Modeling Correlation in Antibody Kinetics: A Hierarchical Bayesian Approach

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Overview

- Incorporates feedback from Dr. Morrison and Dr. Aiemjoy
- Builds on (Teunis and Eijkeren 2016) framework for antibody kinetics
- Focus on covariance structure: parameter covariance within each biomarker ($\Sigma_{P,j}$, 5×5 per biomarker) and biomarker covariance across j (Σ_B, across biomarkers)
- Uses updated parameterization: $\log(y_0)$, $\log(y_1 - y_0)$, $\log(t_1)$, $\log(\alpha)$, $\log(\rho - 1)$
- Current stage: block-diagonal covariance (independent biomarkers)
- Planned extension: full Σ_B to capture correlation between biomarkers

Observation Model (Data Level)

Observed (log-transformed) antibody levels:

$$\log(y_{\text{obs},ij}) \sim \mathcal{N}(\mu_{\log y,ij}, \tau_j^{-1}) \tag{1}$$

Where:

- $y_{\text{obs},ij}$: Observed antibody level for subject i and biomarker j
- $\mu_{\log y,ij}$ is the **expected log antibody level**, computed from the two-phase model using subject-level parameters θ_{ij}.
- θ_{ij}: Subject-level latent parameters (e.g., y_0, α, ρ) used to define the predicted antibody curve
- τ_j: Measurement precision (inverse of variance) specific to biomarker j

Measurement precision prior:

$$\tau_j \sim \text{Gamma}(a_j, b_j) \tag{2}$$

Parameter Summary

Table 1: Parameter summary for antibody kinetics model.

Symbol	Description
μ_y	Antibody production rate (growth phase)
μ_b	Pathogen replication rate
γ	Clearance rate (by antibodies)
α	Antibody decay rate
ρ	Shape of antibody decay (power-law)
t_1	Time of peak response
y_1	Peak antibody concentration

Note: Only the first 6 are typically estimated. y_1 is derived from the ODE solution at t_1.

Within-Host ODE System (Teunis and Eijkeren 2016)

Two-phase within-host antibody kinetics:

$$\frac{dy}{dt} = \begin{cases} \mu_y y(t), & t \le t_1 \\ -\alpha y(t)^\rho, & t > t_1 \end{cases} \quad \text{with } \frac{db}{dt} = \mu_b b(t) - \gamma y(t) \tag{3}$$

Initial conditions: $y(0) = y_0$, $b(0) = b_0$
Key transition: t_1 is the time when $b(t_1) = 0$
Derived quantity: $y_1 = y(t_1)$

Closed-Form Solutions

Antibody concentration $y(t)$

- $t \leq t_1$:

$$y(t) = y_0 e^{\mu_y t}$$

- $t > t_1$:

$$y(t) = y_1 \left(1 + (\rho - 1)\alpha y_1^{\rho-1}(t - t_1)\right)^{-\frac{1}{\rho-1}}$$

Pathogen load $b(t)$

- $t \leq t_1$:

$$b(t) = b_0 e^{\mu_b t} - \frac{\gamma y_0}{\mu_y - \mu_b}\left(e^{\mu_y t} - e^{\mu_b t}\right)$$

- $t > t_1$:

Time of Peak Response

Peak Time t_1

$$t_1 = \frac{1}{\mu_y - \mu_b} \log\left(1 + \frac{(\mu_y - \mu_b)b_0}{\gamma y_0}\right) \tag{4}$$

Peak Antibody Level y_1

$$y_1 = y_0 e^{\mu_y t_1} \tag{5}$$

Model Comparison: (Teunis and Eijkeren 2016) vs serodynamics

Table 2: Comparison of Teunis (2016) model and serodynamic's model assumptions.

Component	(Teunis and Eijkeren 2016)	serodynamics
Pathogen ODE	$\mu_0 b(t) - cy(t)$	$\mu_b b(t) - \gamma y(t)$
Antibody ODE (pre-t_1)	$\mu y(t)$	$\mu_y y(t)$
Antibody ODE (post-t_1)	$-\alpha y(t)^r$	$-\alpha y(t)^\rho$
Antibody growth type	Pathogen-driven	Self-driven exponential
Antibody rate name	μ	μ_y
t_1 formula	Uses μ_0, μ, b_0, c, y_0	Uses μ_b, μ_y, etc.

Note:

Full Parameter Model (7 Parameters)

Subject-level parameters:

$$\theta_{ij} \sim \mathcal{N}(\mu_j, \Sigma_{P,j}), \quad \theta_{ij} = \begin{bmatrix} y_{0,ij} \\ b_{0,ij} \\ \mu_{b,ij} \\ \mu_{y,ij} \\ \gamma_{ij} \\ \alpha_{ij} \\ \rho_{ij} \end{bmatrix}$$

Where:

- θ_{ij}: parameter vector for subject i, biomarker j
- μ_j: population-level mean vector for biomarker j
- $\Sigma_{P,j} \in \mathbb{R}^{7\times 7}$: covariance matrix **across parameters** for biomarker j
  - Subscript P: denotes that this is covariance over the **P parameters**
  - Subscript j: indicates the biomarker index

Hyperparameters — Means:

From Full 7 Parameters to 5 Latent Parameters

- Although the model estimates 7 parameters, for modeling antibody kinetics $y(t)$, we focus on **5-parameter subset**:

$$y_0, \quad t_1(\text{derived}), \quad y_1(\text{derived}), \quad \alpha, \quad \rho$$

- These 5 parameters are **log-transformed** into the latent parameters θ_ij used for modeling.

5 Core Parameters Used for Curve Drawing

In this presentation, we focus on **5 key parameters** required to draw antibody curves:

- y_0: initial antibody level
- t_1: time of peak antibody response
- y_1: peak antibody level
- α: decay rate
- ρ: shape of decay

Note: t_1 and y_1 are **derived from the full model** - These 5 are sufficient for prediction and plotting

Classifying Model Parameters ((Teunis and Eijkeren 2016) Structure)

Estimated Parameters (7 total):

- **Core model parameters (5):** μ_b, μ_y, γ, α, ρ
- **Initial conditions (2):** y_0, b_0

Derived Quantity (not estimated):

- y_1: peak antibody level computed as $y(t_1)$

Subject-Level Parameters (Latent Version = serodynamics)

Each subject i and biomarker j has latent parameters:

$$\theta_{ij} = \begin{bmatrix} \log(y_{0,ij}) \\ \log(y_{1,ij} - y_{0,ij}) \\ \log(t_{1,ij}) \\ \log(\alpha_{ij}) \\ \log(\rho_{ij} - 1) \end{bmatrix} \in \mathbb{R}^5 \tag{6}$$

Distribution:

$$\theta_{ij} \sim \mathcal{N}(\mu_j, \Sigma_{P,j})$$

Where:

- μ_j: population-level mean vector for biomarker j
- $\Sigma_{P,j} \in \mathbb{R}^{5\times 5}$: covariance matrix **across the** $P = 5$ parameters for biomarker j

Why y_1 Is Not Fit Directly

- y_1 is the antibody level at the time the pathogen is cleared:

$$y_1 = y(t_1) \quad \text{where } b(t_1) = 0$$

- y_1 is not an "input" — it is **computed** from:
  - μ_y, y_0, b_0, μ_b, γ
  - via solution of ODEs to find t_1 and compute $y(t_1)$

In other words: y_1 is a **derived output**, not a fit parameter.

How y_1 Is Computed

- y_1 is computed by solving the ODE system:

$$\frac{dy}{dt} = \mu_y y(t), \quad \frac{db}{dt} = \mu_b b(t) - \gamma y(t)$$

- Evaluate $y(t)$ at $t = t_1$ using ODE solution:

$$y_1 = y(t_1; \mu_y, y_0, b_0, \mu_b, \gamma)$$

Recap: What We Estimate

Seven model parameters (7-parameter model for full dynamics):

- μ_b, μ_y, γ, α, ρ (biological process)
- y_0, b_0 (initial state)

Derived quantity:

- $y_1 = y(t_1)$ — not directly estimated, computed

5-parameter subset for curve visualization:

- y_0, y_1, t_1, α, ρ

Hierarchical Bayesian Structure (serodynamics)

Individual parameters:

$$\theta_{ij} = \begin{bmatrix} \log(y_{0,ij}) \\ \log(y_{1,ij} - y_{0,ij}) \\ \log(t_{1,ij}) \\ \log(\alpha_{ij}) \\ \log(\rho_{ij} - 1) \end{bmatrix} \sim \mathcal{N}(\mu_j, \Sigma_{P,j})$$

Hyperparameters:

- μ_j: population-level mean vector for biomarker j
- $\Sigma_{P,j} \in \mathbb{R}^{P \times P}$, $P = 5$: covariance matrix **across the parameters** for biomarker j

Subject-Level Parameters: θ_{ij}

$$\theta_{ij} \sim \mathcal{N}(\mu_j, \Sigma_{P,j}), \quad \theta_{ij} \in \mathbb{R}^5$$

Where:

$$\theta_{ij} = \begin{bmatrix} \log(y_{0,ij}) \\ \log(y_{1,ij} - y_{0,ij}) \\ \log(t_{1,ij}) \\ \log(\alpha_{ij}) \\ \log(\rho_{ij} - 1) \end{bmatrix}, \quad \Sigma_{P,j} \in \mathbb{R}^{P \times P},\ P = 5$$

Each subject i has a unique 5-parameter vector per biomarker j, capturing individual-level variation in antibody dynamics.

Hyperparameters: Priors on Population Means

Population-level means:

$$\mu_j \sim \mathcal{N}(\mu_{\text{hyp},j}, \Omega_{\text{hyp},j})$$

Interpretation:

- μ_j: average parameter vector for biomarker j
- $\mu_{\text{hyp},j}$: prior guess (e.g., vector of zeros)
- $\Omega_{\text{hyp},j}$: covariance matrix encoding uncertainty

Example:

$$\mu_{\text{hyp},j} = 0, \quad \Omega_{\text{hyp},j} = 100 \cdot I_5$$

Hyperparameters: Priors on Covariance

Covariance across parameters:

$$\Sigma_{P,j}^{-1} \sim \mathcal{W}(\Omega_j, \nu_j)$$

- $\Sigma_{P,j}$: 5×5 covariance matrix of subject-level parameters for biomarker j
- Ω_j: prior scale matrix (dimension 5×5)
- ν_j: degrees of freedom

Example:

$$\Omega_j = 0.1 \cdot I_5, \quad \nu_j = 6$$

Measurement Error and Precision Priors

Observed antibody levels:

$$\log(y_{\text{obs},ij}) \sim \mathcal{N}(\log(y_{\text{pred},ij}), \tau_j^{-1})$$

Precision prior:

$$\tau_j \sim \text{Gamma}(a_j, b_j)$$

- τ_j: shared measurement precision for biomarker j
- Gamma prior allows flexible noise modeling

Matrix Algebra Computation

Let $P = 5$ (parameters), B biomarkers. Then:

$$\Theta_i = \begin{bmatrix} \theta_{i1} & \theta_{i2} & \cdots & \theta_{iB} \end{bmatrix} \in \mathbb{R}^{P \times B}$$

Assume:

$$\text{vec}(\Theta_i) \sim \mathcal{N}(\text{vec}(M), \Sigma_P \otimes I_B)$$

Matrix Algebra – Simplified Structure

Setup: $\Theta_i \in \mathbb{R}^{P \times B}$

Model:

$$\text{vec}(\Theta_i) \sim \mathcal{N}(\text{vec}(M), \Sigma_P \otimes I_B)$$

- Σ_P: 5×5 covariance (same across biomarkers)
- I_B: biomarkers assumed uncorrelated
- Block-diagonal covariance

Understanding vec(Θ_i)

Each $\theta_{ij} \in \mathbb{R}^5$:

$$\theta_{ij} = \begin{bmatrix} \log(y_{0,ij}) \\ \log(y_{1,ij} - y_{0,ij}) \\ \log(t_{1,ij}) \\ \log(\alpha_{ij}) \\ \log(\rho_{ij} - 1) \end{bmatrix}$$

Flattening:

$$\text{vec}(\Theta_i) \in \mathbb{R}^{5B \times 1}$$

Understanding vec(M)

Let $M = [\mu_1\, \mu_2\, \cdots\, \mu_B] \in \mathbb{R}^{5\times B}$

Example for $B = 3$:

$$M = \begin{bmatrix} \mu_{1,1} & \mu_{1,2} & \mu_{1,3} \\ \mu_{2,1} & \mu_{2,2} & \mu_{2,3} \\ \mu_{3,1} & \mu_{3,2} & \mu_{3,3} \\ \mu_{4,1} & \mu_{4,2} & \mu_{4,3} \\ \mu_{5,1} & \mu_{5,2} & \mu_{5,3} \end{bmatrix}$$

Covariance Structure: $\Sigma_P \otimes I_B$

$$\text{Cov}(\text{vec}(\Theta_i)) = \Sigma_P \otimes I_B$$

- Σ_P: parameter covariance matrix
- I_B: biomarker-wise independence
- Kronecker product yields block-diagonal matrix

Example: Kronecker Product with $P = 5$, $B = 3$

Let:

$$\Sigma_P = \begin{bmatrix} \sigma_{y_0,y_0} & \sigma_{y_0,y_1-y_0} & \sigma_{y_0,t_1} & \sigma_{y_0,\alpha} & \sigma_{y_0,\rho-1} \\ \sigma_{y_1-y_0,y_0} & \sigma_{y_1-y_0,y_1-y_0} & \sigma_{y_1-y_0,t_1} & \sigma_{y_1-y_0,\alpha} & \sigma_{y_1-y_0,\rho-1} \\ \sigma_{t_1,y_0} & \sigma_{t_1,y_1-y_0} & \sigma_{t_1,t_1} & \sigma_{t_1,\alpha} & \sigma_{t_1,\rho-1} \\ \sigma_{\alpha,y_0} & \sigma_{\alpha,y_1-y_0} & \sigma_{\alpha,t_1} & \sigma_{\alpha,\alpha} & \sigma_{\alpha,\rho-1} \\ \sigma_{\rho-1,y_0} & \sigma_{\rho-1,y_1-y_0} & \sigma_{\rho-1,t_1} & \sigma_{\rho-1,\alpha} & \sigma_{\rho-1,\rho-1} \end{bmatrix}, \quad I_B =$$

Then:

$$\Sigma_P \otimes I_B \in \mathbb{R}^{15\times 15}$$

Expanded Matrix: $\Sigma_P \otimes I_B$

$$\Sigma_P \otimes I_B = \begin{bmatrix} \Sigma_P & 0 & 0 \\ 0 & \Sigma_P & 0 \\ 0 & 0 & \Sigma_P \end{bmatrix} \in \mathbb{R}^{15\times 15}$$

where each block Σ_P is the 5×5 covariance across parameters:

$$\Sigma_P = \begin{bmatrix} \sigma_{y_0,y_0} & \cdots & \sigma_{y_0,\rho-1} \\ \vdots & \ddots & \vdots \\ \sigma_{\rho-1,y_0} & \cdots & \sigma_{\rho-1,\rho-1} \end{bmatrix}$$

Next Steps: Modeling Correlation Across Biomarkers

Current Limitation:

- Biomarkers assumed independent: I_B

Planned Extension:

- Use full covariance Σ_B:

$$\text{Cov}(\text{vec}(\Theta_i)) = \Sigma_P \otimes \Sigma_B$$

Extending to Correlated Biomarkers

Assume $P = 5$, $B = 3$

Define:

$$\Sigma_P = \begin{bmatrix} \sigma_{y_0,y_0} & \sigma_{y_0,y_1-y_0} & \sigma_{y_0,t_1} & \sigma_{y_0,\alpha} & \sigma_{y_0,\rho-1} \\ \sigma_{y_1-y_0,y_0} & \sigma_{y_1-y_0,y_1-y_0} & \sigma_{y_1-y_0,t_1} & \sigma_{y_1-y_0,\alpha} & \sigma_{y_1-y_0,\rho-1} \\ \sigma_{t_1,y_0} & \sigma_{t_1,y_1-y_0} & \sigma_{t_1,t_1} & \sigma_{t_1,\alpha} & \sigma_{t_1,\rho-1} \\ \sigma_{\alpha,y_0} & \sigma_{\alpha,y_1-y_0} & \sigma_{\alpha,t_1} & \sigma_{\alpha,\alpha} & \sigma_{\alpha,\rho-1} \\ \sigma_{\rho-1,y_0} & \sigma_{\rho-1,y_1-y_0} & \sigma_{\rho-1,t_1} & \sigma_{\rho-1,\alpha} & \sigma_{\rho-1,\rho-1} \end{bmatrix}, \quad \Sigma_B =$$

Here:

- Σ_P: covariance across the 5 parameters (size 5×5)
- Σ_B: covariance across the B biomarkers (size $B \times B$)

Kronecker Product Structure: $\Sigma_P \otimes \Sigma_B$

$$\text{Cov}(\text{vec}(\Theta_i)) = \Sigma_P \otimes \Sigma_B$$

- Σ_P: 5×5 covariance across parameters
- Σ_B: $B \times B$ covariance across biomarkers
- The Kronecker product expands to a $(5B) \times (5B)$ covariance matrix
- Not block-diagonal — allows both parameter correlations *and* cross-biomarker correlations

Practical To-Do List (for Chapter 2)

Model Implementation:

- Define parameter covariance $\Sigma_{P,j}$ (within each biomarker j)
- Define biomarker covariance Σ_B (across biomarkers)
- Full covariance structure: $\text{Cov}(\text{vec}(\theta_i)) = \Sigma_P \otimes \Sigma_B$
- Priors: $\Sigma_{P,j}^{-1} \sim \mathcal{W}(\Omega_j, \nu_j)$, $\Sigma_B^{-1} \sim \mathcal{W}(\Omega_B, \nu_B)$

Simulation Study (first step):

- Generate fake longitudinal data with known Σ_P and Σ_B
- Fit independence model (I_B) vs. correlated model (Σ_B)
- Evaluate recovery of true covariance structure

Validation on Real Data (next step):

- Apply to Shigella longitudinal data
- Compare independence vs. correlated models (DIC, WAIC, posterior predictive checks)
- Summarize implications for epidemiologic utility