Biomarker-Treatment Interaction Mechanism

Clustered N-of-1 Trial Simulation

December 2025

Abstract

This document provides a comprehensive mathematical and computational explanation of how the clustered N-of-1 simulation generates biomarker-treatment interactions through two complementary mechanisms: (1) covariance structure via biomarker-response correlation, and (2) mean-level modulation via treatment effect scaling. These mechanisms work synergistically to create realistic pharmacogenomics scenarios and extend the Hendrickson et al. (2020) framework to explicitly study biomarker-driven heterogeneity in treatment response.

Contents

1 Overview

The clustered simulation generates biomarker-treatment interactions through two distinct mechanisms:

1. **Covariance structure**: Biomarker and responses are correlated in the sampling distribution via the cross-covariance matrix $\mathbf{\Sigma}_{12}$
2. **Mean-level modulation**: The drug response rate itself is scaled by the observed biomarker level through multiplicative modulation

These mechanisms work together to produce realistic heterogeneous treatment responses where individual biomarker status fundamentally shapes the magnitude of treatment benefit.

2 Terminology and Parameter Definitions

To ensure clarity throughout, we establish consistent naming conventions:

Concept	Code Variable	param_grid Name	Controls
Baseline response value	`baseline`	—	Random intercept per participant
Biomarker value	`biomarker`	—	Individual characteristic (random)
BM-treatment interaction	`bm_mod`	`biomarker_moderation`	Effect modulation (**MEANS**)
BM-response correlation	`c.bm`	`biomarker_correlation`	Covariance structure (**COVARIAN**

Table 1: Consistent terminology used throughout the simulation.

biomarker_moderation (bm_mod): Controls the strength of biomarker modulation of the drug response rate. Affects **means only**.

biomarker_correlation (*c.bm*): Controls the correlation between biomarker and response variables in the covariance matrix. Affects **covariance structure only**.

3 Two-Level Interaction Mechanism

The interaction emerges from two complementary pathways:

3.1 Level 1: Covariance Structure via Biomarker-Response Correlation

The parameter *c.bm* (biomarker_correlation) creates correlation between the biomarker and responses through the cross-covariance matrix $\mathbf{\Sigma}_{12}$. This is implemented using conditional normal sampling:

```
# Stage 1: Generate baseline values independently
stage1 <- mvrnorm(1, mu = c(biomarker_mean, baseline_mean), Sigma = Sigma_22)
biomarker <- stage1[1]
baseline <- stage1[2]

# Stage 2: Generate responses CONDITIONAL on biomarker
z <- c(biomarker - biomarker_mean, baseline - baseline_mean)
cond_mean <- as.vector(Sigma_12 %*% solve(Sigma_22) %*% z)
responses <- mvrnorm(1, mu = cond_mean, Sigma = Sigma_cond)
```

Effect: Observed biomarker values shift the response distributions upward or downward proportionally to their deviation from the mean. Higher *c.bm* creates stronger shifts.

3.2 Level 2: Treatment Effect Modulation via Biomarker-Treatment Interaction

The parameter bm_mod (biomarker_moderation) scales the drug response rate multiplicatively:

```
bm_centered = (biomarker - biomarker_mean) / biomarker_sd
effective_BR_rate <- BR_rate * (1 + bm_mod * bm_centered)

# Example: BR_rate = 0.5, bm_mod = 0.45, biomarker is 1 SD above mean
# effective_BR_rate = 0.5 * (1 + 0.45 * 1) = 0.725

BR_mean = weeks_on_drug * effective_BR_rate
BR = BR_mean + br_random
response = baseline + BR + ER + TR
```

Effect: The drug effect slope itself varies by biomarker value through multiplicative scaling. High biomarker individuals experience stronger drug effects; low biomarker individuals experience weaker effects.

4 Block-Partitioned Covariance Matrix Structure

The full 26-dimensional covariance matrix is structured as a 2×2 block matrix:

$$\boldsymbol{\Sigma} = \begin{pmatrix} \boldsymbol{\Sigma}_{11} & \boldsymbol{\Sigma}_{12} \\ \boldsymbol{\Sigma}_{12}^T & \boldsymbol{\Sigma}_{22} \end{pmatrix}$$

where:

$\boldsymbol{\Sigma}_{11} : 24 \times 24$ (response covariances)
$\boldsymbol{\Sigma}_{12} : 24 \times 2$ (cross-covariance: responses and baseline)
$\boldsymbol{\Sigma}_{22} : 2 \times 2$ (baseline covariances)

4.1 Sigma_22: Covariance of Baseline Factors

$$\boldsymbol{\Sigma}_{22} = \begin{pmatrix} \sigma^2_{\text{BM}} & \rho_{\text{BM,BL}}\sigma_{\text{BM}}\sigma_{\text{BL}} \\ \rho_{\text{BM,BL}}\sigma_{\text{BM}}\sigma_{\text{BL}} & \sigma^2_{\text{BL}} \end{pmatrix}$$

In the simulation:

```
Sigma_22 <- matrix(c(
  biomarker_sd^2, # = 4.0
  c.bm_baseline * biomarker_sd * between_subject_sd, # = 0.3 * 2 * 2 = 1.2
  c.bm_baseline * biomarker_sd * between_subject_sd,
  between_subject_sd^2 # = 4.0
), 2, 2)
```

4.2 Sigma_11: Response Covariances

The 24×24 response covariance matrix consists of three response factors at 8 timepoints:

$$\begin{aligned} \text{BR (Biological Response)} &: 8 \text{ timepoints, } c.br = 0.8 \text{ autocorrelation} \\ \text{ER (Expectancy Response)} &: 8 \text{ timepoints, } c.er = 0.8 \text{ autocorrelation} \\ \text{TR (Time-Variant Response)} &: 8 \text{ timepoints, } c.tr = 0.8 \text{ autocorrelation} \end{aligned}$$

Within-factor blocks use time-based AR(1) structure:

$$\Sigma_{\text{BR}}[i, j] = \sigma^2 \cdot \rho^{|t_i - t_j|}$$

Cross-factor blocks use compound symmetry with same-time ($c.cf1t = 0.2$) and different-time ($c.cfct = 0.1$) correlations.

4.3 Sigma_12: Cross-Covariance (Critical for Interaction)

This 24×2 matrix encodes correlations between responses and baseline factors:

```
Sigma_12[br_idx, 1] <- c.bm * within_subject_sd * biomarker_sd
Sigma_12[er_idx, 1] <- c.bm * 0.5 * within_subject_sd * biomarker_sd
Sigma_12[tr_idx, 1] <- c.bm * 0.5 * within_subject_sd * biomarker_sd
Sigma_12[br_idx, 2] <- c.baseline * within_subject_sd * between_subject_sd
Sigma_12[er_idx, 2] <- c.baseline * within_subject_sd * between_subject_sd
Sigma_12[tr_idx, 2] <- c.baseline * within_subject_sd * between_subject_sd
```

Key observation: Every element of $\boldsymbol{\Sigma}_{12}$ is scaled by $c.bm$ (biomarker_correlation), making this matrix the locus of biomarker-response dependence.

5 Concrete Example: How Biomarker Correlation Creates Response Shifts

Assume:

$$\begin{aligned} c.bm &= 0.3 \text{ (biomarker\_correlation)} \\ \sigma_{\text{within}} &= 1.8 \text{ (within-subject SD)} \\ \sigma_{\text{BM}} &= 2.0 \text{ (biomarker SD)} \end{aligned}$$

The cross-covariance entry for biomarker → BR is:

$$\boldsymbol{\Sigma}_{12}[\text{br\_idx}, 1] = 0.3 \times 1.8 \times 2.0 = 1.08$$

5.1 Scenario 1: High Biomarker (1 SD above mean)

$$\begin{aligned} \text{biomarker} &= \mu_{\text{BM}} + 1\sigma_{\text{BM}} = 5 + 2 = 7 \\ \mathbf{z} &= \begin{pmatrix} 7 - 5 \\ \text{baseline} - 10 \end{pmatrix} = \begin{pmatrix} 2 \\ 0 \end{pmatrix} \end{aligned}$$

Response shift via conditional distribution:

$$\text{shift} = \boldsymbol{\Sigma}_{12}\boldsymbol{\Sigma}_{22}^{-1}\mathbf{z} \approx 1.08 \times 0.5 \times 2 = +1.08 \text{ units}$$

Result: BR responses are generated approximately 1.08 units **higher** for high-biomarker individuals.

5.2 Scenario 2: Low Biomarker (1 SD below mean)

$$\begin{aligned} \text{biomarker} &= 5 - 2 = 3 \\ \mathbf{z} &= \begin{pmatrix} -2 \\ 0 \end{pmatrix} \end{aligned}$$

Response shift:

$$\text{shift} = 1.08 \times 0.5 \times (-2) = -1.08 \text{ units}$$

Result: BR responses are generated approximately 1.08 units **lower** for low-biomarker individuals.

6 How Both Mechanisms Create Synergistic Interaction

The two interaction mechanisms amplify each other:

6.1 High Biomarker Individuals

1. **Covariance effect** (*c.bm*): Higher baseline response level

$$\text{response shift} = +1.08 \times \frac{\text{biomarker} - \mu_{\text{BM}}}{\sigma_{\text{BM}}} \tag{1}$$

2. **Mean modulation effect** (bm_mod): Stronger drug response

$$\text{effective\_BR\_rate} = 0.5 \times (1 + 0.45 \times 1) = 0.725 \tag{2}$$

3. **Combined result:** Higher baseline + stronger slope ⇒ larger treatment effect ⇒ easier to detect statistically

6.2 Low Biomarker Individuals

1. **Covariance effect:** Lower baseline response level
2. **Mean modulation effect:** Weaker drug response
3. **Combined result:** Lower baseline + weaker slope ⇒ smaller treatment effect

This synergy means that *c.bm* (covariance correlation) and bm_mod (mean modulation) interact multiplicatively to determine effect sizes and statistical power.

7 The Role of c.bm Parameter

The parameter *c.bm* controls the magnitude of covariance-based response shifts:

7.1 Case: $c.bm = 0$ (No Correlation)

$$\boldsymbol{\Sigma}_{12}[\text{br\_idx}, 1] = 0 \times 1.8 \times 2.0 = 0$$

- Responses independent of biomarker in covariance structure
- No shift in conditional means
- Only mean-level interaction from bm_mod

7.2 Case: $c.bm = 0.3$ (Moderate Correlation)

$$\boldsymbol{\Sigma}_{12}[\text{br\_idx}, 1] = 0.3 \times 1.8 \times 2.0 = 1.08$$

- Responses shift by $\approx \pm 1$ unit per SD of biomarker
- Moderate covariance-based amplification
- Combined with bm_mod creates synergistic interaction

7.3 Case: $c.bm = 0.6$ (High Correlation)

$$\mathbf{\Sigma}_{12}[\text{br\_idx}, 1] = 0.6 \times 1.8 \times 2.0 = 2.16$$

- Responses shift by $\approx \pm 2$ units per SD of biomarker
- Strong covariance-based amplification
- Powerful synergy with bm_mod produces largest effect sizes

8 Implications for Statistical Power

The covariance structure ($c.bm$) amplifies the mean-level interaction (bm_mod):

$c.bm$	**bm_mod**	**Effect**	**Power**
0	0.5	Only mean-level; modest	Low–Moderate
0.3	0.5	Combined covariance + mean; larger	Moderate–High
0.6	0.5	Strong covariance + mean; largest	High

Table 2: How $c.bm$ amplifies power to detect biomarker-treatment interaction.

8.1 Design of Parameter Grid

The simulation contains:

3 unique sigma structures : (design $\times$ $c.bm$ combinations)
36 parameter combinations : including all bm_mod values

This design tests: *Given a fixed covariance structure (c.bm), how does increasing biomarker_moderation affect power to detect the interaction?*

The fact that only 3 sigma structures exist (despite 36 conditions) means:

- Each unique (design, $c.bm$) pair generates the same correlation structure
- Different bm_mod values reuse the same sigma
- This isolates the effect of mean-level modulation from covariance effects

9 Mathematical Formulation

9.1 Conditional Normal Distribution

The responses conditional on baseline factors follow:

$$\mathbf{X}_1 \mid \mathbf{X}_2 = \mathbf{x}_2 \sim \mathcal{N}\left(\boldsymbol{\mu}_1 + \mathbf{\Sigma}_{12}\mathbf{\Sigma}_{22}^{-1}(\mathbf{x}_2 - \boldsymbol{\mu}_2),\ \mathbf{\Sigma}_{\text{cond}}\right) \tag{3}$$

where:

$$\begin{aligned} \mathbf{X}_1 &: \text{responses (24-dimensional)} \\ \mathbf{X}_2 &: \text{baseline factors (2-dimensional)} \\ \boldsymbol{\Sigma}_{12}\boldsymbol{\Sigma}_{22}^{-1}(\mathbf{x}_2 - \boldsymbol{\mu}_2) &: \text{shift dependent on observed biomarker} \\ \boldsymbol{\Sigma}_{\text{cond}} = \boldsymbol{\Sigma}_{11} - \boldsymbol{\Sigma}_{12}\boldsymbol{\Sigma}_{22}^{-1}\boldsymbol{\Sigma}_{12}^T &: \text{conditional covariance} \end{aligned}$$

9.2 Treatment Effect Modulation

The biological response rate is modulated as:

$$\text{BR}_{\text{rate},i} = \text{BR}_{\text{base}} \times (1 + \text{bm\_mod} \times \tilde{x}_i) \tag{4}$$

where:

$$\begin{aligned} \text{BR}_{\text{base}} &= 0.5 \quad \text{(fixed base rate)} \\ \text{bm\_mod} &\in \{0, 0.25, 0.35, 0.45, 0.55, 0.65\} \quad \text{(biomarker\_moderation)} \\ \tilde{x}_i &= \frac{x_i - \mu_x}{\sigma_x} \quad \text{(standardized biomarker for participant } i\text{)} \end{aligned}$$

The final response is:

$$Y_i = \text{baseline}_i + \text{BR}_i + \text{ER}_i + \text{TR}_i \tag{5}$$

where BR_i, ER_i, TR_i are generated from the conditional distribution with modulated mean for BR_i.

10 Comparison to Hendrickson et al. (2020)

Hendrickson et al. (2020) provided the foundational framework for N-of-1 trials with multiple randomization structures. The current simulation extends this work:

Aspect	**Hendrickson**	**Current Simulation**
Primary focus	Treatment detection	Biomarker × treatment
Biomarker role	Fixed (if present)	Systematically varied
BM-response correlation	Fixed/not studied	Varies: $\{0, 0.3\}$
Interaction type	Not emphasized	Explicit interaction
Interaction mechanism	N/A	Multiplicative on effect rate
Covariance structure	Fixed Hendrickson params	Extended with BM correlation
Carryover modeling	Included	Included (extended)

Table 3: Comparison of Hendrickson et al. framework and current simulation.

10.1 Key Innovation

The current simulation adds **explicit modeling of biomarker-driven heterogeneity** in treatment response through two mechanisms:

1. **Structural:** Biomarker and responses are correlated in the sampling distribution
2. **Functional:** Drug effect strength scales with biomarker value

This enables power analysis for *precision medicine* designs where treatment benefit is fundamentally linked to individual biomarker status—a core concept that Hendrickson's framework was not designed to study.

11 Summary

The biomarker-treatment interaction in the clustered N-of-1 simulation emerges from complementary mechanisms:

1. **Covariance mechanism:** Parameter *c.bm* creates correlation between biomarker and responses via $\mathbf{\Sigma}_{12}$, causing observed biomarker values to shift response distributions
2. **Mean mechanism:** Parameter bm_mod scales drug effect rates multiplicatively, causing biomarker to modulate treatment slope

Together, these mechanisms create:

- **High biomarker individuals:** Higher baseline + stronger drug effect = larger detectable treatment benefit
- **Low biomarker individuals:** Lower baseline + weaker drug effect = smaller treatment benefit
- **Overall:** Heterogeneous treatment responses where biomarker status predicts both the baseline level and treatment response magnitude

This realistic pharmacogenomics scenario enables rigorous power analysis for precision medicine designs where treatment efficacy depends on individual biomarker characteristics.

A Parameter Grid Structure

```
param_grid <- bind_rows(
  # OL+BDC power conditions
  expand_grid(
    design = "ol_bdc",
    biomarker_moderation = c(0.25, 0.35, 0.45, 0.55, 0.65), # 5 values
    biomarker_correlation = c(0.3),                    # 1 value
```

```
    carryover = c(0, 0.5, 1)                                    # 3 values
  ),  # 15 combinations

  # OL+BDC Type I error
  expand_grid(
    design = "ol_bdc",
    biomarker_moderation = c(0),
    biomarker_correlation = c(0),
    carryover = c(0, 0.5, 1)
  ),  # 3 combinations

  # Hybrid design
  expand_grid(
    design = "hybrid",
    biomarker_moderation = c(0, 0.25, 0.35, 0.45, 0.55, 0.65), # 6 values
    biomarker_correlation = c(0.3),                             # 1 value
    carryover = c(0, 0.5, 1)                                    # 3 values
  )   # 18 combinations
)
# Total: 36 combinations across 3 sigma structures
```

B Fixed Correlation Parameters

All following parameters are held constant (from Hendrickson et al., 2020):

$$
\begin{aligned}
c.br &= 0.8 && \text{(BR autocorrelation)} \\
c.er &= 0.8 && \text{(ER autocorrelation)} \\
c.tr &= 0.8 && \text{(TR autocorrelation)} \\
c.cf1t &= 0.2 && \text{(same-time cross-correlation)} \\
c.cfct &= 0.1 && \text{(different-time cross-correlation)} \\
c.bm\_baseline &= 0.3 && \text{(biomarker-baseline correlation)} \\
c.baseline\_resp &= 0.4 && \text{(baseline-response correlation)}
\end{aligned}
$$