Simplified N-of-1 Trial Simulation: Mathematical Foundations and Design Rationale

pmsimstats2025 Project

2025-11-22

Contents

1 Executive Summary

This white paper documents the systematic simplification of an N-of-1 clinical trial simulation based on Hendrickson et al. (2020). The original implementation used complex Gompertz response curves and a monolithic 26×26 covariance matrix. We present a series of mathematically equivalent but conceptually clearer simplifications:

1. **Rate-based response model** replacing Gompertz curves

2. **Time-based AR(1) correlation** replacing compound symmetry
3. **Two-stage data generation** separating participant and response variables
4. **Guaranteed positive-definiteness** via grid-snapping

Each simplification is justified mathematically and evaluated for conceptual clarity, computational efficiency, and biological plausibility.

---

2 Introduction

2.1 Background

N-of-1 trials are randomized crossover designs where a single participant serves as their own control. The hybrid design combines an open-label run-in with blinded crossover periods to estimate individual treatment effects while accounting for placebo (expectancy) effects.

2.2 Original Complexity

The original Hendrickson-based simulation involved:

- **Three response factors**: Biological Response (BR), Expectancy Response (ER), Time-variant Response (TR)
- **Gompertz trajectories**: Sigmoidal curves with 3 parameters each (max, displacement, rate)
- **26×26 covariance matrix**: 3 factors × 8 timepoints + biomarker + baseline
- **Non-transparent construction**: Correlations filled element-by-element without PD guarantees

2.3 Goals of Simplification

1. **Conceptual clarity**: Each component should be independently understandable
2. **Mathematical transparency**: All assumptions explicit and justified
3. **Robustness**: Guaranteed valid (positive definite) covariance matrices
4. **Flexibility**: Easy to modify individual components

---

3 Simplification 1: Rate-Based Response Model

3.1 Original: Gompertz Curves

The original model used Gompertz functions for each response factor:

$$f(t) = \max \cdot \exp\left(-\text{disp} \cdot \exp(-\text{rate} \cdot t)\right)$$

This S-shaped curve has three parameters:

- **max**: Asymptotic maximum effect
- **disp**: Displacement (horizontal shift)
- **rate**: Growth rate

3.1.1 Problems with Gompertz

1. **Over-parameterized**: 3 parameters per factor × 3 factors = 9 response parameters
2. **Non-intuitive**: Displacement and rate interact in complex ways
3. **Asymptotic behavior**: Effect plateaus, but clinical effects often accumulate linearly

3.2 Simplified: Linear Rate Model

We replace Gompertz with simple linear accumulation:

$$\text{Effect}(t) = \text{rate} \times \text{time}$$

3.2.1 Three-Factor Rate Model

For each factor, we define a single rate parameter (points per week):

$$\text{BR}_{\text{rate}} = 0.5 \text{ points/week on drug} \tag{1}$$
$$\text{ER}_{\text{rate}} = 0.2 \text{ points/week} \times \text{expectancy} \tag{2}$$
$$\text{TR}_{\text{rate}} = 0.1 \text{ points/week} \tag{3}$$

The response at time t is:

$$\text{BR}(t) = \text{BR}_{\text{rate}} \times (\text{cumulative weeks on drug}) \tag{4}$$
$$\text{ER}(t) = \text{ER}_{\text{rate}} \times \sum_{s \le t} \text{expectancy}(s) \tag{5}$$
$$\text{TR}(t) = \text{TR}_{\text{rate}} \times (\text{weeks in trial}) \tag{6}$$

3.2.2 Carryover Model

When drug is discontinued, BR doesn't immediately drop to zero. We model carryover as a partial effect at the first off-drug timepoint:

$$\text{BR}(t) = \begin{cases} \text{BR}_{\text{rate}} \times \text{weeks\_on\_drug} & \text{if on drug} \\ \text{BR}_{\text{accumulated}} \times \text{carryover\_decay\_rate} & \text{if first week off} \\ 0 & \text{if subsequent weeks off} \end{cases}$$

For example, with carryover_decay_rate = 0.5:

- Week 10 (on drug, 4 weeks): BR $= 0.5 \times 4 = 2.0$
- Week 11 (first week off): BR $= 2.0 \times 0.5 = 1.0$
- Week 12 (second week off): BR $= 0$

3.2.3 Why This Is Better

Aspect	Gompertz	Linear Rate
Parameters	9 (3 per factor)	3 (1 per factor)
Interpretation	Complex	Direct (points/week)
Flexibility	Fixed asymptote	Unbounded accumulation
Clinical face validity	Moderate	High

Intuition: Clinicians think in terms of "improvement per week," not asymptotic limits and displacement parameters.

---

4 Simplification 2: Time-Based AR(1) Correlation

4.1 Original: Compound Symmetry

The original model used compound symmetry within each response type:

$$\text{Corr}(Y_i, Y_j) = \rho \quad \text{for all } i \neq j$$

This means measurements at week 4 and week 8 (4 weeks apart) have the same correlation as measurements at week 8 and week 9 (1 week apart).

4.1.1 Problems with Compound Symmetry

1. **Biologically implausible**: Nearby measurements should be more correlated
2. **Wastes correlation budget**: High correlation everywhere leaves less room for cross-correlations
3. **More prone to PD failures**: Concentrates eigenvalues

4.2 Simplified: Time-Based AR(1)

We use an autoregressive structure based on actual time lags:

$$\text{Corr}(Y_{t_i}, Y_{t_j}) = \rho^{|t_i - t_j|}$$

where t_i and t_j are the actual week numbers.

4.2.1 Example Correlation Matrix

For measurement weeks $\{4, 8, 9, 10, 11, 12, 16, 20\}$ with $\rho = 0.8$:

Table 2: Time-based AR(1) correlation matrix

	W4	W8	W9	W10	W11	W12	W16	W20
W4	1.00	0.41	0.33	0.26	0.21	0.17	0.07	0.03
W8	0.41	1.00	0.80	0.64	0.51	0.41	0.17	0.07
W9	0.33	0.80	1.00	0.80	0.64	0.51	0.21	0.09
W10	0.26	0.64	0.80	1.00	0.80	0.64	0.26	0.11
W11	0.21	0.51	0.64	0.80	1.00	0.80	0.33	0.13
W12	0.17	0.41	0.51	0.64	0.80	1.00	0.41	0.17
W16	0.07	0.17	0.21	0.26	0.33	0.41	1.00	0.41
W20	0.03	0.07	0.09	0.11	0.13	0.17	0.41	1.00

4.2.2 Key Comparisons

Week Pair	Time Lag	Compound Symmetry	Time-Based AR(1)
W4 - W8	4 weeks	0.80	$0.8^4 = 0.41$
W8 - W9	1 week	0.80	$0.8^1 = 0.80$
W12 - W16	4 weeks	0.80	$0.8^4 = 0.41$
W4 - W20	16 weeks	0.80	$0.8^{16} = 0.03$

4.2.3 Guaranteed Positive Definiteness

The AR(1) correlation function $K(t_1, t_2) = \rho^{|t_1 - t_2|}$ is a valid positive definite kernel for $\rho \in (0, 1)$. This is the exponential covariance function, widely used in spatial statistics and time series.

Proof sketch: The AR(1) process $Y_t = \rho Y_{t-1} + \epsilon_t$ has this covariance structure, and valid stochastic processes always have PD covariance matrices.

4.2.4 Why This Is Better

Aspect	Compound Symmetry	Time-Based AR(1)
Biological realism	Low	High
Eigenvalue spread	Concentrated	Distributed
PD robustness	Lower	Higher
Interpretability	"Same correlation everywhere"	"Correlation decays with time"

Intuition: Your blood pressure yesterday is more predictive of today's than last month's. Correlation should decay with time.

---

5 Simplification 3: Two-Stage Data Generation

5.1 Original: Monolithic 26×26 Matrix

The original approach built a single 26×26 covariance matrix:

$$\Sigma_{26\times 26} = \begin{pmatrix} \Sigma_{\text{BR}} & \Sigma_{\text{BR,ER}} & \Sigma_{\text{BR,TR}} & \Sigma_{\text{BR,BM}} & \Sigma_{\text{BR,BL}} \\ \Sigma_{\text{ER,BR}} & \Sigma_{\text{ER}} & \Sigma_{\text{ER,TR}} & \Sigma_{\text{ER,BM}} & \Sigma_{\text{ER,BL}} \\ \vdots & & \ddots & & \vdots \\ \Sigma_{\text{BL,BR}} & \cdots & & & \Sigma_{\text{BL}} \end{pmatrix}$$

Then generated all 26 variables jointly:

$$\mathbf{X} \sim \mathcal{N}(\mathbf{0}, \Sigma_{26\times 26})$$

5.1.1 Problems with Monolithic Approach

1. **Opaque structure**: Hard to see how biomarker affects responses
2. **All-or-nothing PD**: If not PD, entire matrix rejected
3. **No clear causal interpretation**: Everything generated simultaneously

5.2 Simplified: Two-Stage Conditional Generation

We partition variables into:

- $\mathbf{X}_2$: Participant variables (biomarker, baseline) - 2 dimensions
- $\mathbf{X}_1$: Response variables (BR, ER, TR at 8 timepoints) - 24 dimensions

5.2.1 Partitioned Covariance

$$\Sigma = \begin{pmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{21} & \Sigma_{22} \end{pmatrix}$$

where:

- Σ_{22}: 2×2 covariance of (biomarker, baseline)
- Σ_{11}: 24×24 covariance of responses
- Σ_{12}: 24×2 cross-covariance (how biomarker/baseline relate to responses)

5.2.2 Conditional Distribution Theorem

For jointly normal variables:

$$\mathbf{X}_1|\mathbf{X}_2 \sim \mathcal{N}(\mu_{1|2}, \Sigma_{1|2})$$

where:

$$\mu_{1|2} = \Sigma_{12}\Sigma_{22}^{-1}(\mathbf{X}_2 - \mu_2) \tag{7}$$

$$\Sigma_{1|2} = \Sigma_{11} - \Sigma_{12}\Sigma_{22}^{-1}\Sigma_{21} \tag{8}$$

5.2.3 Two-Stage Algorithm

Stage 1: Generate participant characteristics

$$\begin{pmatrix} \text{biomarker} \\ \text{baseline} \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} \mu_{\text{BM}} \\ \mu_{\text{BL}} \end{pmatrix}, \Sigma_{22} \right)$$

Stage 2: Generate responses conditional on participant characteristics

$$\begin{pmatrix} \text{BR}_1 \\ \vdots \\ \text{TR}_8 \end{pmatrix} \sim \mathcal{N}\left(\Sigma_{12}\Sigma_{22}^{-1} \begin{pmatrix} \text{biomarker} - \mu_{\text{BM}} \\ \text{baseline} - \mu_{\text{BL}} \end{pmatrix}, \Sigma_{1|2} \right)$$

5.2.4 Mathematical Equivalence

This two-stage procedure is **exactly equivalent** to generating from the joint 26×26 distribution. The conditional distribution formula preserves all correlations.

Proof: By construction, the joint density factors as $p(\mathbf{X}_1, \mathbf{X}_2) = p(\mathbf{X}_2) \cdot p(\mathbf{X}_1|\mathbf{X}_2)$.

5.2.5 Why This Is Better

Aspect	Monolithic	Two-Stage
Causal interpretation	Unclear	Clear (BM → responses)
Matrix inversion	None	2×2 only (trivial)
Debugging	Hard	Test each stage
Conceptual model	Simultaneous	Sequential

Intuition: A participant's biomarker level is determined before the trial starts. Then their responses depend on this biomarker. The two-stage approach matches this causal structure.

---

6 Simplification 4: Guaranteed Positive Definiteness

6.1 The Problem

For a covariance matrix to be valid, it must be positive definite (PD): all eigenvalues must be positive. When constructing correlation matrices element-by-element, PD is not guaranteed.

6.1.1 Common Failure Mode

High correlations "use up" the positive definiteness budget:

$$\lambda_{\min}(\Sigma) = \sigma^2(1 - \rho_{\max})$$

When cross-correlations are added, $\lambda_{\min}$ can become negative.

6.2 Solution: Independent Construction with Schur Complement

6.2.1 The Schur Complement Condition

For the partitioned matrix to be PD:

$$\Sigma_{1|2} = \Sigma_{11} - \Sigma_{12}\Sigma_{22}^{-1}\Sigma_{21} > 0$$

This is the **Schur complement** condition.

6.2.2 Construction Strategy

1. **Build Σ_{22} (2×2)**: Always PD for $|\rho| < 1$
2. **Build Σ_{11} (24×24)**: Use time-based AR(1), guaranteed PD
3. **Build Σ_{12} (24×2)**: Regression coefficients
4. **Check Schur complement**: If not PD, scale down Σ_{12}

6.2.3 Grid-Snapping Algorithm

Rather than continuous scaling, we snap to a predefined grid of correlation values:

```
allowed_correlations <- c(0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6)
```

Algorithm:

1. User requests biomarker correlation $\rho_{\text{requested}}$
2. Try $\rho \in \{\rho_{\text{requested}}, \rho_{\text{requested}} - 0.1, \ldots, 0\}$
3. For each ρ, check if $\Sigma_{1|2}$ is PD
4. Use largest valid ρ from grid

6.2.4 Example

- Requested: $\rho = 0.5$
- System checks: 0.5 (not PD), 0.4 (PD!)
- Uses: $\rho_{\text{effective}} = 0.4$
- Reports: "Snapped biomarker correlation: 0.50 → 0.40"

6.2.5 Why Grid-Snapping Is Better Than Continuous Scaling

Aspect	Continuous	Grid-Snapping
Result values	Arbitrary (0.423…)	Clean (0.4)
Visualization	Hard to bin	Natural grid
Reproducibility	Exact but odd values	Clean categories
Interpretation	"Scaled by 0.847"	"Using 0.4"

Intuition: For reporting and visualization, we want results on a regular grid. Grid-snapping ensures this automatically.

---

7 Complete Response Model

7.1 Biomarker Moderation of Treatment Effect

A critical feature of the simulation is that participants with different biomarker levels respond differently to treatment. This creates the **treatment × biomarker interaction** that the analysis aims to detect.

7.1.1 The Moderation Mechanism

The biological response rate is scaled by the participant's biomarker level:

$$\text{BR}_{\text{effective}} = \text{BR}_{\text{rate}} \times \left(1 + \beta_{\text{mod}} \times \frac{\text{biomarker}_i - \mu_{\text{BM}}}{\sigma_{\text{BM}}}\right)$$

where:

- BR_{rate}: Base treatment effect (0.5 points/week)
- β_{mod}: Moderation strength (0.15 = 15% change per SD)
- $\mu_{\text{BM}}, \sigma_{\text{BM}}$: Population biomarker mean and SD

7.1.2 Example

For a participant with biomarker 1 SD above the mean:

$$\text{BR}_{\text{effective}} = 0.5 \times (1 + 0.15 \times 1) = 0.575 \text{ points/week}$$

For a participant with biomarker 1 SD below the mean:

$$\text{BR}_{\text{effective}} = 0.5 \times (1 + 0.15 \times (-1)) = 0.425 \text{ points/week}$$

7.1.3 Why Explicit Moderation vs. Correlation-Based

The original Hendrickson approach and our simplified approach both create valid treatment × biomarker interactions, but through fundamentally different mechanisms.

7.1.3.1 The Hendrickson Correlation-Based Approach Hendrickson creates the interaction through **treatment-conditional correlations** in the covariance matrix:

- On treatment: $\text{Cor}(\text{biomarker}, \text{BR}) = c_{\text{bm}}$
- Off treatment: $\text{Cor}(\text{biomarker}, \text{BR}) = 0$

How this creates an interaction: When we draw from the multivariate normal, participants with high biomarkers will tend to have high BR values *only during on-treatment periods*. During off-treatment periods, BR is uncorrelated with biomarker.

Mathematically, let Z_{BM} be the standardized biomarker and Z_{BR} be the standardized BR random effect. Under Hendrickson:

$$E[Z_{\text{BR}}|Z_{\text{BM}}, \text{treatment} = 1] = c_{\text{bm}} \cdot Z_{\text{BM}}$$

$$E[Z_{\text{BR}}|Z_{\text{BM}}, \text{treatment} = 0] = 0$$

The difference in conditional expectations *is* the interaction:

$$\Delta E[Z_{\text{BR}}] = c_{\text{bm}} \cdot Z_{\text{BM}}$$

This is elegant because the interaction emerges naturally from the joint distribution without explicit computation.

7.1.3.2 The Explicit Moderation Approach Our simplified approach directly scales the treatment effect by biomarker:

$$\text{BR}_{\text{effective}} = \text{BR}_{\text{rate}} \times (1 + \beta_{\text{mod}} \cdot Z_{\text{BM}})$$

How this creates an interaction: The treatment effect magnitude varies directly with biomarker level. A participant with $Z_{\text{BM}} = 1$ gets a $(1 + \beta_{\text{mod}})$ times stronger effect than a participant with $Z_{\text{BM}} = 0$.

The interaction effect per week on drug is:

$$\frac{\partial^2 \text{BR}}{\partial \text{treatment} \cdot \partial Z_{\text{BM}}} = \text{BR}_{\text{rate}} \times \beta_{\text{mod}}$$

7.1.3.3 Mathematical Equivalence Both approaches generate data where the treatment × biomarker coefficient in the analysis model will be non-zero. To see why, consider the regression model:

$$Y = \beta_0 + \beta_1 \text{treatment} + \beta_2 \text{biomarker} + \beta_3(\text{treatment} \times \text{biomarker}) + \epsilon$$

Under Hendrickson: $\beta_3 \neq 0$ because $\text{Cov}(Y, \text{treatment} \times \text{biomarker})$ differs from what's explained by main effects alone. The differential correlation structure creates residual covariance that the interaction term captures.

Under explicit moderation: $\beta_3 \neq 0$ because we directly constructed BR $\propto$ treatment × biomarker.

Both produce valid power estimates for detecting the interaction, though the effect sizes may differ in scale.

7.1.3.4 Key Differences

Aspect	Hendrickson (Correlation)	Simplified (Explicit)
Mechanism	Differential Σ by treatment	Direct effect scaling
Effect location	In random component	In mean component
Tuning	Via c_{bm} correlation	Via β_{mod} coefficient
Sigma matrix	Treatment-conditional (complex)	Single matrix (simple)

Aspect	Hendrickson (Correlation)	Simplified (Explicit)
Interpretability	Requires MVN theory	Direct formula
Causal model	Latent variable	Explicit moderation

7.1.3.5 When to Use Each

Use Hendrickson (correlation-based) when:

- You want the interaction embedded in the latent structure
- You're modeling scenarios where the biomarker-response relationship is fundamentally correlational
- You need exact alignment with Hendrickson et al. (2020) for replication

Use explicit moderation when:

- You want transparent, easily auditable code
- You need to precisely control the interaction effect size
- You're teaching or learning the simulation mechanics
- Computational simplicity is important (single sigma matrix)

7.1.3.6 Why Both Are Valid

The critical insight is that **statistical power to detect an interaction depends on whether the interaction exists in the data, not on how it was generated**.

Both methods ensure that:

1. $E[\hat{\beta}_3] \neq 0$ (the interaction estimate is non-zero in expectation)
2. $\text{Var}(\hat{\beta}_3)$ is determined by sample size and noise (comparable between methods)
3. Power $= P(|\hat{\beta}_3/\text{SE}| > t_\alpha)$ depends on signal-to-noise ratio

The Hendrickson approach is more "natural" in the sense that it models the interaction as arising from correlated latent factors. The explicit approach is more "mechanical" but equally valid for power analysis purposes.

For the simplified learning version, explicit moderation is preferred because:

1. **More transparent**: The interaction mechanism is visible in one formula
2. **Easier to tune**: β_{mod} directly controls interaction strength
3. **Computationally simpler**: No need for treatment-conditional sigma matrices
4. **Pedagogically clearer**: Students can trace exactly how biomarker affects outcome

7.2 Total Response Formula

Combining all simplifications, the response at timepoint t for participant i is:

$$
\begin{aligned}
Y_{it} = & \underbrace{\text{baseline}_i}_{\text{from } \Sigma_{22}} && (9)\\
& + \underbrace{\text{BR}_{\text{effective}} \times \text{weeks\_on\_drug}_{it} + \text{br\_random}_{it}}_{\text{Biological Response (moderated)}} && (10)\\
& + \underbrace{\text{ER}_{\text{rate}} \times \sum_{s \leq t} \text{expectancy}_{is} + \text{er\_random}_{it}}_{\text{Expectancy Response}} && (11)\\
& + \underbrace{\text{TR}_{\text{rate}} \times (t - t_0) + \text{tr\_random}_{it}}_{\text{Time-variant Response}} && (12)
\end{aligned}
$$

where:

- baseline_i: Participant's baseline (from Σ_{22}, correlated with biomarker)

- $\text{BR}_{\text{effective}}$: Biomarker-moderated treatment rate (see above)
- br_random_{it}, er_random_{it}, tr_random_{it}: Correlated random effects (from $\Sigma_{1|2}$)
- Carryover modifies BR when off drug

7.3 Correlation Structure

The random components $(\text{br\_random}, \text{er\_random}, \text{tr\_random})$ are correlated:

1. **Within factor, across time**: AR(1) with time-based decay
2. **Across factors, same time**: Cross-correlation $c_{\text{cf1t}} = 0.2$
3. **Across factors, different time**: Cross-correlation $c_{\text{cfct}} = 0.1$ with decay
4. **With biomarker**: BR correlated at c_{bm}, ER/TR at $0.5 \times c_{\text{bm}}$

Note: The sigma correlations provide realistic noise structure, but the treatment × biomarker interaction comes from the explicit moderation formula above.

---

8 Hybrid Trial Design

8.1 Design Structure

Week	Phase	Treatment	Expectancy	Description
4, 8	Open-label	All active	1.0	Run-in period
9	Blinded	All active	0.5	Transition
10	Blinded	Randomized	0.5	Paths 1,2 active; 3,4 placebo
11, 12	Blinded	All placebo	0.5	Washout
16	Blinded	Crossover	0.5	Paths 1,3 active; 2,4 placebo
20	Blinded	Crossover	0.5	Paths 1,3 placebo; 2,4 active

8.2 Four-Path Randomization

Participants are randomized to one of four paths, ensuring balanced treatment sequences:

Path	W10	W11-12	W16	W20
1	Active	Placebo	Active	Placebo
2	Active	Placebo	Placebo	Active
3	Placebo	Placebo	Active	Placebo
4	Placebo	Placebo	Placebo	Active

---

9 Parallel Design

9.1 Design Structure

The parallel design provides a simpler comparison where participants are randomized once at the start:

- **Treatment group**: Active drug at all 8 timepoints
- **Control group**: Placebo at all 8 timepoints
- **Expectancy**: 0.5 throughout (all blinded)

Week	Treatment Group	Control Group
4, 8, 9, 10, 11, 12, 16, 20	Active	Placebo

9.2 Key Differences from Hybrid

Aspect	Hybrid	Parallel
Within-subject comparison	Yes (crossover)	No
Carryover effects	Relevant	Not applicable
Sample efficiency	Higher	Lower
Design complexity	Complex	Simple

9.2.1 Why Parallel Has Lower Power

The parallel design cannot leverage within-subject comparisons. Each participant only experiences one treatment condition, so:

1. **No crossover**: Cannot compare same participant on/off drug
2. **Between-subject only**: Treatment effect confounded with individual differences
3. **Carryover irrelevant**: No treatment switches means carryover parameter has no effect

---

10 Simulation Parameter Grid

10.1 Effect Size Variation

To evaluate both Type I error and power across effect sizes, we vary the biomarker moderation parameter:

β_{mod}	Interpretation	Purpose
0.00	No interaction	Type I error (size of test)
0.25	Weak effect	Low power regime
0.35	Moderate effect	Medium power
0.45	Strong effect	High power regime

10.2 Complete Parameter Grid

```
param_grid <- bind_rows(
  # Hybrid design with carryover variations
  expand_grid(
    design = "hybrid",
    biomarker_moderation = c(0, 0.25, 0.35, 0.45),
    carryover_decay_rate = c(0, 0.5)
  ),
  # Parallel design (carryover not applicable)
  expand_grid(
    design = "parallel",
    biomarker_moderation = c(0, 0.25, 0.35, 0.45),
    carryover_decay_rate = c(0)
  )
)
```

This yields 12 conditions: 8 for hybrid (4 moderation $\times$ 2 carryover) + 4 for parallel.

10.3 Expected Results

Under the null ($\beta_{\text{mod}} = 0$):

- Type I error should be approximately 5%
- Any significant results are false positives

Under alternatives ($\beta_{\text{mod}} > 0$):

- Power should increase with effect size
- Hybrid should outperform parallel due to within-subject comparisons
- Higher carryover should reduce power for hybrid (blurs on/off distinction)

---

11 Statistical Analysis

11.1 Mixed Effects Model

The analysis model is:

$$Y_{it} = \beta_0 + \beta_1 \text{treatment}_{it} + \beta_2 \text{biomarker}_i + \beta_3 (\text{treatment} \times \text{biomarker})_{it} + \beta_4 \text{week}_t + \gamma_i + \epsilon_{it}$$

where:

- β_3: Treatment × biomarker interaction (primary outcome)
- $\gamma_i \sim \mathcal{N}(0, \sigma^2_{\text{between}})$: Random intercept
- $\epsilon_{it} \sim \mathcal{N}(0, \sigma^2_{\text{within}})$: Residual

11.2 Power Calculation

Statistical power is the probability of detecting a significant treatment × biomarker interaction:

$$\text{Power} = P(p < 0.05 | H_1 \text{ true})$$

Estimated via Monte Carlo simulation over multiple iterations.

---

12 Computational Considerations

12.1 Efficiency Comparison

Operation	Old Method	New Method
Build covariance	26×26 at once	2×2 + 24×24
PD check	Full eigendecomposition	Schur complement
Failure mode	Reject	Snap to grid
Cholesky	26×26	2×2 + 24×24
Matrix inverse	None	2×2 (trivial)

12.2 Cholesky Decomposition Cost

$$\text{Cost} \propto n^3$$

- Old: $26^3 = 17,576$
- New: $2^3 + 24^3 = 8 + 13,824 = 13,832$

Approximately 20% reduction, plus avoided failures.

---

13 Conclusions

13.1 Summary of Simplifications

1. **Rate-based response**: 3 parameters vs 9, clinically interpretable
2. **Time-based AR(1)**: Biologically plausible decay, more robust
3. **Two-stage generation**: Clear causal structure, easier debugging
4. **Grid-snapping**: Guaranteed PD, clean visualization

13.2 Trade-offs

Simplification	Gained	Lost
Rate model	Interpretability	Asymptotic saturation
AR(1)	Realism, robustness	Compound symmetry option
Two-stage	Clarity	Nothing (mathematically equivalent)
Grid-snapping	Guaranteed PD	Exact requested correlation

13.3 Recommendations

These simplifications are recommended for:

- **Teaching**: Much easier to understand
- **Development**: Easier to debug and modify
- **Production**: More robust, fewer failures

The original Gompertz/monolithic approach may still be preferred for:

- **Publication**: Exact replication of Hendrickson
- **Asymptotic effects**: When saturation is clinically meaningful

---

14 References

Hendrickson, E., et al. (2020). N-of-1 trials with multiple randomization structures for individualized treatment. *Statistics in Medicine*.

Raskind, M., et al. (2013). Pilot RCT data used for biomarker and baseline estimates. [Source for parameter values]

---

15 Appendix: R Implementation

15.1 Key Functions

```r
# Build guaranteed-PD sigma with time-based AR(1)
build_sigma_guaranteed_pd <- function(weeks, c.bm, params) {
  # Stage 1: Sigma_22 (2×2)
  # Stage 2: Sigma_11 (24×24) with AR(1)
  # Stage 3: Sigma_12 (24×2)
  # Stage 4: Grid-snap to ensure PD
}

# Two-stage data generation
generate_participant_twostage <- function(sigma_parts, idx) {
  # Stage 1: Generate (biomarker, baseline)
  x2 <- mvrnorm(1, mu = c(0, 0), Sigma = sigma_parts$Sigma_22)

  # Stage 2: Generate responses | participant vars
  mu_cond <- Sigma_12 %*% Sigma_22_inv %*% x2
  x1 <- mvrnorm(1, mu = mu_cond, Sigma = sigma_parts$Sigma_cond)
}
```

15.2 Biomarker Moderation

```r
# Parameters
biomarker_moderation <- 0.15  # 15% change per SD

# In data generation (inside mutate)
bm_centered = (biomarker - biomarker_mean) / biomarker_sd,

BR_mean = {
  # Treatment effect moderated by biomarker
  effective_BR_rate <- BR_rate * (1 + biomarker_moderation * bm_centered)

  # Accumulate while on drug, with carryover
  ifelse(treatment == 1,
         weeks_on_drug * effective_BR_rate,
         ifelse(first_off,
                br_accumulated * carryover_decay_rate,
                0))
}
```

15.3 Grid-Snapping Algorithm

```r
allowed_correlations <- c(0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6)

find_valid_correlation <- function(Sigma_11, Sigma_22_inv, c.bm_requested, ...) {
  for (c.bm_try in sort(allowed[allowed <= c.bm_requested], decreasing = TRUE)) {
    # Build Sigma_12 with c.bm_try
    # Check if Schur complement is PD
    if (min_eigenvalue > 0) return(c.bm_try)
  }
  return(0)  # Fallback
```

```
}
```