | 0 | 0 | 4.25733e-02 | 0 |
| 78.1788 | 207.868 | 7.13567 | 7.37614 | 29.0706 | 0.386793 | 0.1120590 | 0 | 0.229197 | 0 | 0 | 1.10849e-02 | 0 |
| 70.42 | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | e-02 | 0 |
| 72.45 | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | e-02 | 0 |
| 70.1317 | 181.916 | 6.35709 | 10.07400 | 36.9336 | 0.614484 | 0.1305550 | 0 | 0.142311 | 0 | 0 | 3.75782e-02 | 0 |
| 75.3637 | 165.523 | 5.40291 | 13.32590 | 47.3354 | 0.711567 | 0.1088070 | 0 | 0.197540 | 0 | 0 | 8.80181e-02 | 0 |
| 81.8706 | 180.612 | 5.84744 | 14.58160 | 47.8523 | 0.500094 | 0.1133710 | 0 | 0.206229 | 0 | 0 | 1.66550e-02 | 0 |
| 80.1339 | 193.143 | 10.17130 | 8.30131 | 35.9364 | 0.524376 | 0.1077170 | 0 | 0.167458 | 0 | 0 | 4.54383e-02 | 0 |
| 72.2611 | 189.345 | 7.02739 | 10.94060 | 39.7045 | 0.590808 | 0.1170220 | 0 | 0.229699 | 0 | 0 | 3.47564e-02 | 0 |
| 87.4499 | 188.969 | 5.77477 | 9.64096 | 38.2691 | 0.400700 | 0.1050200 | 0 | 0.186759 | 0 | 0 | 7.05388e-02 | 0 |
| 76.3858 | 180.004 | 4.87934 | 9.24225 | 35.5641 | 0.553712 | 0.1105240 | 0 | 0.164901 | 0 | 0 | 7.51390e-02 | 0 |
| 76.9455 | 167.172 | 6.74738 | 8.96678 | 35.6594 | 0.703699 | 0.1093990 | 0 | 0.166276 | 0 | 0 | 6.86325e-02 | 0 |
| 66.5364 | 163.174 | 4.30772 | 12.83680 | 42.4348 | 1.139320 | 0.1069100 | 0 | 0.227534 | 0 | 0 | 1.81235e-02 | 0 |
| 89.0809 | 210.186 | 7.98011 | 7.84637 | 32.7716 | 0.532804 | 0.1216850 | 0 | 0.196216 | 0 | 0 | 2.99445e-02 | 0 |
| 75.4385 | 187.590 | 6.70469 | 10.08790 | 38.2204 | 0.770196 | 0.1230070 | 0 | 0.169305 | 0 | 0 | 5.43827e-02 | 0 |
| 79.6935 | 177.214 | 4.72871 | 11.53630 | 42.3676 | 0.517813 | 0.1200820 | 0 | 0.195516 | 0 | 0 | 2.70341e-02 | 0 |

1 row = 1 parameter vector =1 simulation replicate

# Typical Workflow When Perform Simulations with Parameter Uncertainty

```
For n=1, …, nrep
    Draw a set of parameters (θn,Ωn,Σn) from the uncertainty distribution
    For i=1, …, nsub
        Draw sample ηni for subject i using Ωn matrix
        *Draw sample εnij for subject i at time j using Σn matrix
        Derive θni = f(θn,covi)
        Calculate response Ynij = f(θni,ηni,εnij)
    End
End
```

Adapted from Hu C. *J Pharmacokinet Pharmacodyn.* 2022 PMID: 35927373.

nrep: number of replicates
nsub: number of subjects
$cov_{i:}$ covariates (e.g., body weight, age, etc) in subject i
*: this step may or may not be needed

# The end