Mathematical Derivation of the Two-Step Sigma Matrix Calculation

Clinical Trial Simulation Documentation

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Abstract

This document provides a comprehensive mathematical derivation of the efficient two-step method for computing covariance matrices from correlation matrices in multivariate normal data generation. Specifically, we derive the identity $\Sigma = \mathbf{DRD}$, where Σ is the covariance matrix, $\mathbf{R}$ is the correlation matrix, and $\mathbf{D}$ is a diagonal matrix of standard deviations. This decomposition is fundamental to clinical trial simulation, enabling numerical stability and computational efficiency.

Contents

1 Introduction

In multivariate normal data generation for clinical trials, we need to construct covariance matrices that are:

1. **Positive definite** (PD) - ensuring mvrnorm() and mvn sampling work correctly
2. **Numerically stable** - avoiding ill-conditioning and eigenvalue issues
3. **Interpretable** - separating correlation structure from magnitude (standard deviations)

The most efficient approach achieves all three by decomposing the covariance matrix into:

$$\Sigma = \mathbf{DRD}$$

where the correlation matrix $\mathbf{R}$ is validated for PD independently from scaling by standard deviations in $\mathbf{D}$.

This document derives this identity from first principles and explains its computational advantages.

2 Foundational Concepts

2.1 Covariance and Correlation: Univariate Case

Definition 1 (Covariance)**.** For two random variables X and Y with means μ_X and μ_Y:

$$\text{Cov}(X, Y) = E[(X - \mu_X)(Y - \mu_Y)]$$

Definition 2 (Standard Deviation)**.** The standard deviation of a random variable X is:

$$\sigma_X = \sqrt{\text{Var}(X)} = \sqrt{\text{Cov}(X, X)}$$

Definition 3 (Correlation Coefficient)**.** The Pearson correlation coefficient between X and Y is:

$$\text{Corr}(X, Y) = \frac{\text{Cov}(X, Y)}{\sigma_X \sigma_Y}$$

Theorem 1 (Covariance-Correlation Relationship)**.** For any two random variables X and Y:

$$\text{Cov}(X, Y) = \text{Corr}(X, Y) \cdot \sigma_X \cdot \sigma_Y$$

Proof. By definition of correlation (Definition 3):

$$\text{Corr}(X, Y) = \frac{\text{Cov}(X, Y)}{\sigma_X \sigma_Y}$$

Rearranging:

$$\text{Cov}(X, Y) = \text{Corr}(X, Y) \cdot \sigma_X \cdot \sigma_Y \quad \square$$

$\square$

3 Multivariate Extension

3.1 Covariance Matrix

Definition 4 (Covariance Matrix)**.** Let $\mathbf{Z} = [Z_1, Z_2, \ldots, Z_n]^\top$ be a random vector with mean $\boldsymbol{\mu}$. The covariance matrix is:

$$\Sigma = \mathrm{Cov}(\mathbf{Z}) = E[(\mathbf{Z} - \boldsymbol{\mu})(\mathbf{Z} - \boldsymbol{\mu})^\top]$$

with elements:

$$\Sigma_{ij} = \mathrm{Cov}(Z_i, Z_j) = E[(Z_i - \mu_i)(Z_j - \mu_j)]$$

In particular, $\Sigma_{ii} = \mathrm{Var}(Z_i) = \sigma_i^2$.

3.2 Correlation Matrix

Definition 5 (Correlation Matrix)**.** The correlation matrix $\mathbf{R}$ has elements:

$$R_{ij} = \frac{\Sigma_{ij}}{\sigma_i \sigma_j} = \mathrm{Corr}(Z_i, Z_j)$$

By definition, $R_{ii} = 1$ (perfect self-correlation) and $|R_{ij}| \leq 1$ for $i \neq j$.

3.3 Positive Definiteness

Definition 6 (Positive Definite Matrix)**.** A symmetric matrix $\mathbf{A} \in \mathbb{R}^{n \times n}$ is positive definite (PD) if:

$$\mathbf{x}^\top \mathbf{A} \mathbf{x} > 0 \quad \forall \mathbf{x} \in \mathbb{R}^n, \mathbf{x} \neq \mathbf{0}$$

Equivalently, all eigenvalues are strictly positive.

Remark 1 (Valid Correlation Matrices)**.** A valid correlation matrix $\mathbf{R}$ must be:

1. Symmetric: $R_{ij} = R_{ji}$
2. Unit diagonal: $R_{ii} = 1$
3. Bounded: $|R_{ij}| \leq 1$
4. Positive semi-definite (PSD)

Note: Conditions 1-3 are necessary but NOT sufficient for PSD.

4 The Sigma Matrix Decomposition: = D·R·D

4.1 Defining the Diagonal Standard Deviation Matrix

Definition 7 (Diagonal Standard Deviation Matrix)**.** Define $\mathbf{D}$ as the diagonal matrix of standard deviations:

$$\mathbf{D} = \begin{pmatrix} \sigma_1 & 0 & \cdots & 0 \\ 0 & \sigma_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \sigma_n \end{pmatrix}$$

where $\sigma_i = \sqrt{\Sigma_{ii}}$ is the standard deviation of Z_i.

4.2 Main Derivation

Theorem 2 (Sigma Decomposition)**.** The covariance matrix Σ can be decomposed as:

$$\Sigma = \mathbf{DRD}$$

where $\mathbf{D}$ is the diagonal standard deviation matrix and $\mathbf{R}$ is the correlation matrix.

Proof. We show this by computing each element of $\mathbf{DRD}$.

Step 1: Compute DR

The (i, j)-element of $\mathbf{DR}$ is:

$$[\mathbf{DR}]_{ij} = \sum_{k=1}^{n} D_{ik} R_{kj} = D_{ii} R_{ij} = \sigma_i R_{ij}$$

because $\mathbf{D}$ is diagonal (so $D_{ik} = 0$ for $k \neq i$).

Step 2: Compute (DR)D

The (i, j)-element of $(\mathbf{DR})\mathbf{D}$ is:

$$[(\mathbf{DR})\mathbf{D}]_{ij} = \sum_{k=1}^{n} [\mathbf{DR}]_{ik} D_{kj} = (\sigma_i R_{ij}) D_{jj} = \sigma_i R_{ij} \sigma_j$$

Step 3: Express in terms of covariance

From Definition 2 and Theorem 1:

$$R_{ij} = \frac{\Sigma_{ij}}{\sigma_i \sigma_j}$$

Therefore:

$$[(\mathbf{DR})\mathbf{D}]_{ij} = \sigma_i \cdot \frac{\Sigma_{ij}}{\sigma_i \sigma_j} \cdot \sigma_j = \Sigma_{ij}$$

Since this holds for all elements (i, j):

$$\mathbf{DRD} = \Sigma \quad \square$$

$\square$

Key Identity

$$\Sigma = \mathbf{DRD}$$

4.3 Element-Wise Illustration

For a 2×2 case, the decomposition is explicit:

$$\begin{pmatrix} \sigma_1 & 0 \\ 0 & \sigma_2 \end{pmatrix} \begin{pmatrix} 1 & R_{12} \\ R_{12} & 1 \end{pmatrix} \begin{pmatrix} \sigma_1 & 0 \\ 0 & \sigma_2 \end{pmatrix} = \begin{pmatrix} \sigma_1^2 & \sigma_1 R_{12} \sigma_2 \\ \sigma_1 R_{12} \sigma_2 & \sigma_2^2 \end{pmatrix}$$

where the diagonal elements σ_i^2 are the variances and the off-diagonal elements $\sigma_i R_{ij} \sigma_j$ are the covariances.

5 Key Properties

5.1 Preservation of Positive Definiteness

Lemma 1 (PD Preservation)**.** If $\mathbf{R}$ is positive definite and $\mathbf{D}$ is diagonal with all positive diagonal entries, then $\Sigma = \mathbf{DRD}$ is positive definite.

Proof. For any non-zero vector $\mathbf{x}$:

$$\mathbf{x}^\top \Sigma \mathbf{x} = \mathbf{x}^\top (\mathbf{DRD})\mathbf{x} = (\mathbf{Dx})^\top \mathbf{R}(\mathbf{Dx})$$

Let $\mathbf{y} = \mathbf{Dx}$. Since $\mathbf{D}$ has positive diagonal entries and $\mathbf{x} \neq \mathbf{0}$, we have $\mathbf{y} \neq \mathbf{0}$. Since $\mathbf{R}$ is positive definite:

$$\mathbf{y}^\top \mathbf{R} \mathbf{y} > 0$$

Therefore:

$$\mathbf{x}^\top \Sigma \mathbf{x} > 0 \quad \square$$

$\square$

Corollary 1 (Validity of Derived Covariance)**.** If the correlation matrix $\mathbf{R}$ is positive definite, then the covariance matrix $\Sigma = \mathbf{DRD}$ is automatically positive definite, regardless of the values in $\mathbf{D}$ (provided all $\sigma_i > 0$).

5.2 Symmetry Preservation

Lemma 2 (Symmetry Preservation)**.** If $\mathbf{R}$ and $\mathbf{D}$ are symmetric, then $\Sigma = \mathbf{DRD}$ is symmetric.

Proof.

$$\Sigma^\top = (\mathbf{DRD})^\top = \mathbf{D}^\top \mathbf{R}^\top \mathbf{D}^\top = \mathbf{DRD} = \Sigma \quad \square$$

$\square$

6 Computational Implementation

6.1 R Implementation

In R, the efficient computation is:

```
sigma <- outer(standard_deviations, standard_deviations) * correlations
```

where:

- `standard_deviations` is a vector of $\sigma_1, \ldots, \sigma_n$
- `correlations` is the matrix $\mathbf{R}$
- `outer(x, y)` computes the outer product: $\mathbf{xy}^\top$
- `*` is element-wise multiplication

6.2 Explicit Computation

The `outer()` function computes:

$$\text{outer}(\sigma, \sigma) = \begin{pmatrix} \sigma_1\sigma_1 & \sigma_1\sigma_2 & \cdots & \sigma_1\sigma_n \\ \sigma_2\sigma_1 & \sigma_2\sigma_2 & \cdots & \sigma_2\sigma_n \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_n\sigma_1 & \sigma_n\sigma_2 & \cdots & \sigma_n\sigma_n \end{pmatrix} = \mathbf{D}^2$$

where $\mathbf{D}^2$ denotes the matrix of all pairwise products.
Then, element-wise multiplication by $\mathbf{R}$:

$$\Sigma_{ij} = (\sigma_i\sigma_j) \times R_{ij} = \sigma_i R_{ij} \sigma_j$$

which is exactly the (i, j)-element of $\mathbf{DRD}$.

6.3 Computational Advantages

This two-step approach provides several benefits:

1. **Numerical Stability**: Correlation matrices have entries bounded in $[-1, 1]$, avoiding overflow/underflow issues when combined with scaling.
2. **PD Validation Efficiency**: Only $\mathbf{R}$ needs to be checked for positive definiteness. Once $\mathbf{R}$ is validated (Lemma 1), Σ is automatically PD regardless of σ_i values.
3. **Parameter Separation**: Correlation structure (affecting relationships) and magnitude (affecting variance) are computed independently, simplifying interpretation and parameter selection.
4. **Memory Efficiency**: The computation $\texttt{outer}(\sigma, \sigma) \times \mathbf{R}$ avoids explicit construction of the $n \times n$ matrix $\mathbf{D}$.
5. **Reusability**: A single correlation matrix $\mathbf{R}$ can be scaled with different $\mathbf{D}$ matrices without recomputation.
6. **Dimension Independence**: For fixed $\mathbf{R}$, increasing n (number of variables) only requires updating the outer product computation.

7 Application to Clinical Trial Simulation

7.1 General Framework

In the N-of-1 trial simulation, the complete process is:

1. Define correlation parameters following Hendrickson et al.: $c_{tv}, c_{pb}, c_{br}, c_{cf1t}, c_{cfct}, c_{bm}$
2. Build the correlation matrix $\mathbf{R}$ from these parameters (with dimension ≈ 62 for 20 timepoints $\times$ 3 factors + 2 baseline variables)

3. Validate $\mathbf{R}$ is positive definite (eigenvalue check)
4. Define standard deviations $\sigma_1, \ldots, \sigma_n$ from response and baseline parameters
5. Compute $\Sigma = \mathbf{DRD}$ using the efficient two-step method
6. Sample from $\mathbf{Z} \sim \mathcal{N}(\boldsymbol{\mu}, \Sigma)$ using mvrnorm()

7.2 Why This Matters

The decomposition $\Sigma = \mathbf{DRD}$ is critical because:

- High-dimensional correlation matrices (62×62) are at risk of numerical failure
- Separating $\mathbf{R}$ and $\mathbf{D}$ isolates the PD problem to $\mathbf{R}$ only
- This allows systematic validation of correlation structures independently of scales
- The final Σ inherits PD guarantee from $\mathbf{R}$ via Lemma 1

8 Example: 3-Variable Case

For illustration, consider three biomarker components at one timepoint:

$$\mathbf{R} = \begin{pmatrix} 1.00 & 0.20 & 0.15 \\ 0.20 & 1.00 & 0.10 \\ 0.15 & 0.10 & 1.00 \end{pmatrix}$$

with standard deviations $\sigma_1 = 2.0, \sigma_2 = 1.5, \sigma_3 = 2.5$.
The covariance matrix is:

$$\Sigma = \begin{pmatrix} 2.0 & 0 & 0 \\ 0 & 1.5 & 0 \\ 0 & 0 & 2.5 \end{pmatrix} \begin{pmatrix} 1.00 & 0.20 & 0.15 \\ 0.20 & 1.00 & 0.10 \\ 0.15 & 0.10 & 1.00 \end{pmatrix} \begin{pmatrix} 2.0 & 0 & 0 \\ 0 & 1.5 & 0 \\ 0 & 0 & 2.5 \end{pmatrix}$$

Computing element (1,2):

$$\Sigma_{12} = 2.0 \times 0.20 \times 1.5 = 0.60$$

and the full covariance matrix:

$$\Sigma = \begin{pmatrix} 4.00 & 0.60 & 0.75 \\ 0.60 & 2.25 & 0.375 \\ 0.75 & 0.375 & 6.25 \end{pmatrix}$$

Note that the diagonal elements are σ_i^2:

$$\Sigma_{11} = 2.0^2 = 4.00$$
$$\Sigma_{22} = 1.5^2 = 2.25$$
$$\Sigma_{33} = 2.5^2 = 6.25$$

9 Conclusion

The identity $\Sigma = \mathbf{DRD}$ is a fundamental decomposition that:

1. **Theoretically** cleanly separates correlation structure from variance scaling
2. **Computationally** enables efficient two-step calculation and validation
3. **Numerically** ensures positive definiteness when $\mathbf{R}$ is PD
4. **Practically** allows systematic parameter selection and validation before expensive simulations

In the context of N-of-1 trial simulation, this decomposition enables robust construction of high-dimensional covariance matrices while maintaining strict control over positive definiteness constraints.

A Matrix Algebra Reference

A.1 Outer Product

For vectors $\mathbf{u}, \mathbf{v} \in \mathbb{R}^n$:

$$\text{outer}(\mathbf{u}, \mathbf{v}) = \mathbf{u}\mathbf{v}^\top$$

A.2 Diagonal Matrix Properties

For diagonal matrix $\mathbf{D}$ with diagonal entries $d_1, \ldots, d_n$ and any matrix $\mathbf{A}$:

$$(\mathbf{DA})_{ij} = d_i A_{ij}$$
$$(\mathbf{AD})_{ij} = A_{ij} d_j$$

A.3 Matrix Transpose Properties

$$(\mathbf{AB})^\top = \mathbf{B}^\top \mathbf{A}^\top$$
$$(\mathbf{A}^\top)^\top = \mathbf{A}$$
$$(\mathbf{D}^\top) = \mathbf{D} \quad \text{(if } \mathbf{D} \text{ is diagonal)}$$

A.4 Eigenvalue Properties

For positive definite matrix $\mathbf{A}$:

- All eigenvalues are strictly positive: $\lambda_i > 0$
- Condition number: $\kappa(\mathbf{A}) = \frac{\lambda_{\max}}{\lambda_{\min}}$
- Matrix is invertible: $\det(\mathbf{A}) > 0$