Hierarchical Model for Antibody Kinetics: Revisions Based on Advisor Feedback

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Overview

- Incorporates feedback from Dr. Morrison
- Aligns with Teunis et al. (2016, 2023) formulations
- Clarifies model parameter roles and their interpretation
- Assumes block-diagonal covariance structure across biomarkers

Full Model Structure

Two-phase within-host antibody kinetics:

$$\frac{dy}{dt} = \begin{cases} \mu_1 b(t), & t < t_1 \\ -\alpha y(t)^r, & t \geq t_1 \end{cases} \quad \text{with } \frac{db}{dt} = \mu_0 b(t) - c y(t) b(t)$$

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

Definition of Model Quantities

Parameters used in the dynamic model:

- μ_0: Pathogen growth rate
- μ_1: Antibody production rate (driven by pathogen)
- c: Clearance rate — how effectively antibodies eliminate pathogen
- α: Antibody decay rate (governs speed of waning)
- r: Shape of antibody decay (nonlinear power)
- y_0: Initial antibody concentration at $t = 0$
- b_0: Initial pathogen concentration at $t = 0$
- $y_1 = y(t_1)$: Peak antibody level — computed at time of pathogen clearance

Note: Only the first 7 are estimated. y_1 is derived from the ODE solution.

Model Comparison: 2016 vs Our Formulation

Component	**Teunis (2016)**	**Our Model**
Pathogen ODE	$\mu_0 b(t) - cy(t)$	$\mu_0 b(t) - cy(t)b(t)$
Antibody ODE (pre-t_1)	$\mu y(t)$	$\mu_1 b(t)$
Antibody ODE (post-t_1)	$-\alpha y(t)^r$	Same
Antibody growth type	Exponential	Pathogen-driven
Antibody rate name	μ	μ_1
t_1 formula	Uses μ	Uses μ_1

Note:

- Antibody production depends on pathogen presence ($b(t)$), not constant exponential growth
- Pathogen clearance is proportional to both antibody and pathogen levels ($c\, y(t)\, b(t)$)

Hierarchical Priors – Subject-Level and Means

Subject-level parameters:

$$\theta_{ij} \sim \mathcal{N}(\mu_j, \Sigma_j), \quad \theta_{ij} = \begin{bmatrix} y_{0,ij} \\ b_{0,ij} \\ \mu_{0,ij} \\ \mu_{1,ij} \\ c_{ij} \\ \alpha_{ij} \\ r_{ij} \end{bmatrix}$$

Hyperparameters – Means:

- μ_j: population-level mean vector for biomarker j
- Prior on μ_j:

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

Clarifying Parameter Roles

Why the confusion about number of parameters?

- The dynamic model contains 8 named parameters:

$$\mu_0, \mu_1, c, \alpha, r, y_0, b_0, y_1$$

- But only 7 are estimated — the 8th (y_1) is computed.
- Let's break this down carefully.

Classification of Parameters

Estimated Parameters (7 total):

- **Core model parameters (5):**

$$\mu_0,\ \mu_1,\ c,\ \alpha,\ r$$

- **Initial conditions (2):**

$$y_0,\ b_0$$

Derived Quantity (not estimated):

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

Time of Pathogen Clearance: t_1

Definition: t_1 is the time at which the pathogen is cleared, i.e., $b(t_1) = 0$

Analytic expression (Teunis et al., 2016):

$$t_1 = \frac{1}{\mu_1 - \mu_0} \log\left(1 + \frac{(\mu_1 - \mu_0)\, b_0}{c\, y_0}\right)$$

Key observations:

- t_1 depends on μ_0, μ_1, b_0, y_0, and c
- Used to determine $y_1 = y(t_1)$ by solving the antibody ODE up to this point
- Not treated as an estimated parameter — it is computed from model inputs

Why It's a Seven-Parameter Model

- Our model estimates 7 parameters:
  - **5 core biological parameters:** $\mu_0,\ \mu_1,\ c,\ \alpha,\ r$
  - **2 initial conditions:** $y_0,\ b_0$
- But we often talk about an eighth quantity, y_1, the highest level of antibody.
- So why isn't y_1 counted as a parameter?

Why y_1 Is Not Fit Directly

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

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

- It is not an "input" to the model — we don't estimate it with MCMC.
- Instead, we **calculate it from the model**:
  - We estimate parameters like μ_1, y_0, b_0...
  - Then we solve the ODEs to find t_1 and compute $y(t_1)$
- In other words: y_1 is a **derived output**, not a parameter being fit.

How y_1 Is Computed

- y_1 is computed by solving the coupled ODE system:

$$\frac{dy}{dt} = \mu_1 b(t), \quad \frac{db}{dt} = \mu_0 b(t) - c y(t) b(t)$$

- The solution is evaluated at $t = t_1$ (pathogen clearance point).
- Therefore:

$$y_1 = y(t_1;\ \mu_1,\ y_0,\ b_0,\ \mu_0,\ c)$$

Recap: What We Estimate

Seven model parameters:

- $\mu_0,\ \mu_1,\ c,\ \alpha,\ r$ (biological process)
- $y_0,\ b_0$ (initial state)

Derived quantity:

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

Hierarchical Bayesian Structure

Individual parameters:

$$\theta_{ij} = \begin{bmatrix} y_{0,ij} \\ b_{0,ij} \\ \mu_{0,ij} \\ \mu_{1,ij} \\ c_{ij} \\ \alpha_{ij} \\ r_{ij} \end{bmatrix} \sim \mathcal{N}(\mu_j, \Sigma_j)$$

Hyperparameters:

- μ_j: population-level means (per biomarker j)
- Σ_j: 7×7 covariance matrix over parameters

Subject-Level Parameters: θ_{ij}

$$\theta_{ij} \sim \mathcal{N}(\mu_j, \Sigma_j), \quad \theta_{ij} \in \mathbb{R}^7$$

Where:

$$\theta_{ij} = \begin{bmatrix} y_{0,ij} \\ b_{0,ij} \\ \mu_{0,ij} \\ \mu_{1,ij} \\ c_{ij} \\ \alpha_{ij} \\ r_{ij} \end{bmatrix}, \quad \Sigma_j \in \mathbb{R}^{7\times 7}$$

Each subject i has a unique 7-parameter vector per biomarker j, capturing individual-level variation in 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:

$$\mu_{\text{hyp},j} = 0, \quad \Omega_{\text{hyp},j} = 100 \cdot I_7$$

Hyperparameters: Priors on Covariance

Covariance across parameters:

$$\Sigma_j^{-1} \sim \mathcal{W}(\Omega_j, \nu_j)$$

- Σ_j: variability/covariance in subject-level parameters
- Ω_j: prior scale matrix
- ν_j: degrees of freedom

Example:

$$\Omega_j = 0.1 \cdot I_7, \quad \nu_j = 8$$

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 $K = 7$ (parameters), J biomarkers. Then:

$$\Theta_i = \begin{bmatrix} \theta_{i1} & \theta_{i2} & \cdots & \theta_{iJ} \end{bmatrix} \in \mathbb{R}^{K \times J}$$

Assume:

$$\text{vec}(\Theta_i) \sim \mathcal{N}(\text{vec}(M), \Sigma_K \otimes I_J)$$

Matrix Algebra – Simplified Structure

Setup: $\Theta_i \in \mathbb{R}^{7 \times J}$

Model:

$$\text{vec}(\Theta_i) \sim \mathcal{N}(\text{vec}(M), \Sigma_K \otimes I_J)$$

- Σ_K: 7×7 covariance (same across biomarkers)
- I_J: biomarkers assumed uncorrelated
- Block-diagonal covariance

Understanding vec(Θ_i)

Each $\theta_{ij} \in \mathbb{R}^7$:

$$\theta_{ij} = \begin{bmatrix} y_0 \\ b_0 \\ \mu_0 \\ \mu_1 \\ c \\ \alpha \\ r \end{bmatrix}$$

Flattening:

$$\text{vec}(\Theta_i) \in \mathbb{R}^{7J \times 1}$$

Understanding vec(M)

Let $M = [\mu_1 \, \mu_2 \, \cdots \, \mu_J] \in \mathbb{R}^{7 \times J}$

Example for $J = 3$:

$$M = \begin{bmatrix} \mu_{1,1} & \mu_{1,2} & \mu_{1,3} \\ \mu_{2,1} & \mu_{2,2} & \mu_{2,3} \\ \mu_{3,1} & \mu_{3,2} & \mu_{3,3} \\ \mu_{4,1} & \mu_{4,2} & \mu_{4,3} \\ \mu_{5,1} & \mu_{5,2} & \mu_{5,3} \\ \mu_{6,1} & \mu_{6,2} & \mu_{6,3} \\ \mu_{7,1} & \mu_{7,2} & \mu_{7,3} \end{bmatrix}$$

Covariance Structure: $\Sigma_K \otimes I_J$

$$\text{Cov}(\text{vec}(\Theta_i)) = \Sigma_K \otimes I_J$$

- Σ_K: parameter covariance matrix
- I_J: biomarker-wise independence
- Kronecker product yields block-diagonal matrix

Example: Kronecker Product with $K = 2$, $J = 3$

Let:

$$\Sigma_K = \begin{bmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{21} & \sigma_{22} \end{bmatrix}, \quad I_3 = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

Then:

$$\Sigma_K \otimes I_3 \in \mathbb{R}^{6 \times 6}$$

Expanded Matrix: $\Sigma_K \otimes I_3$

$$\Sigma_K \otimes I_3 = \begin{bmatrix} \sigma_{11} & 0 & 0 & \sigma_{12} & 0 & 0 \\ 0 & \sigma_{11} & 0 & 0 & \sigma_{12} & 0 \\ 0 & 0 & \sigma_{11} & 0 & 0 & \sigma_{12} \\ \sigma_{21} & 0 & 0 & \sigma_{22} & 0 & 0 \\ 0 & \sigma_{21} & 0 & 0 & \sigma_{22} & 0 \\ 0 & 0 & \sigma_{21} & 0 & 0 & \sigma_{22} \end{bmatrix}$$

Next Steps: Modeling Correlation Across Biomarkers

Current Limitation:

- Biomarkers assumed independent: I_J

Planned Extension:

- Use full covariance Σ_J:

$$\text{Cov}(\text{vec}(\Theta_i)) = \Sigma_K \otimes \Sigma_J$$

Extending to Correlated Biomarkers

Assume $K = 3,\ J = 3$

Define:

$$\Sigma_K = \begin{bmatrix} \sigma_{11} & \sigma_{12} & \sigma_{13} \\ \sigma_{21} & \sigma_{22} & \sigma_{23} \\ \sigma_{31} & \sigma_{32} & \sigma_{33} \end{bmatrix}, \quad \Sigma_J = \begin{bmatrix} \tau_{11} & \tau_{12} & \tau_{13} \\ \tau_{21} & \tau_{22} & \tau_{23} \\ \tau_{31} & \tau_{32} & \tau_{33} \end{bmatrix}$$

Kronecker Product Structure: $\Sigma_K \otimes \Sigma_J$

$$\Sigma_K \otimes \Sigma_J = \begin{bmatrix} \sigma_{11}\Sigma_J & \sigma_{12}\Sigma_J & \sigma_{13}\Sigma_J \\ \sigma_{21}\Sigma_J & \sigma_{22}\Sigma_J & \sigma_{23}\Sigma_J \\ \sigma_{31}\Sigma_J & \sigma_{32}\Sigma_J & \sigma_{33}\Sigma_J \end{bmatrix}$$

Now biomarkers and parameters can be correlated.

Expanded Form: $\Sigma_K \otimes \Sigma_J$ (3x3)

The 9×9 matrix contains all combinations $\sigma_{ab}\tau_{cd}$

Not block-diagonal — includes cross-biomarker correlation

Practical To-Do List (for Chapter 2)

Model Implementation:

- Define full Σ_J and prior: $\Sigma_J^{-1} \sim \mathcal{W}(\Psi, \nu)$
- Implement $\Sigma_K \otimes \Sigma_J$ in JAGS

Simulation + Validation:

- Simulate individuals with correlated biomarkers
- Fit both block-diagonal and full-covariance models
- Compare fit: DIC, WAIC, predictive checks