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 parameters
  - Fixed effects (θ): parameters describing structural/covariate model
  - Random effects: parameters describing variability
    - Inter-individual/occasion variability (IIV/IOV, ω^2)
    - Residual variability (RV, σ^2)
- Parameter uncertainty/precision
  - How <u>confident/precise</u> in estimating the population parameters
  - Both fixed effects & random effects
- Covariates
  - Patient characteristics (e.g., body weight, height, age, etc)
- Replicate
  - A single set of simulation incorporate <u>all trial components</u>

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

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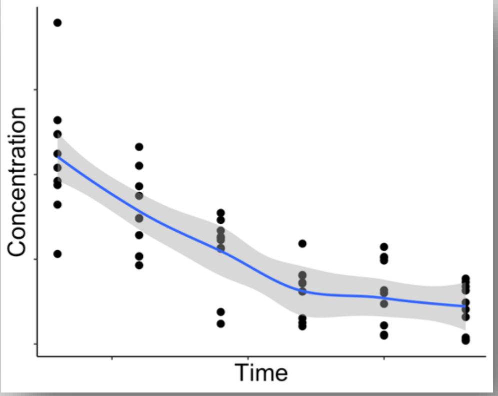
- **General Modeling Process**
- General Simulation Process

Model Development



WT	AGE	SEX	...
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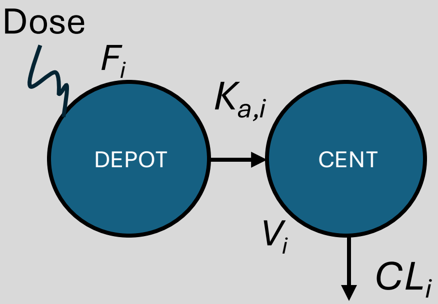

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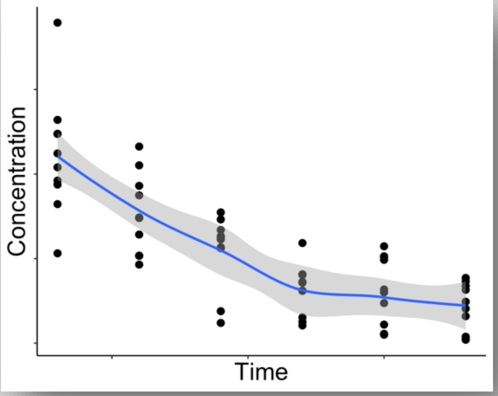

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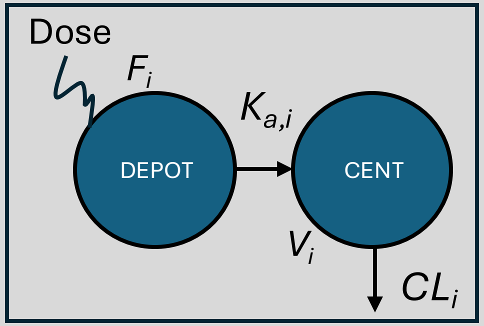

$$CL_i = \theta_1 \times \frac{WT_i}{70kg}^{\theta_2} \times e^{\eta_{1,i}}$$

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

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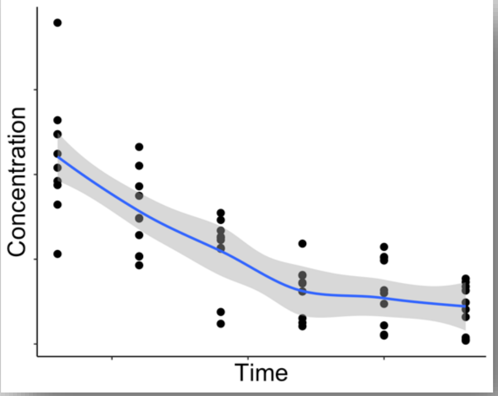

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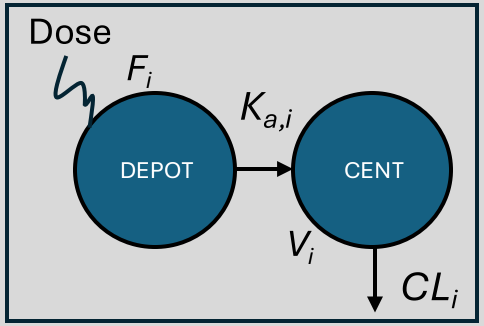

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Population parameters (`.ext`)

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2. Random-effect

   2.1 Ω matrix

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

   2.2 Σ matrix

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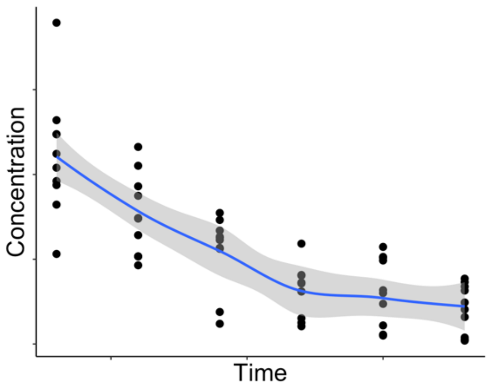

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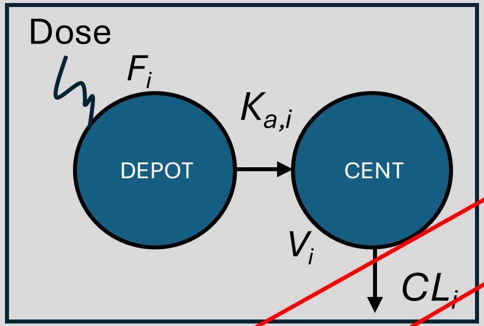

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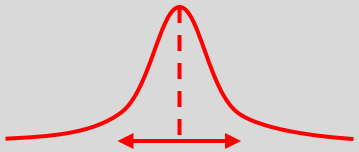

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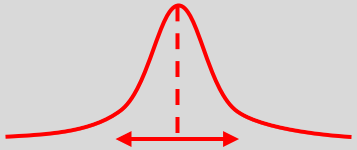

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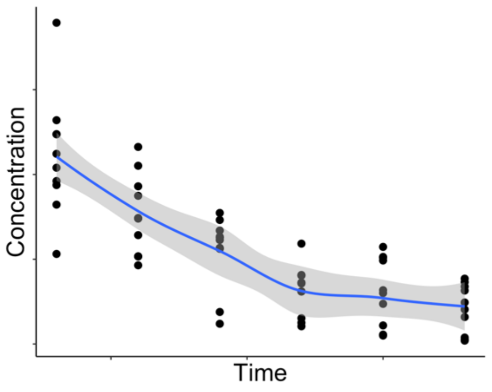

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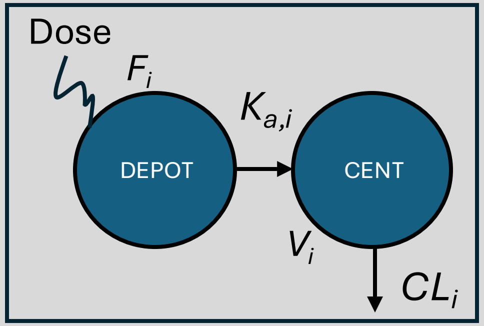

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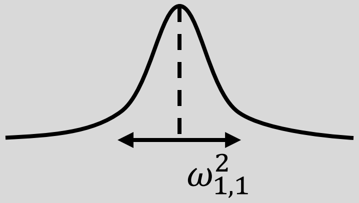

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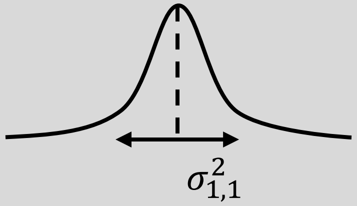
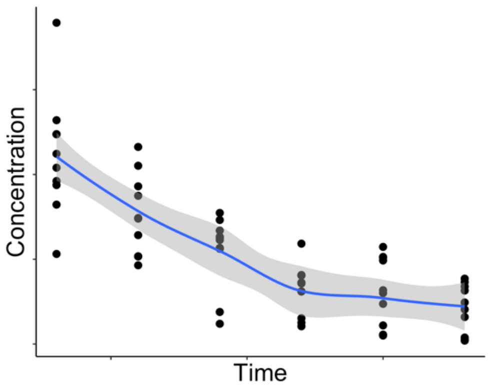


Individual random effects (`.phi`)
(Empirical-bayes estimates, EBE)
For each individual *i*:
$\boldsymbol{\eta_{1,i}}, \boldsymbol{\eta_{2,i}} \ldots$

Model Development



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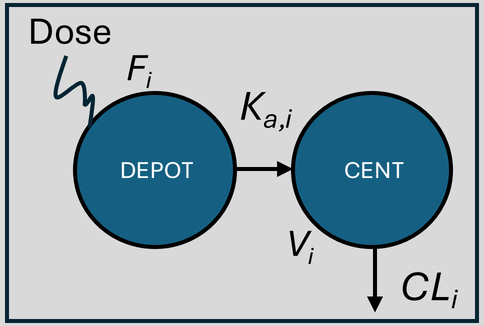

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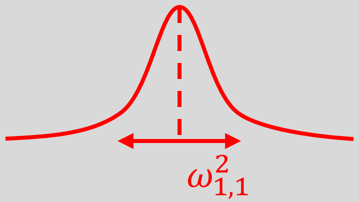

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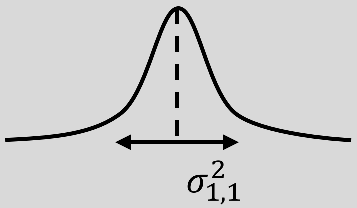

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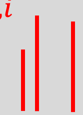

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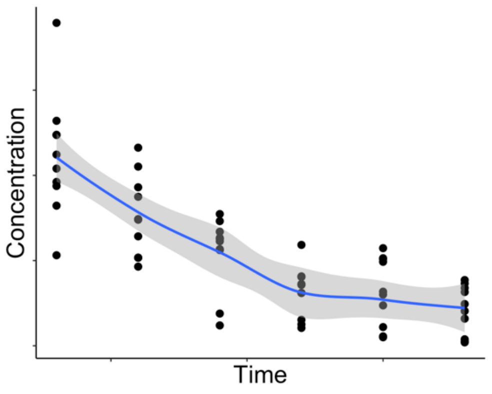

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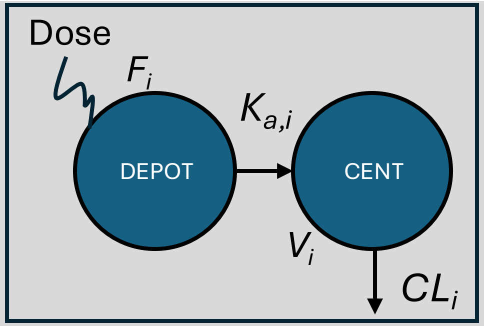
Parameter precision (.cov)
(Variance-Covariance Matrix)

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



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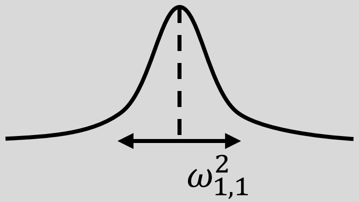

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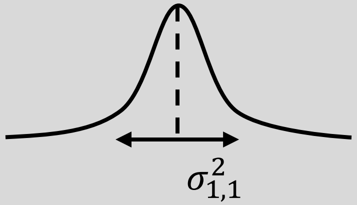

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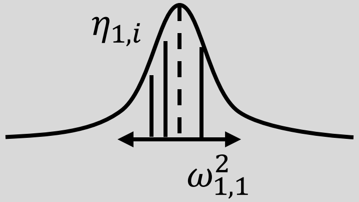

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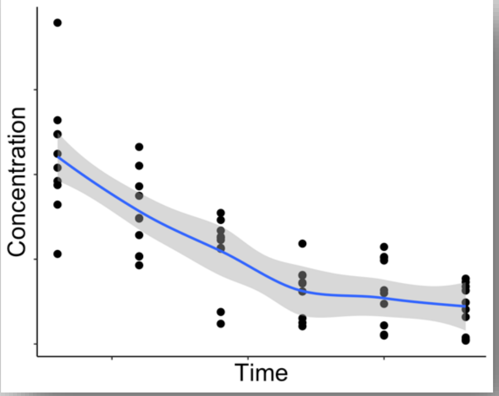

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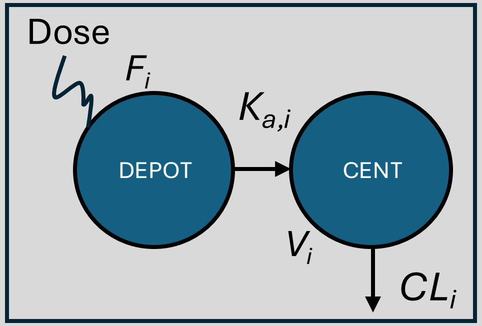

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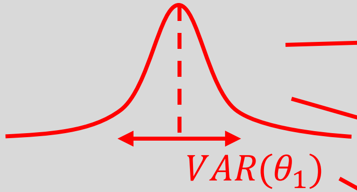

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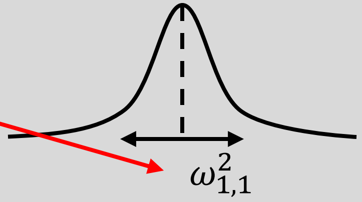

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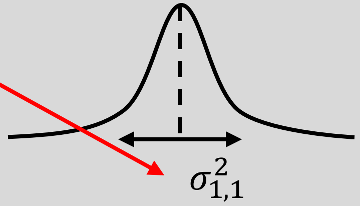

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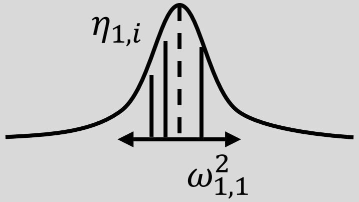

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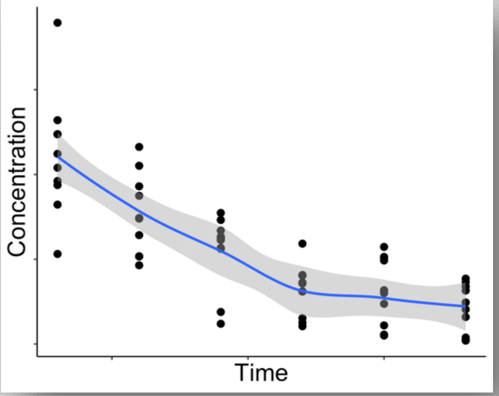

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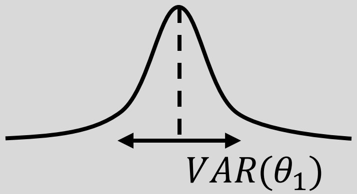

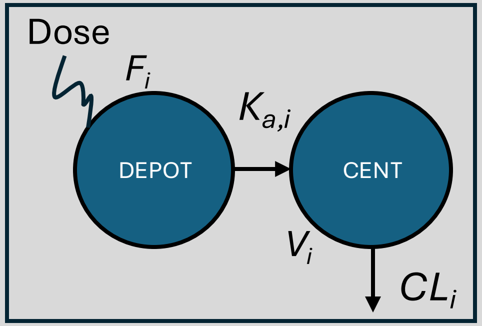

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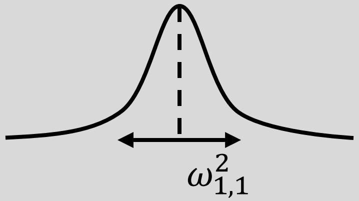

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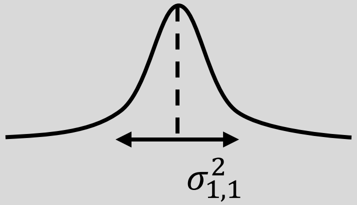

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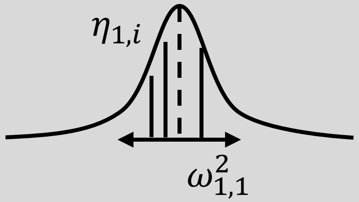

Simulation

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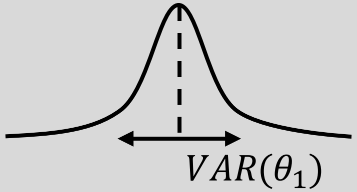

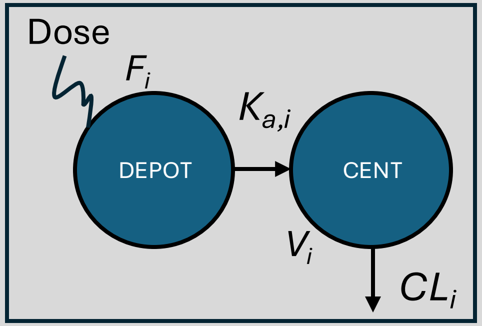

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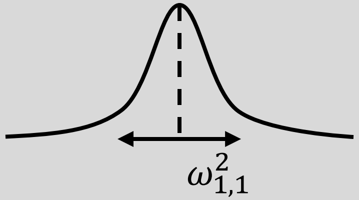

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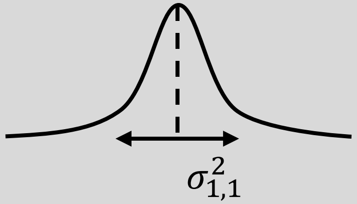

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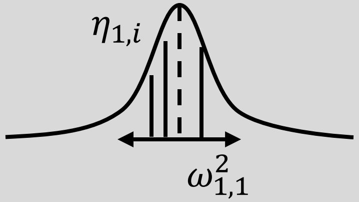

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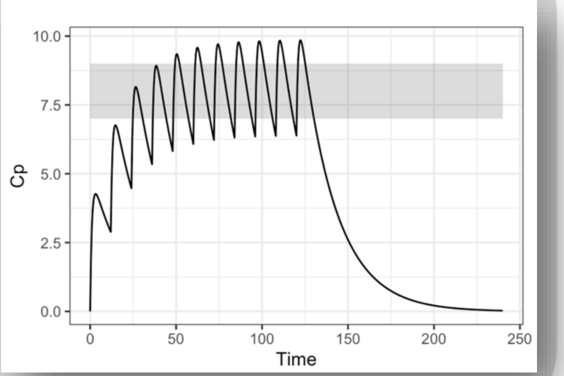
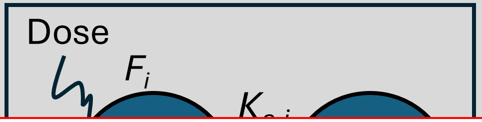
Simulation

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



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

?



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

...

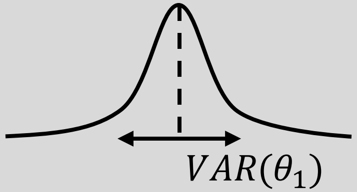
$$IPRED_{ij} = \frac{F_i \times Dose \times K_{a,i}}{V_i \times (K_{a,i} - \frac{CL_i}{V_i})} \times \left(e^{-\frac{CL_i}{V_i} \times t_{ij}} - e^{-K_{a,i} \times t_{ij}}\right)$$

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

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

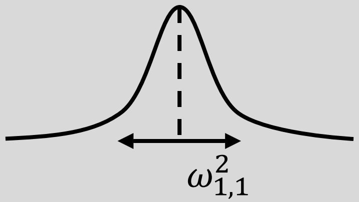
...

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

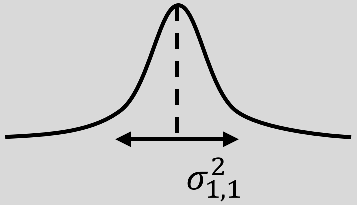


?

Population parameters (`.ext`)
1. Fixed-effect
   $\boldsymbol{\theta_1}, \boldsymbol{\theta_2}$ ...
2. Random-effect
   2.1 Ω matrix

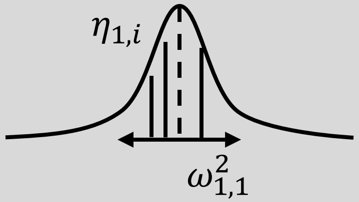


   2.2 Σ matrix



?

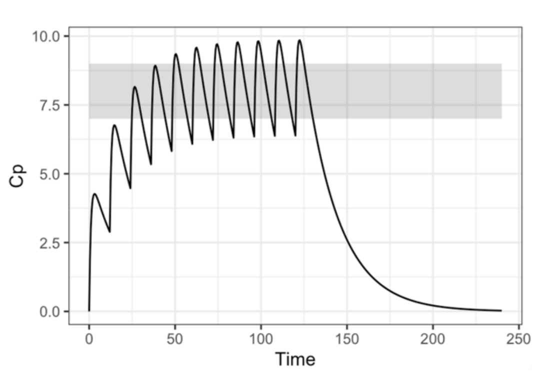
Individual random effects (`.phi`)
(Empirical-bayes estimates, EBE)



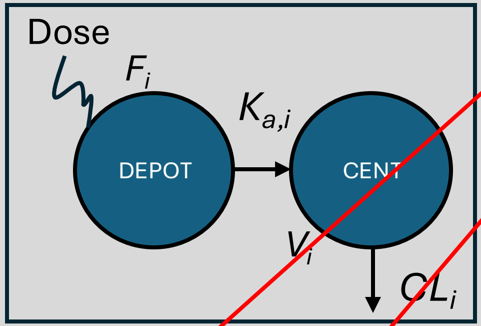
The incorporation of simulation components depend on the type of simulation and the question to be answered

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	...
...	...	...	...



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

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

...

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

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

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

...

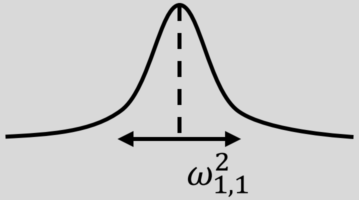
Population parameters (`.ext`)

1. Fixed-effect

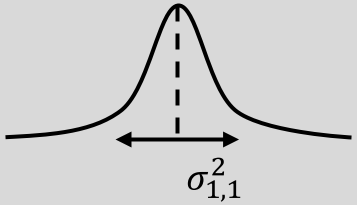
   $\boldsymbol{\theta_1}, \boldsymbol{\theta_2}$ ...

2. Random-effect

   2.1 Ω matrix



   2.2 Σ matrix



Typical Workflow When Perform Typical Value Simulations

```
For i=1, …, nsub
    Fix η_i=0 for subject i
    Fix ε_ij=0 for subject i at time j
    Derive θ_i = f(θ,cov_i)for subject i
    Calculate response Y_ij = f(θ_i,η_i=0,ε_ij=0)
End
```

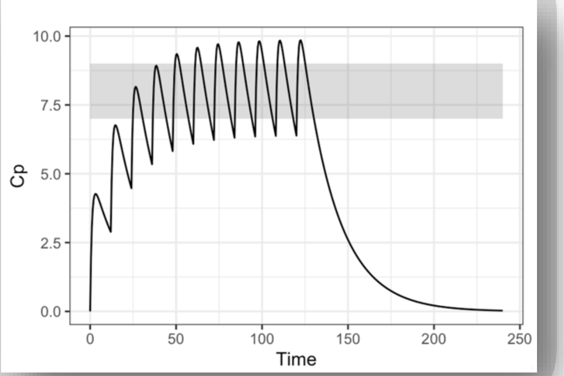
nsub: number of subjects

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

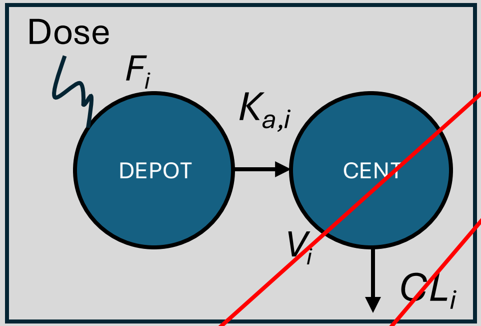
Adapted from Hu C. *J Pharmacokinet Pharmacodyn.* 2022 PMID: 35927373.

Deterministic Simulation-EBE simulation

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



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



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

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

...

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

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

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

...

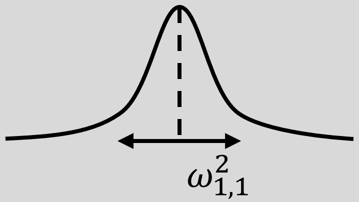
Population parameters (`.ext`)

1. Fixed-effect

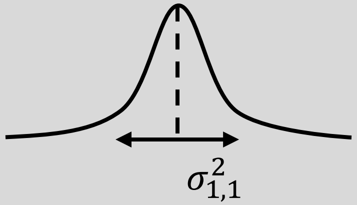
   $\boldsymbol{\theta_1}, \boldsymbol{\theta_2}$ ...

2. Random-effect

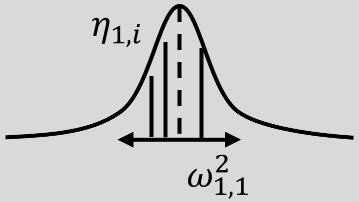
   2.1 Ω matrix



   2.2 Σ matrix



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



Typical Workflow When Perform EBE Simulations

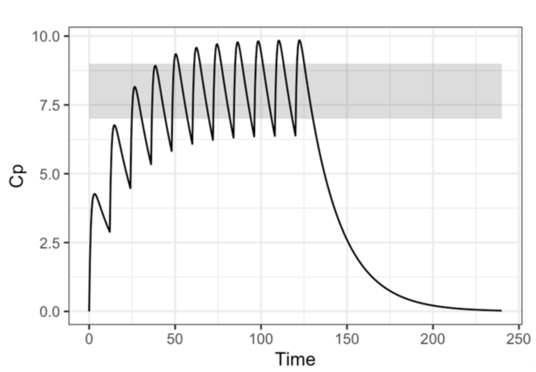
```
For i=1, …, nsub
   Fix ηi=ηi in model output for subject i
   Fix εij=0 for subject i at time j
   Derive EBEi= f(θ, covi, ηi) for subject i
   Calculate response Yij = f(EBEi,εij=0)
End
```

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

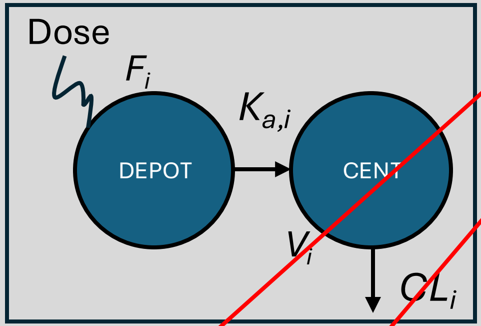
Adapted from Hu C. *J Pharmacokinet Pharmacodyn.* 2022 PMID: 35927373.

Stochastic Simulation

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



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



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

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

...

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

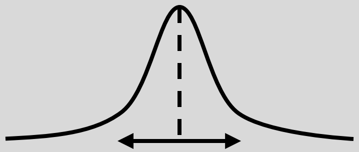
$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

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

...

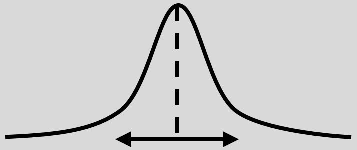
Population parameters (`.ext`)

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



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

   - 2.2 Σ matrix



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

Typical Workflow When Perform Stochastic Simulations

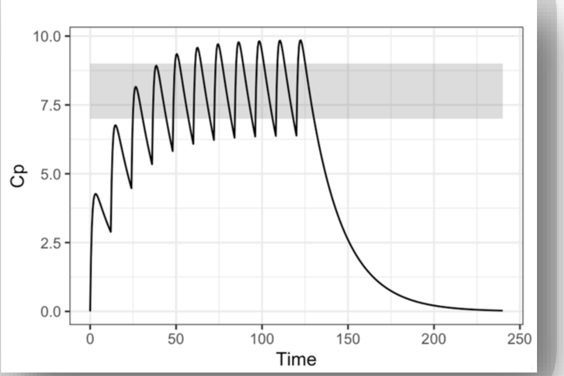
```
For i=1, …, nsub
    Draw sample ηi for subject i using Ω matrix
    *Draw sample εij for subject i at time j using Σ matrix/Fix εij=0
    Derive θi = f(θ,covi)
    Calculate response Yij = f(θi,ηi,εij)
End
```

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

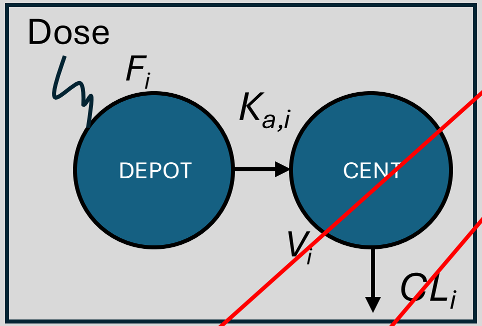
Adapted from Hu C. *J Pharmacokinet Pharmacodyn.* 2022 PMID: 35927373.

Covariate (Virtual Patient) Simulations

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



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



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

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

...

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

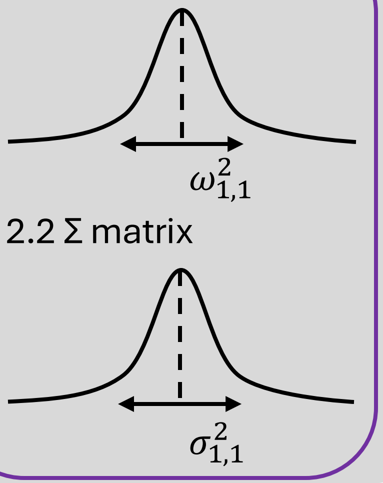
$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

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

...

Population parameters (`.ext`)

1. Fixed-effect
   θ_1, θ_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

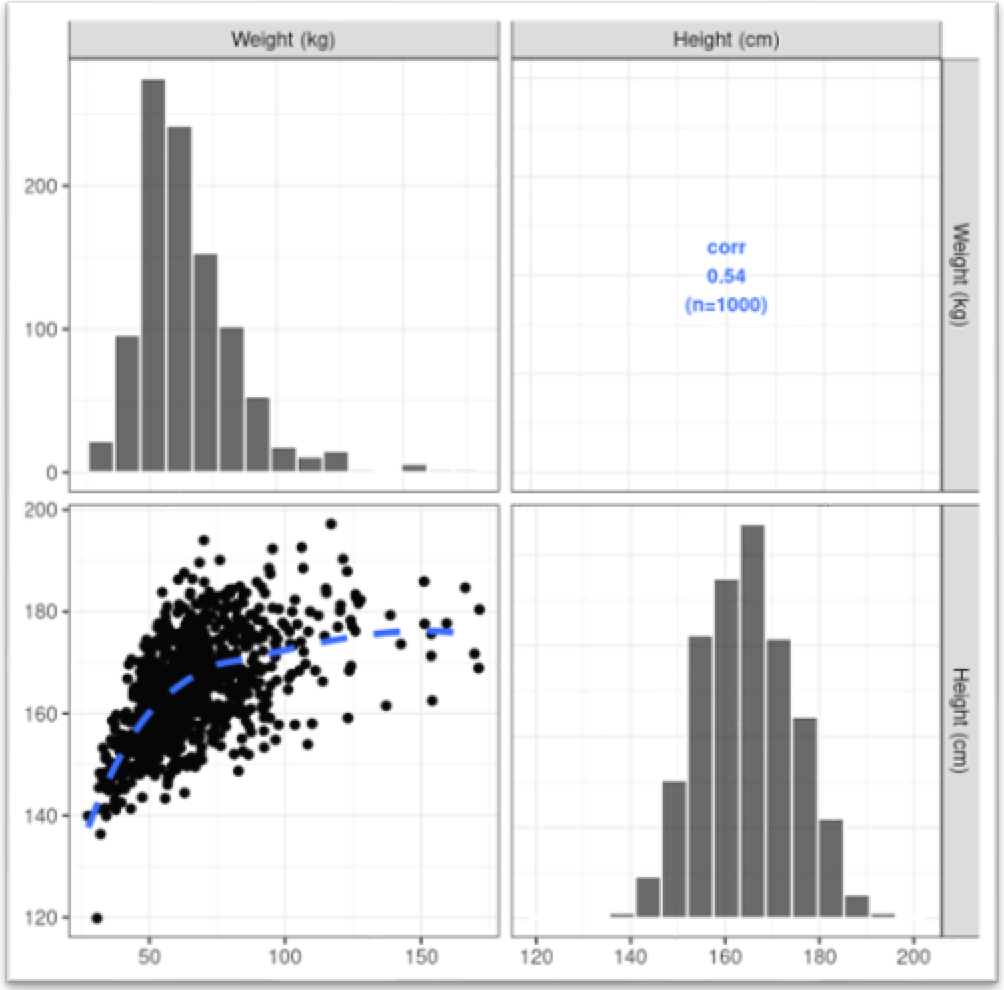
Adapted from Hu C. *J Pharmacokinet Pharmacodyn.* 2022 PMID: 35927373.

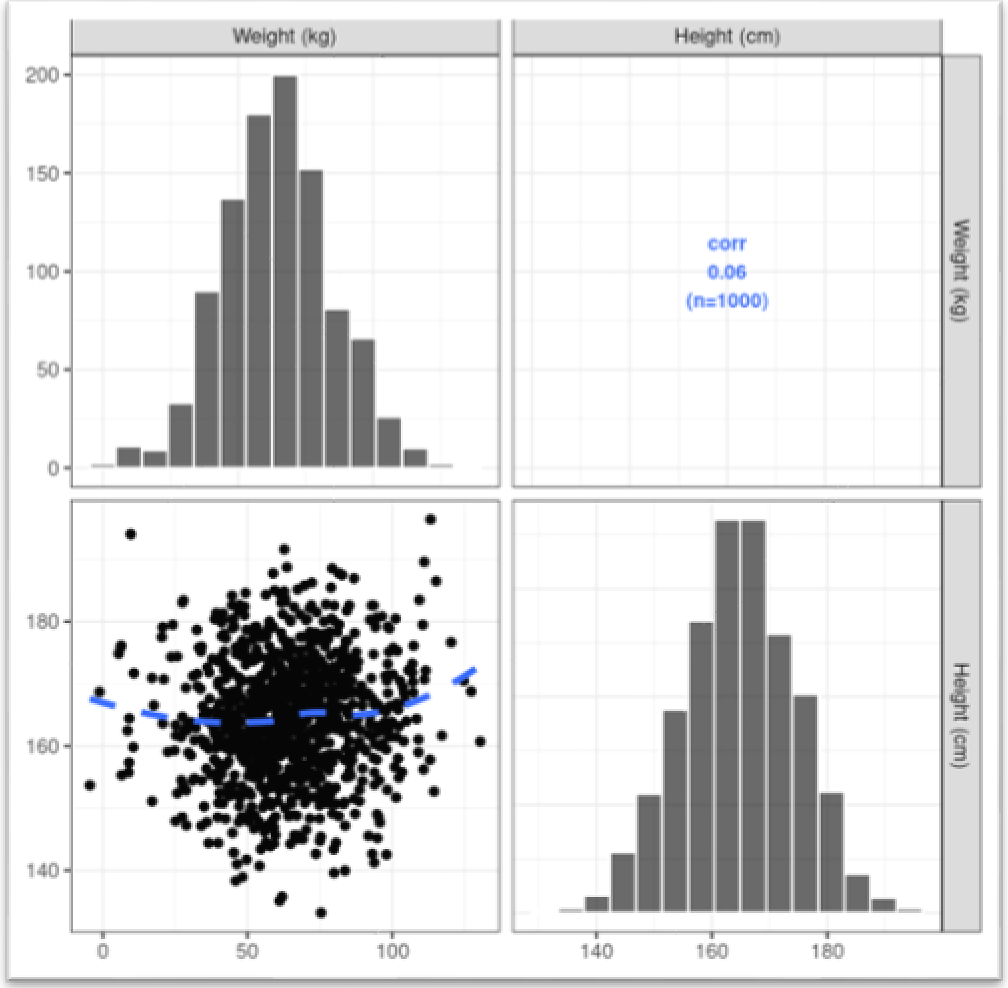
The Importance of Realistic Covariates/Virtual Patients

```
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)
                                    )
                 )
```

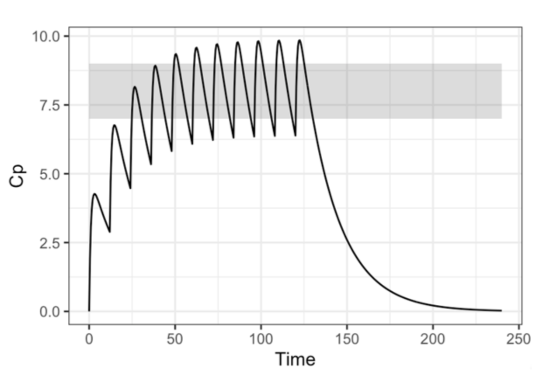
The Importance of Realistic Covariates/Virtual Patients



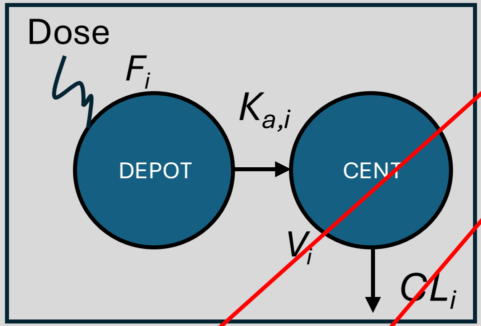


Stochastic Simulation-Multiple Replicates

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



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



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

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

...

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

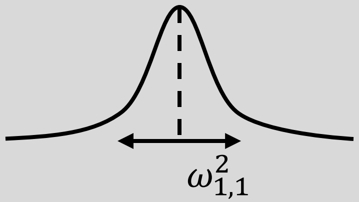
$$OBS_{ij} = IPRED_{ij} + \epsilon_{1,ij}$$

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

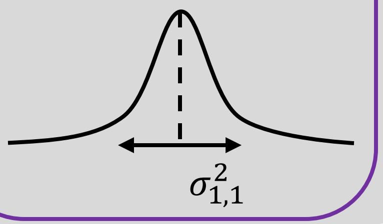
...

Population parameters (`.ext`)

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



   2.2 Σ matrix



100 simulation replicates...

e.g., Visual Predictive Check (VPC)

Typical Workflow When Perform Stochastic Simulations with Replicates

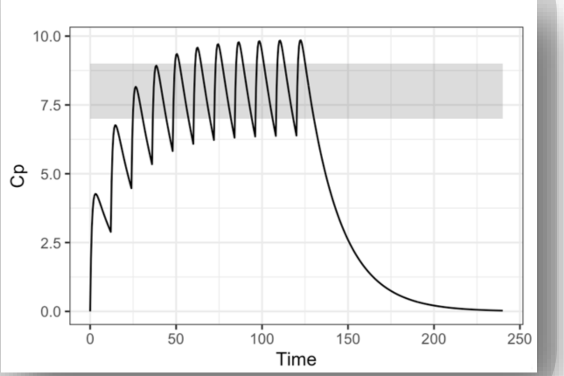
```
For i=1, …, nrep
    Fixed population parameters (θi,Ωi,Σi)
    For j=1, …, nsub
        Draw sample ηij for subject j using Ωi matrix
        *Draw sample εijk for subject j at time k using Σi matrix/Fix εijk=0
        Derive θij = f(θi,covj)
        Calculate response Yijk = f(θij,ηij,εijk)
    End
End
```

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

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

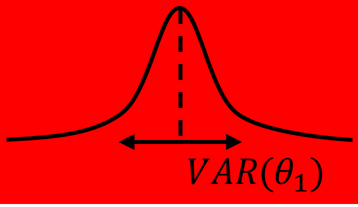
Simulations with Parameter Uncertainty

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)



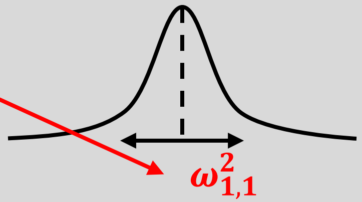
Population parameters (`.ext`)

1. Fixed-effect

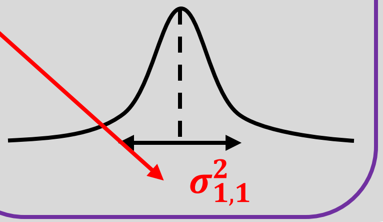
$\boldsymbol{\theta_1, \theta_2}$ ...

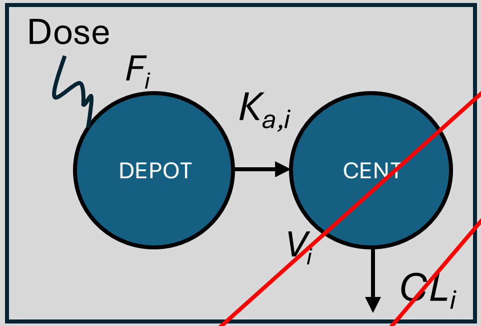
2. Random-effect

2.1 Ω matrix



2.2 Σ matrix





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

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

...

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

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

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

...

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 (θ)
    - Inverse wishart distribution for random effects (ω^2, σ^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											e-02	0
72.45											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 i=1, …, nrep
    Draw a set of parameters (θi,Ωi,Σi) from the uncertainty distribution
    For j=1, …, nsub
        Draw sample ηij for subject j using Ωi matrix
        *Draw sample εijk for subject j at time k using Σi matrix/Fix εijk=0
        Derive θij = f(θi,covj)
        Calculate response Yijk = f(θij,ηij,εijk)
    End
End
```

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

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

The end