Understanding Correlation Parameters in N-of-1 Trial Simulations: A Practical Guide

Technical Documentation

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Abstract

This document provides a comprehensive guide to understanding and selecting the six correlation parameters that define the covariance structure in N-of-1 trial simulations. We explain what each parameter represents, provide intuitive interpretations, and give practical guidance for choosing appropriate values. This guide complements the theoretical treatment in `correlation_structure_design.pdf`.

Contents

1 The Six Correlation Parameters

1.1 Overview

The correlation structure for N-of-1 trial simulations is completely specified by **six parameters**. These parameters control how measurements relate to each other across time and across the three response components (time-variant, pharmacologic/expectancy, and biological response).

1.2 Parameter Definitions

Table 1: The Six Correlation Parameters

Parameter	Name	Meaning	Hendrickson	PDF Rec.
`c.tv`	TV autocorrelation	Corr(tv_t, tv_s) for $t \neq s$	0.8	0.65
`c.pb`	PB autocorrelation	Corr(pb_t, pb_s) for $t \neq s$	0.8	0.65
`c.br`	BR autocorrelation	Corr(br_t, br_s) for $t \neq s$	0.8	0.65
`c.cf1t`	Same-time cross	Corr(comp1_t, comp2_t)	0.2	0.18
`c.cfct`	Diff-time cross	Corr(comp1_t, comp2_s) for $t \neq s$	0.1	0.09
`c.bm`	Biomarker	Corr(biomarker, br_t)	0–0.6	0–0.6

where:

- **tv** = time-variant factor (natural disease progression)
- **pb** = pharmacologic/biomarker factor (expectancy/placebo effect)
- **br** = biological response factor (true drug effect)
- **comp1, comp2** = any pair of different components (tv, pb, or br)

1.3 Visual Structure

For a design with 3 timepoints (t1, t2, t3), the correlation matrix has this structure:

$$\mathbf{R} = \begin{bmatrix} \mathbf{I}_2 & \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{R}_{\text{tv}} & \mathbf{C}_{12} & \mathbf{C}_{13} & \\ \mathbf{0} & \mathbf{C}_{21} & \mathbf{R}_{\text{pb}} & \mathbf{C}_{23} & \\ \mathbf{0} & \mathbf{C}_{31} & \mathbf{C}_{32} & \mathbf{R}_{\text{br}} & \end{bmatrix} \tag{1}$$

where:

- $\mathbf{I}_2$ represents biomarker and baseline (uncorrelated by construction)
- $\mathbf{R}_{\text{tv}}$ has `c.tv` in all off-diagonal positions
- $\mathbf{C}_{ij}$ has `c.cf1t` on diagonal, `c.cfct` off-diagonal
- Biomarker row/column has `c.bm` for BR positions only

1.4 Expanded Example

For 3 timepoints, the full correlation matrix looks like:

	bm	BL	tv_1	tv_2	tv_3	pb_1	pb_2	pb_3	br_1	br_2	br_3
bm	1	0	0	0	0	0	0	0	*c.bm*	*c.bm*	*c.bm*
BL	0	1	0	0	0	0	0	0	0	0	0
tv_1	0	0	1	*c.tv*	*c.tv*	*c.cf1t*	*c.cfct*	*c.cfct*	*c.cf1t*	*c.cfct*	*c.cfct*
tv_2	0	0	*c.tv*	1	*c.tv*	*c.cfct*	*c.cf1t*	*c.cfct*	*c.cfct*	*c.cf1t*	*c.cfct*
tv_3	0	0	*c.tv*	*c.tv*	1	*c.cfct*	*c.cfct*	*c.cf1t*	*c.cfct*	*c.cfct*	*c.cf1t*
pb_1	0	0	*c.cf1t*	*c.cfct*	*c.cfct*	1	*c.pb*	*c.pb*	*c.cf1t*	*c.cfct*	*c.cfct*
pb_2	0	0	*c.cfct*	*c.cf1t*	*c.cfct*	*c.pb*	1	*c.pb*	*c.cfct*	*c.cf1t*	*c.cfct*
pb_3	0	0	*c.cfct*	*c.cfct*	*c.cf1t*	*c.pb*	*c.pb*	1	*c.cfct*	*c.cfct*	*c.cf1t*
br_1	*c.bm*	0	*c.cf1t*	*c.cfct*	*c.cfct*	*c.cf1t*	*c.cfct*	*c.cfct*	1	*c.br*	*c.br*
br_2	*c.bm*	0	*c.cfct*	*c.cf1t*	*c.cfct*	*c.cfct*	*c.cf1t*	*c.cfct*	*c.br*	1	*c.br*
br_3	*c.bm*	0	*c.cfct*	*c.cfct*	*c.cf1t*	*c.cfct*	*c.cfct*	*c.cf1t*	*c.br*	*c.br*	1

1.5 What Each Parameter Controls

1.5.1 Within-Component Autocorrelations (Parameters 1–3)

```
# c.tv controls ALL these correlations:
Corr(tv_1, tv_2) = 0.8
Corr(tv_1, tv_3) = 0.8
Corr(tv_2, tv_3) = 0.8
# Same pattern for c.pb and c.br
```

Key Point: Same correlation regardless of time lag (not AR(1)-style decay).

1.5.2 Cross-Component, Same Time (Parameter 4)

```
# c.cf1t controls same-time cross-component correlations:
Corr(tv_1, pb_1) = 0.2  # time 1
Corr(tv_2, pb_2) = 0.2  # time 2
Corr(tv_3, pb_3) = 0.2  # time 3
Corr(tv_1, br_1) = 0.2
Corr(pb_1, br_1) = 0.2
# etc. for all same-time pairs
```

1.5.3 Cross-Component, Different Times (Parameter 5)

```
# c.cfct controls different-time cross-component correlations:
Corr(tv_1, pb_2) = 0.1  # tv at time 1, pb at time 2
Corr(tv_1, br_3) = 0.1  # tv at time 1, br at time 3
Corr(pb_1, br_2) = 0.1  # pb at time 1, br at time 2
# etc. for all different-time pairs
```

1.5.4 Biomarker-Response (Parameter 6)

```
# c.bm controls ONLY biomarker-BR correlations:
Corr(biomarker, br_1) = 0.3
Corr(biomarker, br_2) = 0.3
Corr(biomarker, br_3) = 0.3

# NOT correlated with tv or pb:
Corr(biomarker, tv_1) = 0
Corr(biomarker, pb_1) = 0
```

1.6 Critical Hierarchy Constraint

For the correlation matrix to be positive definite, you **must maintain**:

$$\boxed{c.cfct < c.cf1t < \min(c.tv, c.pb, c.br)} \tag{2}$$

Example 1 (Valid Hierarchy).

```
c.tv = 0.8, c.pb = 0.8, c.br = 0.8     # autocorrelations
c.cf1t = 0.2                            # 0.2 < 0.8 (checkmark)
c.cfct = 0.1                            # 0.1 < 0.2 (checkmark)
```

Example 2 (Invalid Hierarchy - FAILS!).

```
c.tv = 0.5                              # autocorrelation
c.cf1t = 0.1                            # same-time cross
c.cfct = 0.4                            # 0.4 > 0.1 VIOLATION!
```

This violates temporal coherence: measurements at **different times** cannot be more correlated than measurements at the **same time**.

2 Recommended Parameter Values

2.1 Three Standard Configurations

2.1.1 Hendrickson Exact (for direct comparison)

```
model_params <- list(
  c.tv = 0.8,
  c.pb = 0.8,
  c.br = 0.8,
  c.cf1t = 0.2,
  c.cfct = 0.1,
  c.bm = 0.3       # or vary: 0, 0.3, 0.6
)
```

Properties:

- Empirically validated (Hendrickson et al., 2020)
- Represents strong individual-level stability
- Works for $T = 8$ timepoints (hybrid design)
- Best for direct comparison with published results

2.1.2 Intermediate (PDF Section 9.1 recommendation)

```r
model_params <- list(
  c.tv = 0.65,
  c.pb = 0.65,
  c.br = 0.65,
  c.cf1t = 0.18,  # 0.28 * 0.65
  c.cfct = 0.09,  # 0.50 * 0.18
  c.bm = 0.3      # or vary
)
```

Properties:

- Guaranteed PD for $T \leq 20$ with $c.bm \leq 0.6$
- Maintains proper correlation hierarchy
- Interpretable: moderate individual-level stability
- Allows moderate parameter variation

2.1.3 Conservative (always works)

```r
model_params <- list(
  c.tv = 0.5,
  c.pb = 0.5,
  c.br = 0.5,
  c.cf1t = 0.15,  # 0.30 * 0.5
  c.cfct = 0.08,  # 0.50 * 0.15
  c.bm = 0.3
)
```

Properties:

- Guaranteed PD for $T \leq 30$
- Very stable across parameter variations
- Lower power for interaction detection
- Represents moderate temporal persistence

2.2 Recommended Ratios (PDF Guideline 2)

To ensure positive definiteness, use these ratios:

$$c.cf1t \approx 0.2 \text{ to } 0.4 \times c_{\text{autocorr}} \tag{3}$$

$$c.cfct \approx 0.5 \text{ to } 0.7 \times c.cf1t \tag{4}$$

3 Intuitive Understanding of Within-Component Autocorrelations

3.1 What Does Autocorrelation Represent?

Within-component autocorrelation (e.g., `c.tv = 0.8`) measures how consistent an individual's **deviation from the mean** is across time.

Intuition 1 (High Autocorrelation)**. High autocorrelation (0.8)** means:
"If someone is above average at time 1, they'll probably be above average at times 2, 3, 4..."
Implication: People have stable "types" or consistent individual characteristics.

Intuition 2 (Low Autocorrelation)**. Low autocorrelation (0.3)** means:
"If someone is above average at time 1, they might be anywhere at time 2—above, below, who knows."
Implication: People's measurements fluctuate randomly; no stable individual characteristics.

3.2 Component-Specific Interpretations

3.2.1 Time-Variant Factor (c.tv)

What it represents: Natural disease trajectory, independent of treatment

High c.tv = 0.8 ("Stable disease trajectory")

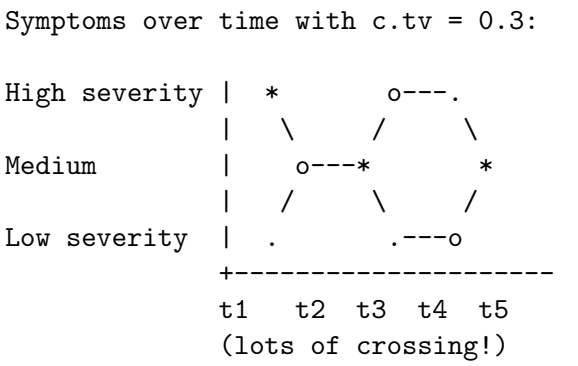
- **Interpretation**: People have consistent symptom patterns over time
- **Example**: Person A always has severe symptoms, Person B always has mild symptoms, regardless of treatment
- **Real-world analogy**: Chronic pain with stable severity
- **Data pattern**: If you plot symptoms over time, each person's line stays in their "lane" (high/medium/low)

```
Symptoms over time with c.tv = 0.8:

High severity |  *---*---*---*---*  (Person A: consistently high)
              |
Medium        |      o---o---o---o  (Person B: consistently medium)
              |
Low severity  |          .---.---.  (Person C: consistently low)
              +---------------------
              t1   t2  t3  t4  t5
```

Low c.tv = 0.3 ("Fluctuating disease")

- **Interpretation**: Disease severity bounces around unpredictably
- **Example**: Person A might be severe at t1, mild at t2, severe again at t3
- **Real-world analogy**: Episodic conditions (migraines, flare-ups)
- **Data pattern**: Spaghetti plot—lines cross each other constantly



3.2.2 Pharmacologic/Expectancy Factor (c.pb)

What it represents: Placebo/expectancy response

High c.pb = 0.8 ("Consistent placebo responders")

- **Interpretation**: Some people always have strong placebo response, others never do
- **Example**: Person A always gets 5-point boost from placebo, Person B always gets 1-point boost
- **Real-world analogy**: Trait-like "suggestibility"—stable individual characteristic
- **Implication**: Placebo response is a person-specific trait

Low c.pb = 0.3 ("Variable placebo response")

- **Interpretation**: Placebo effectiveness varies within same person across trials
- **Example**: Person A gets 5-point boost on Monday, 1-point boost on Friday
- **Real-world analogy**: Context-dependent placebo effects (mood, stress, etc.)
- **Implication**: Placebo response depends on state, not trait

3.2.3 Biological Response Factor (c.br)

What it represents: True drug effect (beyond placebo)

High c.br = 0.8 ("Stable drug responders")

- **Interpretation**: If drug works well for you at t1, it'll work well at t2, t3...
- **Example**: Person A always gets 10-point improvement from drug, Person B always gets 3-point improvement
- **Real-world analogy**: Pharmacogenetics—your genetics determine drug response consistently
- **Implication**: "Responders" vs "non-responders" is a stable classification

Low c.br = 0.3 ("Inconsistent drug response")

- **Interpretation**: Same person responds differently at different times
- **Example**: Person A: 10-point improvement week 1, 2-point improvement week 3
- **Real-world analogy**: Tolerance, receptor saturation, or environmental interactions
- **Implication**: No stable "responder" types—response varies within person

3.3 Mathematical Intuition

3.3.1 What the Correlation Measures

For person i, let their TV component at time t be: tv_{it}

The **autocorrelation** is:

$$c.tv = \text{Corr}(\text{tv}_{i1}, \text{tv}_{i2}) = \text{Corr}(\text{tv}_{i1}, \text{tv}_{i3}) = \cdots \tag{5}$$

This measures: **Do individual differences persist over time?**

3.3.2 Decomposing the Variance

Each measurement can be decomposed as:

$$\text{tv}_{it} = \underbrace{\mu_t}_{\substack{\text{overall mean}}} + \underbrace{\alpha_i}_{\substack{\text{stable} \\ \text{person effect}}} + \underbrace{\epsilon_{it}}_{\substack{\text{random} \\ \text{fluctuation}}} \tag{6}$$

High autocorrelation $\Rightarrow$ Large α_i, small ϵ_{it}

- Variance mostly *between* people (stable differences)
- Little variance *within* people over time

Low autocorrelation $\Rightarrow$ Small α_i, large ϵ_{it}

- Variance mostly *within* people over time
- Little stable individual difference

3.3.3 Variance Partition

If $c.tv = 0.8$:

$$\text{Total Variance} = \underbrace{80\%}_{\text{between-person}} + \underbrace{20\%}_{\text{within-person}} \tag{7}$$

If $c.tv = 0.3$:

$$\text{Total Variance} = \underbrace{30\%}_{\text{between-person}} + \underbrace{70\%}_{\text{within-person}} \tag{8}$$

This is closely related to the **Intraclass Correlation Coefficient (ICC)**:

$$\text{ICC} = \frac{\sigma^2_{\text{between}}}{\sigma^2_{\text{between}} + \sigma^2_{\text{within}}} \approx c.\text{tv} \tag{9}$$

4 Effect on Statistical Power

4.1 High Autocorrelation (c.tv = 0.8)

4.1.1 Advantages

- ✓ **Better power to detect between-person effects** (biomarker × treatment interaction)
- ✓ Stable individual differences are easy to detect
- ✓ Biomarker can predict who responds well (if `c.bm` is also high)

4.1.2 Disadvantages

- × **Harder to see within-person treatment effects** (less room for change)
- × If someone starts high, they tend to stay high even with treatment

4.1.3 Best For

Detecting **moderators** (who benefits?) rather than main effects

4.2 Low Autocorrelation (c.tv = 0.3)

4.2.1 Advantages

- ✓ **More room for treatment effects** to show through
- ✓ Measurements are more independent ⇒ more effective sample size
- ✓ Can see within-person changes more clearly

4.2.2 Disadvantages

- × **Noisy baseline measurements** make biomarker prediction harder
- × Hard to identify stable "responder" types
- × Lower power for interaction detection

4.2.3 Best For

Detecting **main effects** (does treatment work overall?)

5 Why Hendrickson Chose High Autocorrelations

5.1 Hendrickson's Choice: c.tv = c.pb = c.br = 0.8

5.1.1 Theoretical Justification

1. **N-of-1 trials assume stable individual characteristics**
   - The whole point is: "Find what works for THIS person"
   - Requires that "this person" has stable trait-like responses

2. **Interaction detection requires between-person variance**
    - Testing biomarker × treatment needs people to differ consistently
    - If everyone's bouncing around randomly, you can't predict who responds
3. **Realistic for chronic conditions**
    - Chronic pain, depression: fairly stable severity within person
    - Treatment response often shows stable individual differences

5.1.2 Practical Impact

```
c.tv = 0.8 means:
- ICC (Intraclass Correlation) ~ 0.8
- 80% of variance is between-person
- Only 20% is random within-person fluctuation
```

This creates **strong individual signatures** that persist across time.

5.2 Visual Comparison

5.2.1 High Autocorrelation (c.br = 0.8): "Responder Types"

```
Drug Response by Person (each line = 1 person):

Strong      |  =========== Person A (consistent strong responder)
Responder   |  ===========
            |
Moderate    |      -------  Person B (consistent moderate)
            |      -------
            |
Weak        |           ...  Person C (consistent weak)
Responder   |           ...
            +------------------------
            t1  t2  t3  t4  t5  t6

-> You can classify people into types
-> Biomarker can predict these stable types
-> Good for precision medicine
```

5.2.2 Low Autocorrelation (c.br = 0.3): "Variable Response"

```
Drug Response by Person:

Strong      |  =     .   -   =
            |    -   =   .     .
Moderate    |  .   =   =   .   -
            |    .   -   =   -   =
Weak        |  -   -   .   -   .
            +------------------------
```

```
            t1  t2  t3  t4  t5  t6

-> Same person bounces between strong/weak
-> Hard to classify people into types
-> Biomarker can't predict (response is unstable)
-> Bad for precision medicine, but realistic for some drugs
```

6 Connection to Study Design

6.1 Crossover Designs (N-of-1)

High autocorrelation is NECESSARY:

- You're comparing drug vs placebo **within the same person**
- Requires that person's **baseline tendency** is stable
- Otherwise you can't tell if change is due to treatment vs random fluctuation

Example 3 (Crossover Data with Different Autocorrelations)**.** Person A's symptoms across alternating drug/placebo periods:

	Drug	**Placebo**	**Drug**	**Placebo**
Week:	1	2	3	4
Low c (0.3):	7	5	9	3
High c (0.8):	7	9	7	9

Analysis:

- With **low autocorrelation**: Can't tell drug effect from noise (baseline bouncing 3–9)
- With **high autocorrelation**: Clear drug effect—person's baseline is stable around 8, drug consistently causes −2 point reduction

6.2 Practical Implications for Your Simulation

6.2.1 What c.tv = 0.8 means for your results

1. **Biomarker interactions will be easier to detect**
   - Stable individual differences ⇒ biomarker can predict them
   - $c.bm = 0.6$ will have strong effect on power
2. **Designs with more participants will do better than more timepoints**
   - Between-person variance is where the action is
   - 70 participants better than 35 with more measurements per person
3. **Carryover effects are more problematic**
   - Person's baseline is stable, so carryover "sticks around"
   - Washout periods are more important

6.2.2 What c.tv = 0.3 would mean

1. **Harder to detect interactions**
   - Biomarker can't predict unstable responses
   - *c.bm* effects would be diluted
2. **More timepoints per person helps**
   - Within-person variance is where the action is
   - Repeated measures improve precision
3. **Carryover less problematic**
   - Random fluctuation swamps carryover signal
   - But also swamps treatment signal!

7 Choosing Values for Your Simulation

7.1 Autocorrelation Guidelines

Table 2: Autocorrelation Value Interpretations

Value	Interpretation	When Realistic
0.3–0.5	Conservative	Moderate stability; episodic conditions
0.5–0.7	Moderate	Most chronic conditions; typical temporal stability
0.7–0.9	High	Very stable traits; pharmacogenetics; N-of-1 context

7.1.1 Conservative (c = 0.5)

- **Interpretation**: "Half the variance is stable individual differences, half is random"
- **When realistic**: Moderate stability conditions
- **Power implications**: Moderate power for interactions

7.1.2 Moderate-High (c = 0.65)

- **Interpretation**: "2/3 stable, 1/3 random"
- **When realistic**: Most chronic conditions
- **Power implications**: Good power for interactions

7.1.3 High (c = 0.8—Hendrickson)

- **Interpretation**: "4/5 stable, 1/5 random"
- **When realistic**: Very stable traits, pharmacogenetics
- **Power implications**: High power for interactions

7.2 Summary Table

Table 3: Configuration Comparison

Aspect	Conservative	Intermediate	Hendrickson
Autocorrelations	0.5	0.65	0.8
Variance partition	50-50	65-35	80-20
Individual types	Moderate	Clear	Very clear
Interaction power	Moderate	Good	High
Main effect power	High	Moderate	Lower
Stability	Very high	High	Moderate
Use case	Exploration	Balanced	Comparison

8 Key Takeaways

8.1 The Six Parameters Control Everything

These six parameters completely determine the correlation structure:

1. `c.tv, c.pb, c.br`: Within-component temporal stability
2. `c.cf1t`: Cross-component synchrony (same time)
3. `c.cfct`: Cross-component lag correlation (different times)
4. `c.bm`: Biomarker predictive value

8.2 Within-Component Autocorrelation is Critical

High autocorrelation (0.6–0.8) answers:

> "Are people consistently different from each other over time?"

Answer: YES

- People have stable "types"—responders vs non-responders
- Essential for N-of-1 trials and precision medicine
- Required for biomarker prediction to work

8.3 Always Maintain the Hierarchy

The single most important constraint:

$$\boxed{c.cfct < c.cf1t < \min(c.tv, c.pb, c.br)} \tag{10}$$

Violating this hierarchy **guarantees** a non-positive-definite matrix.

8.4 Hendrickson's Choice is Well-Justified

For N-of-1 trials focused on detecting biomarker × treatment interactions:

- **High autocorrelations (0.8)** are theoretically appropriate
- Reflects stable individual characteristics
- Enables precision medicine approach
- Empirically validated in published simulations

8.5 Practical Recommendations

1. **For Hendrickson comparison**: Use exact values (all 0.8, 0.2, 0.1)
2. **For general use**: Use intermediate values (0.65, 0.18, 0.09)
3. **For sensitivity**: Test conservative to high range
4. **Always**: Validate positive definiteness before running simulations

9 References

1. Hendrickson, E., Hatfield, L. A., & Hodges, J. S. (2020). N-of-1 trials with multiple randomization structures: Design, power, and carryover effects.
2. See companion document: `correlation_structure_design.pdf` for theoretical treatment and troubleshooting
3. See companion document: `correlation_structure_discussion.md` for additional context and recommendations