Should Carryover Effects Modify Correlation Parameters in Clinical Trial Simulations?

Technical Analysis

November 12, 2025

Abstract

This document examines whether carryover effects (residual treatment effects after discontinuation) should modify the correlation structure of multivariate normal distributions used in clinical trial simulations. We compare Hendrickson et al.'s approach (carryover affects means only) with an alternative approach (carryover affects both means and correlations), analyzing the theoretical and statistical implications of each.

1 The Core Question

Should carryover effects, which modify the mean structure of simulated data, also modify the correlation structure of the multivariate normal distribution from which we sample?

This question addresses a fundamental distinction between:

1. **Mean structure** (expected values)
2. **Covariance structure** (variability and correlations)

2 The Statistical Model

The simulation generates data from a multivariate normal distribution:

$$\mathbf{Y} \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma}) \tag{1}$$

where:

- $\mathbf{Y}$ = vector of outcomes [biomarker, baseline, $\text{tv}_1, \text{tv}_2, \ldots, \text{pb}_1, \text{pb}_2, \ldots, \text{br}_1, \text{br}_2, \ldots$]
- $\boldsymbol{\mu}$ = means vector (includes carryover effects in Hendrickson's approach)
- $\boldsymbol{\Sigma}$ = covariance matrix (correlation structure $\times$ standard deviations)

3 Argument 1: Carryover Should NOT Change Correlations

3.1 Position

Carryover is a **mean effect**, not a **variance/correlation effect**.

3.2 Reasoning

3.2.1 Carryover Represents Systematic Persistence

Carryover represents systematic persistence of treatment effect:

- If a drug effect at time t was +5 points
- At time $t+1$ (off drug), we expect +2.5 points (with $t_{1/2} = 1$)
- This is a **shift in expected value**, not a change in variance

3.2.2 Correlation Parameters Represent Residual Dependencies

Correlation parameters represent residual dependencies after accounting for means:

- $c_{\text{br}} = 0.8$ means: "After accounting for treatment/carryover effects, an individual's deviation from expected response at time t correlates 0.8 with their deviation at time $t+1$"
- This individual-level variability structure shouldn't change just because the population mean shifted

3.2.3 Analogy to Linear Mixed Models

Consider a standard linear mixed model:

$$Y_{ij} = \beta_0 + \beta_1 \cdot \text{Treatment} + \beta_2 \cdot \text{Carryover} + b_i + \varepsilon_{ij} \tag{2}$$

where:

- β_2 (carryover coefficient) affects means
- $\text{Var}(b_i)$ and $\text{Var}(\varepsilon_{ij})$ are variance components (unchanged by carryover)
- This is exactly what Hendrickson's approach implements

3.2.4 Statistical Independence of Parameters

Mean parameters and correlation parameters are orthogonal aspects of the distribution:

- Mean parameters: $\{\text{max}, \text{disp}, \text{rate}, \text{carryover\_t1half}\}$
- Correlation parameters: $\{c_{\text{tv}}, c_{\text{pb}}, c_{\text{br}}, c_{\text{cf1t}}, c_{\text{cfct}}\}$

3.3 Hendrickson's Implementation

```
# Carryover affects means:
brmeans[p] <- brmeans[p] + brmeans[p-1] * (1/2)^(tsd/t1half)

# Correlations are FIXED:
correlations[n1,n2] <- modelparam$c.br  # Same regardless of carryover
```

The only exception is the biomarker correlation logic (checking if $\mu \neq 0$), which is arguably a modeling artifact rather than a theoretical choice.

4 Argument 2: Carryover SHOULD Change Correlations

4.1 Position

Carryover creates **temporal dependency**, which fundamentally alters correlation structure.

4.2 Reasoning

4.2.1 Carryover Creates Mechanistic Correlation

- Without carryover: BR at time t and time $t+1$ are independent given covariates
- With carryover: BR at time t **causally influences** BR at time $t+1$
- This should be reflected in the correlation structure

4.2.2 Autocorrelation Should Increase with Carryover

If effects persist longer, observations are more similar across time:

- Strong carryover (long $t_{1/2}$) $\rightarrow$ high temporal correlation
- Weak carryover (short $t_{1/2}$) $\rightarrow$ low temporal correlation

This is implemented in the alternative approach:

```
carryover_strength <- carryover_halflife / (1 + carryover_halflife)
autocorr_boost <- 0.3 * carryover_strength
adjusted_br <- min(0.95, base_autocorr + autocorr_boost * 1.2)
```

4.2.3 Distinguishing Within-Person vs Between-Person Effects

- Carryover creates **within-person temporal dependency**
- This is distinct from **between-person trait stability** (random effects)
- The correlation structure should capture both

4.2.4 Cross-Time Correlations Matter

With carryover, TV_1, PB_1, and BR_1 should correlate more strongly with BR_2:

- Without carryover: weak cross-time correlations
- With carryover: stronger cross-time correlations

Alternative approach: `cross_time_boost <- 0.4 * carryover_strength`

5 What Does the Literature Say?

5.1 Time Series / Longitudinal Data Perspective

Consider an autoregressive model:

$$Y_t = \phi Y_{t-1} + \varepsilon_t \tag{3}$$

where:

- ϕ (autoregression coefficient) $\approx$ carryover effect
- Implied correlation: $\text{Cor}(Y_t, Y_{t-k}) = \phi^k$
- **Correlation structure is a CONSEQUENCE of the autoregressive process**

This supports the alternative approach: carryover parameter should determine correlation structure.

5.2 Multivariate Normal Sampling Perspective

Standard approach:

$$\mathbf{Y} \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma}) \tag{4}$$

where:

- $\boldsymbol{\mu}$ captures systematic effects (including carryover)
- $\boldsymbol{\Sigma}$ captures residual variability
- **These are independent parameters**

This supports Hendrickson's approach: correlations are separate from means.

6 The Critical Distinction

6.1 Hendrickson's Model

Carryover enters ONLY through means:

1. Generate $\mathbf{Y} \sim \mathcal{N}(\boldsymbol{\mu}_{\text{carryover}}, \boldsymbol{\Sigma}_{\text{fixed}})$
2. Carryover is already "baked into" the sampled values
3. The MVN is a **single snapshot** – all time points sampled simultaneously
4. Temporal dependency is implicit in the mean structure

Interpretation: The covariance matrix represents **how individuals deviate from their expected trajectory**, not the temporal dependency itself.

6.2 Alternative Model Enhancement

Carryover enters through BOTH means AND correlations:

1. Generate $\mathbf{Y} \sim \mathcal{N}(\boldsymbol{\mu}_{\text{carryover}}, \boldsymbol{\Sigma}_{\text{carryover}})$
2. Stronger carryover → higher temporal correlations
3. This makes the **residual structure** explicitly time-dependent

Interpretation: The covariance matrix represents **both individual variability AND mechanistic temporal dependency**.

7 Which is Correct?

Both approaches are defensible, but they represent **different modeling philosophies**.

7.1 Hendrickson's Approach (Means Only) is Correct If:

You believe carryover is a **deterministic, population-level phenomenon**:

- Everyone's carryover follows $(1/2)^{t/t_{1/2}}$ exactly
- Individual variation around this is captured by fixed c_{br} correlation
- The correlation structure represents stable individual traits

Analogy: Like a dose-response curve – everyone follows the same curve, just with different baseline sensitivities.

7.2 Alternative Approach (Means + Correlations) is Correct If:

You believe carryover creates **individual-level temporal dependency**:

- People don't all follow $(1/2)^{t/t_{1/2}}$ exactly
- There's individual variation in carryover rate
- Stronger carryover → more "memory" in the system → higher autocorrelation

Analogy: Like a pharmacokinetic model – elimination rates vary by individual, creating person-specific temporal dependencies.

8 Assessment

8.1 Mathematically/Statistically

8.1.1 Hendrickson's Approach is Cleaner:

✓ Clean separation of mean and covariance

✓ Standard multivariate normal framework

✓ Easier to interpret parameters

✓ Carryover fully captured in mean structure

8.1.2 Alternative Approach is More Mechanistically Accurate:

✓ Explicitly models temporal dependency induced by carryover

✓ Captures the idea that longer carryover → stronger autocorrelation

✓ More aligned with time series thinking

However:

× **Potentially double-counting carryover** (once in means, once in correlations)

8.2 The Double-Counting Problem

Critical Issue: When implementing the alternative approach:

```
# Step 1: Adjust means for carryover
bio_response_means <- apply_carryover_to_component(...)

# Step 2: Adjust correlations for carryover
adjusted_br <- base_autocorr + autocorr_boost * carryover_strength

# Step 3: Sample from MVN
Y ~ MVN(mu_with_carryover, Sigma_with_carryover)
```

You might be **over-representing** carryover effects:

- Sampled values inherit temporal dependency from $\boldsymbol{\Sigma}$
- Then you ALSO add carryover through $\boldsymbol{\mu}$
- Result: Too much persistence?

8.3 Hendrickson's Approach Avoids This

```
# Step 1: Adjust means for carryover
brmeans[p] <- brmeans[p] + brmeans[p-1] * (1/2)^(t/t_half)

# Step 2: Sample from MVN with FIXED correlations
Y ~ MVN(mu_with_carryover, Sigma_fixed)
```

All temporal dependency from carryover is in the means. The correlation captures only **residual individual-level variation**.

9 Recommendation

9.1 Hendrickson's Approach is Theoretically Cleaner

Why:

1. **Carryover is already fully specified** in the mean structure through the exponential decay formula
2. **Correlation parameters should represent residual variability** after accounting for all systematic effects (treatment, carryover, time trends)

3. **Avoids double-counting** temporal dependency
4. **Aligns with standard multilevel modeling** where:
   - Fixed effects (including carryover) → means
   - Random effects (individual traits) → correlations
5. **Simpler parameter interpretation** – c_{br} means "individual-level stability" not "mechanistic persistence"

9.2 However, the Alternative Enhancement Could Be Justified If:

You're trying to model **individual heterogeneity in carryover rates**:

- Some people eliminate drugs faster (short personal $t_{1/2}$)
- Some people eliminate slower (long personal $t_{1/2}$)
- Population-level carryover_t1half is the average
- Higher correlation represents this individual variation in elimination

But then you should:

1. Keep the base carryover in means (population average)
2. Use correlation adjustment to represent **variance in individual carryover rates**
3. Be explicit that you're modeling heterogeneous carryover, not just carryover

10 Conclusion

10.1 Answer to the Core Question

Modified means due to carryover should NOT change correlation parameters in the standard simulation framework because:

- ✓ Carryover is a **mean effect** (systematic shift in expected value)
- ✓ Correlations represent **residual dependencies** after accounting for means
- ✓ Adjusting both creates **double-counting** of temporal dependency
- ✓ Hendrickson's approach (carryover in means only) is the **standard statistical approach**

10.2 Implications

The alternative approach (adjusting both means and correlations) could be valid if reframed as modeling "individual heterogeneity in carryover rates" but would need careful theoretical justification to avoid double-counting.

For direct comparison to Hendrickson and standard statistical practice, the recommendation is to **remove the dynamic correlation adjustment** and keep carryover effects only in the mean structure.