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

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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.

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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

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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 $\times$ 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.

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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.

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5 Simplification 3: Two-Stage Data Generation

5.1 Original: Monolithic 26×26 Matrix

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