

# Extending the Hierarchical Model for Antibody Kinetics

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2025-04-30

- Incorporates feedback from Dr. Morrison and Dr. Aiemjoy
- Focus exclusively on Teunis et al. (Teunis and Eijkeren 2016) model
- Clarifies model dynamics: growth, clearance, decay
- Uses updated parameter notation:  $\mu_y$ ,  $\mu_b$ ,  $\gamma$ ,  $\alpha$ ,  $\rho$
- Assumes block-diagonal covariance structure across biomarkers

# Within-Host ODE System (Teunis et al., (Teunis and Eijkeren 2016))

## Two-phase within-host antibody kinetics:

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

**Initial conditions:**  $y(0) = y_0$ ,  $b(0) = b_0$

**Key transition:**  $t_1$  is the time when  $b(t_1) = 0$

**Derived quantity:**  $y_1 = y(t_1)$

# 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 $b(t)$

- $t \leq t_1$ :

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

- $t > t_1$ :

# Time of Peak Response

**Peak Time**  $t_1$

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

**Peak Antibody Level**  $y_1$

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

# Parameter Summary

Symbol	Description
$\mu_y$	Antibody production rate (growth phase)
$\mu_b$	Pathogen replication rate
$\gamma$	Clearance rate (by antibodies)
$\alpha$	Antibody decay rate
$\rho$	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  $t_1$ .

# Model Comparison: Teunis (Teunis and Eijkeren 2016) vs This Presentation

Component	Teunis (Teunis and Eijkeren 2016)	This Presentation
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	$\mu$	$\mu_y$
$t_1$ formula	Uses $\mu_0, \mu, b_0, c, y_0$	Uses $\mu_b, \mu_y$ , etc.

## Note:

- Teunis (Teunis and Eijkeren 2016) uses **linear clearance**:  $cy(t)$ , not

# Full Parameter Model (7 Parameters)

**Subject-level parameters:**

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

**Hyperparameters – Means:**

- $\mu_j$ : population-level mean vector for biomarker  $j$
- Prior on  $\mu_j$ :

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



# 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
- $\alpha$ : decay rate
- $\rho$ : 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):**  $\mu_b, \mu_y, \gamma, \alpha, \rho$
- **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 when the pathogen is cleared, i.e.,  $b(t_1) = 0$

**Analytic expression:**

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

**Key observations:**  $t_1$  depends on  $\mu_b$ ,  $\mu_y$ ,  $b_0$ ,  $y_0$ , and  $y_1 = y(t_1)$  is computed based on this time point

# Why It's a Seven-Parameter Model

- Our model estimates **7 parameters**:
  - 5 biological parameters:  $\mu_b, \mu_y, \gamma, \alpha, \rho$
  - 2 initial conditions:  $y_0, b_0$
- But we often refer to an 8th quantity:  $y_1$
- So why isn't  $y_1$  a parameter?

Answer:  $y_1$  is a **computed value**, not directly estimated.

# 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:
  - $\mu_y, y_0, b_0, \mu_b, \gamma$
  - 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):**

- $\mu_b, \mu_y, \gamma, \alpha, \rho$  (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:**

- $y_0, y_1, t_1, \alpha, \rho$

# Hierarchical Bayesian Structure

## Individual parameters:

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

## Hyperparameters:

- $\mu_j$ : population-level means (per biomarker  $j$ )
- $\Sigma_j$ :  $7 \times 7$  covariance matrix over parameters



## Subject-Level Parameters: $\theta_{ij}$

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

**Where:**

$$\theta_{ij} = \begin{bmatrix} y_{0,ij} \\ b_{0,ij} \\ \mu_{b,ij} \\ \mu_{y,ij} \\ \gamma_{ij} \\ \alpha_{ij} \\ \rho_{ij} \end{bmatrix}, \quad \Sigma_j \in \mathbb{R}^{7 \times 7}$$

Each subject  $i$  has a unique 7-parameter vector per biomarker  $j$ , capturing individual-level variation in antibody dynamics.

# Hyperparameters: Priors on Population Means

## Population-level means:

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

## Interpretation:

- $\mu_j$ : 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:

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

- $\Sigma_j$ : variability/covariance in subject-level parameters
- $\Omega_j$ : prior scale matrix
- $\nu_j$ : degrees of freedom

## Example:

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

**Observed antibody levels:**

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

**Precision prior:**

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

- $\tau_j$ : shared measurement precision for biomarker  $j$
- Gamma prior allows flexible noise modeling

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

$$\Theta_i = [\theta_{i1} \quad \theta_{i2} \quad \cdots \quad \theta_{iJ}] \in \mathbb{R}^{K \times J}$$

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:

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

- $\Sigma_K$ :  $7 \times 7$  covariance (same across biomarkers)
- $I_J$ : biomarkers assumed uncorrelated
- Block-diagonal covariance

# Understanding $\text{vec}(\Theta_i)$

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 $\text{vec}(M)$

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: $\Sigma_K \otimes I_J$

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

- $\Sigma_K$ : 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  $\Sigma_J$ :

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

# 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  $9 \times 9$  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  $\Sigma_J$  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

Teunis, Peter F. M., and J. C. H. van Eijkeren. 2016. “Linking the Seroresponse to Infection to Within-Host Heterogeneity in Antibody Production.” *Epidemics* 16: 33–39.  
<https://doi.org/10.1016/j.epidem.2016.04.001>.