Hierarchical Bayesian Modeling of Antibody Kinetics: Extensions and Refinements

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1 Overview

- Incorporates feedback from Dr. Morrison, Dr. Aiemjoy, and lab discussion
- Focus exclusively on (Teunis and Eijkeren 2016) two-phase within-host model
- Clarifies full hierarchical Bayesian modeling structure
- Explicitly distinguishes between priors, hyperpriors, transformations
- Reorders: **Start from observation model → build upward**

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2 Big Picture: What Are We Modeling?

We are modeling **how antibody levels change over time** in response to infection, using multiple individuals and multiple biomarkers (antigen-isotype combinations, (j = 1, 2, ..., 10)).

Goals:

- Understand the **average pattern** for each biomarker
- Allow for **individual-level variation**
- **Share information** across individuals to improve inference

This motivates using a **hierarchical Bayesian model**.

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3 Step 1: 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

The expression above corresponds to line 54 of `model.jags`:

```
54      logy[subj,obs,cur_antigen_iso] ~ dnorm(mu.logy[subj,obs,cur_antigen_iso], prec.logy[cu
```

Measurement precision prior:

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

Where:

- τ_j: Precision (inverse of variance) of the measurement noise for biomarker j
- (a_j, b_j): Shape and rate hyperparameters of the Gamma prior for precision, which control its expected value and variability

The expression above corresponds to line 75 of `model.jags`:

```
75   prec.logy[cur_antigen_iso] ~ dgamma(prec.logy.hyp[cur_antigen_iso,1], prec.logy.hyp[cur_ar
```

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4 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.

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5 Step 2: Within-Host ODE System (Teunis and Eijkeren 2016)

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

- Initial conditions: $y(0) = y_0$, $b(0) = b_0$
- Transition at t_1: when $b(t_1) = 0$

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6 Step 3: Closed-Form Solutions

Antibody concentration:

- For $t \leq t_1$:

$$y(t) = y_0 e^{\mu_y t} \tag{4}$$

- For $t\, t_1$:

$$y(t) = y_1 \left(1 + (\rho - 1)\alpha y_1^{\rho-1}(t - t_1)\right)^{-\frac{1}{\rho-1}} \tag{5}$$

The expression above corresponds to lines 18-50 of `model.jags`:

```
18      mu.logy[subj, obs, cur_antigen_iso] <- ifelse(
19
20         # `step(x)` returns 1 if x >= 0;
21         # here we are determining which phase of infection we are in;
22         # active or recovery;
23         # `smpl.t` is the time when the blood sample was collected,
24         # relative to estimated start of infection;
25         # so we are determining whether the current observation is after `t1`
26         # the time when the active infection ended.
27         step(t1[subj,cur_antigen_iso] - smpl.t[subj,obs]),
28
29         ## active infection period:
30         # this is equation 15, case t <= t_1, but on a logarithmic scale
31         log(y0[subj,cur_antigen_iso]) + (beta[subj,cur_antigen_iso] * smpl.t[subj,obs]),
32
33         ## recovery period:
34         # this is equation 15, case t > t_1
35         1 / (1 - shape[subj,cur_antigen_iso]) *
36            log(
37               # this is `log{y_1^(1-r)}`;
38               # the exponent cancels out with the factor outside the log
39               y1[subj, cur_antigen_iso]^(1 - shape[subj, cur_antigen_iso]) -
40
41                # this is (1-r); not sure why switched from paper
```

```
                (1 - shape[subj,cur_antigen_iso]) *

                    # (there's no missing y1^(r-1) term here; the math checks out)

                   # alpha is `nu` in Teunis 2016; the "decay rate" parameter
                  alpha[subj,cur_antigen_iso] *

                   # this is `t - t_1`
                   (smpl.t[subj,obs] - t1[subj,cur_antigen_iso])))
```

Pathogen load:

- For $t \leq t_1$:

$$b(t) = b_0 e^{\mu_b t} - \frac{\gamma y_0}{\mu_y - \mu_b} \left(e^{\mu_y t} - e^{\mu_b t} \right) \tag{6}$$

- For $t\, t_1$:

$$b(t) = 0$$

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7 Step 4: Derived Quantities

- **Clearance Time** t_1:

$$t_1 = \frac{1}{\mu_y - \mu_b} \log \left(1 + \frac{(\mu_y - \mu_b) b_0}{\gamma y_0} \right) \tag{7}$$

The expression above is indirectly represented by lines 8-12 of `model.jags`:

```
8       beta[subj, cur_antigen_iso] <-
9         log(
10          y1[subj,cur_antigen_iso] / y0[subj,cur_antigen_iso]
11          ) /
12        t1[subj,cur_antigen_iso]
```

- **Peak Antibody Level** y_1:

$$y_1 = y_0 e^{\mu_y t_1} \tag{8}$$

The expression above corresponds to line 59 of `model.jags`:

```
59    y1[subj,cur_antigen_iso]    <- y0[subj,cur_antigen_iso] + exp(par[subj,cur_antigen_iso,2]
```

Important: t_1 and y_1 are **derived**, not fit parameters.

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8 Full Parameter Model (7 Parameters)

Subject-level parameters for each subject$i$ and biomarker j:

$$\theta_{ij} \sim \mathcal{N}(\mu_j, \Sigma_j), \quad \theta_{ij} = \begin{bmatrix} y_{0,ij} \\ b_{0,ij} \\ \mu_{b,ij} \\ \mu_{y,ij} \\ \gamma_{ij} \\ \alpha_{ij} \\ \rho_{ij} \end{bmatrix} \tag{9}$$

- These 7 parameters represent the **full biological model** (antibody + pathogen dynamics)

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9 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.

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10 Core Parameters Used for Curve Drawing

Although the full model estimates **7 parameters**, only **5 key parameters** required to draw antibody curves:

- y_0: initial antibody level
- t_1: time of peak antibody response (derived)
- y_1: peak antibody level (derived)
- 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

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11 Step 5: Subject-Level Parameters (Latent Version)

Each subject i and biomarker j has latent parameters:

$$\theta_{ij} = \begin{bmatrix} \log(y_{0,ij}) \\ \log(y_{1,ij} - y_{0,ij}) \\ \log(t_{1,ij}) \\ \log(\alpha_{ij}) \\ \log(\rho_{ij} - 1) \end{bmatrix} \tag{10}$$

Distribution:

$$\theta_{ij} \sim \mathcal{N}(\mu_j, \Sigma_j)$$

The expression above reflects the prior distribution specified on line 66 of `model.jags`:

```
66    par[subj, cur_antigen_iso, 1:n_params] ~ dmnorm(mu.par[cur_antigen_iso,], prec.par[cur_ar
```

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12 Step 6: Parameter Transformations (log scale priors)

JAGS implements latent parameters (par) as:

Table 2: Log-Scale Transformations of Antibody Model Parameters in JAGS.

Model Parameter	Transformation in JAGS
y_0	$\exp(\text{par}_1)$
y_1	$y_0 + \exp(\text{par}_2)$
t_1	$\exp(\text{par}_3)$
α	$\exp(\text{par}_4)$
ρ	$\exp(\text{par}_5) + 1$

The table above corresponds to lines 58-62 of `model.jags`:

```
58    y0[subj,cur_antigen_iso]    <- exp(par[subj,cur_antigen_iso,1])
59    y1[subj,cur_antigen_iso]    <- y0[subj,cur_antigen_iso] + exp(par[subj,cur_antigen_iso,2]
60    t1[subj,cur_antigen_iso]    <- exp(par[subj,cur_antigen_iso,3])
61    alpha[subj,cur_antigen_iso] <- exp(par[subj,cur_antigen_iso,4]) # `nu` in the paper
62    shape[subj,cur_antigen_iso] <- exp(par[subj,cur_antigen_iso,5]) + 1 # `r` in the paper
```

All priors are thus applied on **log scale** (or log-minus-one for ρ).

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13 Step 7: Population-Level Parameters (Priors)

The biomarker-specific mean vector μ_j has a **hyperprior** :

$$\mu_j \sim \mathcal{N}(\mu_{\text{hyp},j}, \Omega_{\text{hyp},j}) \tag{11}$$

Where:

- $\mu_{\text{hyp},j}$: **prior mean** for the population-level parameters
- $\Omega_{\text{hyp},j}$: **prior covariance** encoding uncertainty about μ_j (e.g., $100 \cdot I_7$ for weakly informative prior)

The expression above corresponds to line 73 of `model.jags`:

```
73  mu.par[cur_antigen_iso, 1:n_params] ~ dmnorm(mu.hyp[cur_antigen_iso,], prec.hyp[cur_antige
```

Clarification:

- $\mu_{\text{hyp},j}$ defines the **center of a distribution, not** a single point guess.
- In Bayesian modeling, **priors and hyperpriors are distributions** over unknown quantities, capturing full uncertainty.

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14 Step 8: Prior on Covariance Matrices

We also don't know how much individual parameters vary. So we assign a **Wishart prior** to the **inverse** covariance matrix:

$$\Sigma_j^{-1} \sim \mathcal{W}(\Omega_j, \nu_j) \tag{12}$$

- Ω_j : prior scale matrix (small variance across parameters, often $0.1 \cdot I_7$)
- ν_j : degrees of freedom

The expression above corresponds to line 74 of `model.jags`:

```
74  prec.par[cur_antigen_iso, 1:n_params, 1:n_params] ~ dwish(omega[cur_antigen_iso,,], wishdf
```

Higher $\nu_j \rightarrow$ more informative prior (stronger prior).

Lower $\nu_j \rightarrow$ more weakly informative (broader prior or weaker prior).

This tells the model how much we expect individuals to vary from the average for biomarker j.

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15 Putting It All Together

The model is built hierarchically across five conceptual levels:

1. **Observed data:** noisy log antibody concentrations from serum samples
2. **Latent individual parameters:** hidden antibody dynamics θ_{ij} for each subject-biomarker pair
3. **Population-level means:** average antibody parameters for each biomarker
4. **Hyperpriors on means:** our belief about the likely range of biomarker-specific population means
5. **Priors on variability:** our belief about how much individual parameters vary around the population mean

This structure allows us to account for uncertainty at every level, while borrowing strength across subjects and biomarkers.

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16 Summary of the Hierarchy

1. **Top Level**:
   - For each biomarker j, the true mean antibody trajectory parameters μ_j come from a prior:
     - $\mu_j \sim \mathcal{N}(\mu_{\text{hyp},j}, \Omega_{\text{hyp},j})$
2. **Middle Level**:
   - For each person i, their parameters:
     - $\theta_{ij} \sim \mathcal{N}(\mu_j, \Sigma_j)$
3. **Bottom Level**:
   - Their actual observed antibody levels are noisy measurements of predictions from θ_{ij}:
     - $\log(y_{\text{obs},ij}) \sim \mathcal{N}(\mu_{\log y,ij}, \tau_j^{-1})$

Where:

- $\mu_{\log y,ij}$ is the **expected log antibody level**, computed from the two-phase model using subject-level parameters θ_{ij}.
- Predictions use θ_{ij} to compute $\mu_{\log y,ij}$, which is then compared to the observed log antibody data.

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17 Clarification: How Bottom Level Depends on Middle Level

We know the following facts:

1. θ_{ij} are the **subject-level latent parameters** (like $y_0, b_0, \mu\_b, \mu\_y, \gamma, \alpha, \rho$).
2. From θ_{ij}, we calculate the expected **log antibody level** $\mu_{\log y,ij}$ using the ODE-based two-phase model.
3. The **observed log-antibody** $\log(y_{\text{obs},ij})$ is modeled as a **noisy version** of $\mu_{\log y,ij}$.
4. τ_j is the precision (measurement noise precision for biomarker j).

Thus, at the **Bottom Level**, we model:

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

Here:

- The **mean** is $\mu_{\log y,ij}$ — derived from the **ODE solution** using θ_{ij}.
- The **variance** is τ_j^{-1} — shared across individuals for a given biomarker.

Summary:

- Observations depend indirectly on latent parameters θ_{ij} via the predicted log antibody levels $\mu_{\log y,ij}$.

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18 Summary Mapping of Notation

Symbol	Meaning	JAGS Variable
i	Subject index	`subj`
j	Antigen-isotype (biomarker) index	`cur_antigen_iso`
$y_{\text{obs},ij}$	Observed antibody concentration at a timepoint	`logy[subj, obs, cur_antigen_iso]`
$\mu_{\log y,ij}$	Expected log antibody level based on ODE model using θ_{ij}	`mu.logy[subj, obs, cur_antigen_iso]`
θ_{ij}	Subject-level latent parameters for modeling $y(t)$	`par[subj, cur_antigen_iso, 1:n_params]`

Symbol	Meaning	JAGS Variable
μ_j	Mean vector of latent parameters across subjects for biomarker j	`mu.par[cur_antigen_iso, ]`
Σ_j	Covariance matrix of latent parameters for biomarker j	`inverse of prec.par[cur_antigen_iso, , ]`
τ_j	Precision (inverse variance) of measurement error for biomarker j	`prec.logy[cur_antigen_iso]`
(a_j, b_j)	Gamma prior hyperparameters for τ_j	`prec.logy.hyp[cur_antigen_iso, 1/2]`
$\mu_{\text{hyp},j}$	Prior mean for μ_j	`mu.hyp[cur_antigen_iso, ]`
$\Omega_{\text{hyp},j}$	Prior precision for μ_j	`prec.hyp[cur_antigen_iso, , ]`
(Ω_j, ν_j)	Wishart scale and degrees of freedom for Σ_j^{-1}	`omega[cur_antigen_iso, , ], wishdf[...]`

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19 Model Comparison (Teunis and Eijkeren 2016) vs. Our Presentation

Table 4: Comparison of Teunis (2016) model and this presentation's model assumptions.

Component	(Teunis and Eijkeren 2016)	This Presentation
Pathogen ODE	$\mu_0 b(t) - cy(t)$	$\mu_b b(t) - \gamma y(t)$
Antibody growth ODE	$\mu y(t)$	$\mu_y y(t)$
Antibody decay ODE	$-\alpha y(t)^r$	$-\alpha y(t)^\rho$
Growth mechanism	Pathogen-driven	Self-driven

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.