mixed_model_comparison_and_best_practices

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Mixed Model Analysis Comparison: Hendrickson vs Your Code

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Executive Summary

This document compares the mixed-effects model specifications between Hendrickson et al. (2020) and your implementation, with recommendations based on current literature best practices.

Key Finding: Your implementation is **more comprehensive and flexible** than Hendrickson's, with options that align with current best practices in the N-of-1 trial literature.

Side-by-Side Comparison

Hendrickson's Model Specification

Location: `/Users/zenn/Dropbox/prj/c265/pmsimstats-master/pmsim-orig/R/lme_analysis.R`

Model Formula Selection Logic Hendrickson uses **conditional model selection** based on design characteristics:

```
# Two key tests determine model specification:

# Test 1: Is there variation in expectancy factor?
varInExp <- length(unique(trialdesign$e[2:length(trialdesign$e)]))

# Test 2: Is there variation in drug status within participants?
datamerged[t>0, meanDb:=mean(Db), by=ptID]
datamerged[t>0, DbVar:=((meanDb!=0)&(meanDb!=1)), by=ptID]
varInDb <- (sum(datamerged[t>0]$DbVar==TRUE)>0)
```

Resulting Model Formulas **When there IS within-subject drug variation** (`varInDb=TRUE`):

```
# Without random slope:
Sx ~ bm + De + Db + t + bm*Db + (1|ptID)

# With random slope:
Sx ~ bm + De + Db + t + bm*Db + (1+t|ptID)
```

When there is NO within-subject drug variation (`varInDb=FALSE`): - Uses **time** instead of **drug status** for interaction - Analyzes ONLY participants who were ever on drug

```
# Without random slope:
Sx ~ bm + t + bm*t + (1|ptID)

# With random slope:
Sx ~ bm + t + bm*t + (1+t|ptID)
```

Key Features

1. **Adaptive formula selection**: Model changes based on design
2. **Expectancy term optional**: Only included if there's variation in `e`
3. **Time random slope**: When used, applies to time effect
4. **Subject filtering**: Excludes never-on-drug participants when no within-subject drug variation
5. **Data structure**: Converts wide to long format, merges with design variables

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Your Model Specification

Location: `/Users/zenn/Dropbox/prj/d08/analysis/scripts/pm_functions.R` (lines 927-1055)

Model Formula Building Your code uses a **flexible options-based approach**:

```
# Base formula always includes:
formula_str <- "symptoms ~ biomarker + drug_binary + biomarker:drug_binary"

# Optional additions:
if (options$use_expectancy) {
  formula_str <- paste(formula_str, "+ t")
}

if (options$simple_carryover) {
  formula_str <- paste(formula_str, "+ tsd_effect")
}

# Random effects:
if (options$random_slope) {
  formula_str <- paste(formula_str, "+ (1 + drug_binary|participant_id)")
```

```
} else {
  formula_str <- paste(formula_str, "+ (1|participant_id)")
}
```

Carryover Modeling Options **Novel feature**: You have TWO ways to model carryover:

Option 1: Simple carryover (`simple_carryover=TRUE`):

```
# Adds tsd as a linear predictor
formula_str <- paste(formula_str, "+ tsd_effect")
```

Option 2: Exponential decay carryover (`carryover_halflife > 0`):

```
# Modifies drug_binary to decay exponentially
drug_binary = dplyr::lag(drug_binary, default = 0) *
              (1/2)^(half_life_factor * tsd)
```

Key Features

1. **Fixed core formula**: Always includes biomarker × drug interaction
2. **Options-driven**: User explicitly chooses model features
3. **Drug random slope**: When used, applies to drug effect (not time)
4. **Carryover flexibility**: Can model carryover in multiple ways
5. **No subject filtering**: All participants analyzed regardless of drug status

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Detailed Comparison Table

Aspect	Hendrickson	Your Code	Notes
Core interaction term	`bm:Db` or `bm:t`	`biomarker:drug_binary`	Hendrickson switches based on design
Formula selection	Adaptive (design-driven)	Fixed (options-driven)	Different philosophies
Expectancy term	Auto-detected	Optional via flag	Your approach more explicit
Time effect	Always included (`t`)	Optional	Hendrickson always models time
Random slope target	Time (`1+t|ptID`)	Drug (`1+drug_binary|ptID`)	**Major difference**
Carryover modeling	None in formula	Linear or exponential	Your enhancement
Subject filtering	Yes (when no drug variation)	No	Hendrickson excludes some subjects

Aspect	Hendrickson	Your Code	Notes
Data preparation	Convert to long, add derived vars	Convert to long, add derived vars	Similar
Package	`lme4::lmer()`	`lme4::lmer()`	Same
Output	β, SE, p, singularity flag	β, SE, p, singularity flag	Same

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Major Conceptual Differences

1. Random Slope Specification

Hendrickson: `(1 + t|participant_id)` - Random slope for **time effect** - Allows each participant to have different disease trajectory slopes - Interpretation: "Disease progression rate varies by person"

Your Code: `(1 + drug_binary|participant_id)` - Random slope for **drug effect** - Allows each participant to have different treatment response magnitudes - Interpretation: "Drug effectiveness varies by person"

Which is Better?

This depends on the research question:

Random Slope For	When Appropriate	Research Focus
Time	Natural disease progression varies	Between-subject heterogeneity in trajectory
Drug	Treatment response varies	Between-subject heterogeneity in drug effect
Both	Both vary (requires more data)	Comprehensive individual differences

2. Interaction Term Target

Hendrickson: Switches between `bm:Db` and `bm:t` - Uses `bm:Db` when there's within-subject drug variation (hybrid/crossover designs) - Uses `bm:t` when drug status is constant within subjects (parallel group-like) - **Rationale**: Choose interaction term that has meaningful variation

Your Code: Always uses `biomarker:drug_binary` - Consistent interaction term regardless of design - **Rationale**: Drug effect is the primary target of inference

Which is Better?

Hendrickson's approach is more statistically sound when drug status doesn't vary within subjects, because: - When all subjects in a participant are on-drug or all off-drug, `drug_binary`

is collinear with participant ID - The biomarker × drug interaction becomes unidentifiable - Switching to `bm:t` provides a different (but still informative) question

Your approach works when: - All designs have within-subject drug variation (true for hybrid and crossover) - This is the case for N-of-1 trials, so your approach is valid

3. Carryover Effect Modeling

Hendrickson: Not modeled in analysis (only in data generation) - Assumes carryover effects are already "baked into" the observed data - Model focuses on contemporaneous drug effect

Your Code: Optionally models carryover explicitly - **Simple carryover**: Treats `tsd` as linear predictor `r symptoms ~ ... + tsd_effect + ...` - **Exponential carryover**: Modifies drug predictor to decay `r drug_binary[off drug] = drug_binary[previous] * (1/2)^(tsd/t½)`

Which is Better?

This is a **major methodological question** with implications for inference:

Approach	Pros	Cons
Ignore carryover (Hendrickson)	Simpler model; Fewer assumptions; Standard practice	May confound drug effect with carryover; Reduced power if carryover exists
Linear carryover term	Explicit modeling; Easy to interpret	Assumes linear decay (biologically unrealistic)
Exponential decay	Biologically realistic; Matches pharmacokinetics	Modifies predictor (unusual); Requires knowing half-life

Literature Perspective: Most crossover trial analyses do NOT explicitly model carryover in the statistical model. Instead, they: 1. Use washout periods to minimize carryover 2. Test for carryover effects separately 3. If carryover detected, analyze only first-period data

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Best Practices from the Literature

1. Random Effects Structure

"Keep it Maximal" (Barr et al., 2013, *Journal of Memory and Language*)

> "The maximal random-effects structure for a design includes all random effects justified by that design."

Recommendation: - If you have **multiple measurements per participant per drug condition**: Include random slope for drug - If you have **long time series with disease progression**: Include random slope for time - **For N-of-1 trials with crossover/hybrid designs**: `(1 + drug_binary|participant_id)` is justified

Exception: If model fails to converge or is singular, simplify:

```
# Full maximal model (if data supports it):
(1 + drug_binary + t|participant_id)

# If singular, try:
(1 + drug_binary||participant_id)  # Uncorrelated random effects

# If still singular, reduce to:
(1|participant_id)  # Random intercept only
```

2. Biomarker × Treatment Interaction

Simulation Study (Ruan et al., 2018, *Trials*)

> "Including prognostic variables associated with the outcome increases power to detect biomarker-treatment interactions."

Best Practice:

```
# Include main effects + interaction
outcome ~ biomarker + treatment + biomarker:treatment + covariates + (1|subject)
```

Important: Always include both main effects, not just the interaction.

3. Crossover Trial Analysis

Mixed Effects Models for Crossover Designs (Wang & Bakhai, 2006)

Standard crossover model includes:

```
outcome ~ treatment + period + sequence + (1|subject)
```

For N-of-1 with biomarker interaction:

```
outcome ~ biomarker*treatment + time + (1|subject)
```

Where: - `time` accounts for period effects - `biomarker*treatment` tests if treatment effect depends on biomarker - Random intercept accounts for between-subject variability

4. Carryover Effects in Crossover Trials

Standard Approach (Senn, 2002, *Cross-over Trials in Clinical Research*):

1. **Test for carryover**: Compare first-period data between sequences
2. **If no carryover**: Analyze all data with standard crossover model
3. **If carryover present**:
   - Analyze only first-period data (between-subjects comparison)
   - OR use longer washout
   - **Not recommended**: Include carryover term in model (leads to biased estimates)

Modern Alternative (Small-N designs, 2020): - Explicitly model carryover as fixed effect if design includes it: `r  outcome ~ treatment + time_since_discontinuation + (1|subject)`

Your approach of exponential decay is **innovative but non-standard**. It's more common in pharmacokinetic modeling than statistical analysis.

5. N-of-1 Trial Specifics

Recent Literature (Kravitz et al., 2021; Schork, 2024):

For N-of-1 trials analyzing aggregated data across individuals:

```
# Standard approach:
outcome ~ treatment + time + (1|patient) + (1|cycle:patient)

# With biomarker:
outcome ~ biomarker*treatment + time + (1|patient) + (1|cycle:patient)
```

Where: - `(1|patient)` = between-patient variation - `(1|cycle:patient)` = within-patient between-cycle variation

Note: Your implementation uses `(1|participant_id)` which is appropriate for the single-level random effect.

6. Complete N-of-1 Design (2025)

Latest Research (April 2025, *Journal of Biopharmaceutical Statistics*):

For complete N-of-1 designs (all treatment permutations):

```
# Linear mixed-effects model with treatment as fixed effect
outcome ~ treatment + (1|subject)

# Estimation focuses on treatment contrasts
contrast_estimate = treatment_A - treatment_B
```

This design achieves lowest estimation variance among N-of-1 designs.

Recommendations for Your Code

Immediate Recommendations (Align with Hendrickson & Standards)

1. Add Adaptive Formula Selection **Issue**: Your code always uses `biomarker:drug_binary`, which may fail when there's no within-subject drug variation.

Fix: Add Hendrickson's logic:

```
lme_analysis <- function(trial_design_set, data, options = list()) {
  # ... existing code ...

  # Check for within-subject drug variation
  data_for_model <- data_for_model %>%
    group_by(participant_id) %>%
```

```
    mutate(mean_drug = mean(drug_binary, na.rm = TRUE)) %>%
    ungroup()

  has_within_drug_variation <- any(
    data_for_model$mean_drug > 0 & data_for_model$mean_drug < 1,
    na.rm = TRUE
  )

  # Build formula conditionally
  if (has_within_drug_variation) {
    # Standard interaction with drug
    formula_str <- "symptoms ~ biomarker + drug_binary + biomarker:drug_binary"
  } else {
    # Use time interaction instead
    formula_str <- "symptoms ~ biomarker + t + biomarker:t"
    # Filter to only participants ever on drug
    data_for_model <- data_for_model %>%
      filter(mean_drug > 0)
  }

  # ... continue with existing code ...
}
```

2. Reconsider Random Slope Target **Current**: `(1 + drug_binary|participant_id)` **Hendrickson**: `(1 + t|participant_id)`

Question to consider: What's more important for your research question? - Individual differences in treatment response? → Keep `drug_binary` - Individual differences in disease trajectory? → Switch to `t`

Compromise (if data supports it):

```
# Both random slopes (requires substantial data)
(1 + drug_binary + t|participant_id)
```

3. Document Carryover Modeling Choice Your exponential decay approach is innovative but non-standard. Add clear documentation:

```
#' @section Carryover Modeling:
#'
#' This implementation offers two non-standard approaches to modeling carryover:
#'
#' 1. **Exponential decay**: Modifies the drug predictor to reflect gradual
#'    washout. This approach is pharmacokinetically motivated but differs from
#'    standard statistical practice. Use when carryover half-life is known.
#'
#' 2. **Linear carryover term**: Adds time-since-discontinuation as a predictor.
```

```
#'    This is more interpretable but assumes linear (not exponential) decay.
#'
#' **Note**: Standard practice in crossover trials is to NOT model carryover
#' explicitly, but rather to use adequate washout periods. These options are
#' provided for simulation studies where carryover is experimentally manipulated.
```

4. Add Time Effect (Match Hendrickson) Hendrickson always includes time effect. Consider making this the default:

```
# Always include time to account for period effects
formula_str <- "symptoms ~ biomarker + drug_binary + t + biomarker:drug_binary"

# Optional: Remove time only if explicitly requested
if (!options$include_time) {
  # Remove time term (not recommended)
}
```

Rationale: Time accounts for: - Period effects in crossover designs - Natural disease progression - Practice effects / habituation

Additional Best Practice Enhancements

5. Add Singularity Handling Both you and Hendrickson check for singularity. Consider automatic simplification:

```
# Try maximal model first
formula_maximal <- symptoms ~ biomarker + drug_binary + t +
                   biomarker:drug_binary + (1 + drug_binary|participant_id)

tryCatch({
  model <- lmer(formula_maximal, data = data_for_model)
  if (isSingular(model)) {
    warning("Maximal model singular, simplifying to random intercept only")
    formula_simple <- symptoms ~ biomarker + drug_binary + t +
                      biomarker:drug_binary + (1|participant_id)
    model <- lmer(formula_simple, data = data_for_model)
  }
}, error = function(e) {
  warning("Model failed to converge, using simplified structure")
  # Fall back to even simpler model
})
```

6. Add Multiple Comparison Correction For Monte Carlo simulations, document that p-values are uncorrected:

```
#' @return A tibble with:
#'   \item{p_value}{Uncorrected p-value for biomarker:treatment interaction.
```

```
#'     For simulation studies with multiple comparisons, consider applying
#'     Bonferroni or FDR correction to control family-wise error rate.}
```

7. Consider Cycle Effects for N-of-1 If your design has multiple cycles, add nested random effect:

```
# If cycle information is available:
formula_str <- paste(formula_str, "+ (1|participant_id/cycle)")
```

Summary Table: Recommendations Priority

Recommendation	Priority	Alignment	Enhancement
Add adaptive formula selection	High	Hendrickson	Standard practice
Always include time effect	High	Hendrickson	Best practice
Document carryover approach	High	Novel	Transparency
Reconsider random slope target	Medium	Hendrickson	Research question dependent
Add singularity auto-handling	Medium	Best practice	Robustness
Add cycle random effects	Low	N-of-1 literature	If design has cycles
Both drug + time random slopes	Low	Maximal structure	If data supports

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Conclusion

What Hendrickson Does Well

1. **Adaptive model selection**: Chooses appropriate interaction term based on design
2. **Conservative random effects**: Random slope for time (well-justified in longitudinal data)
3. **Standard approach**: No explicit carryover modeling (aligns with crossover trial conventions)

What Your Code Does Well

1. **Flexibility**: Options allow users to test different model specifications
2. **Innovation**: Exponential decay carryover is pharmacologically realistic
3. **Explicitness**: No hidden automatic decisions, everything is user-controlled

4. **Drug-focused random effects**: Directly models individual treatment response heterogeneity

Recommended Path Forward

For direct Hendrickson comparison: - Add adaptive formula selection (high priority) - Always include time effect - Keep carryover options but document as experimental

For novel contribution: - Keep your flexible options-based approach - Add automatic simplification on singularity - Clearly document where you diverge from standards and why - Run sensitivity analyses comparing different specifications

For publication: - Present results with BOTH your approach and Hendrickson-aligned approach - Show robustness of findings across specifications - Discuss trade-offs in Methods section

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References

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Appendix: Example Model Specifications

Hendrickson's Typical Model (Hybrid/Crossover Design)

```
# With expectancy, without random slope:
Sx ~ bm + De + Db + t + bm:Db + (1|ptID)

# Variables:
# Sx = symptoms (outcome)
# bm = biomarker
# De = expectancy factor (1 = expect drug, 0 = expect placebo)
# Db = drug binary (1 = on drug, 0 = off drug)
# t = time (week number)
# ptID = participant ID
```

Your Typical Model (Hybrid/Crossover Design)

```
# With time, without random slope, no carryover:
symptoms ~ biomarker + drug_binary + t + biomarker:drug_binary + (1|participant_id)

# With drug random slope and exponential carryover:
symptoms ~ biomarker + drug_binary_decayed + t +
           biomarker:drug_binary_decayed + (1 + drug_binary_decayed|participant_id)

# Where drug_binary_decayed includes exponential decay when off drug
```

Recommended Hybrid Model (Best of Both)

```
# Adaptive selection:
if (has_within_drug_variation) {
  # Standard N-of-1 model
  symptoms ~ biomarker + drug_binary + t + biomarker:drug_binary +
             (1 + drug_binary|participant_id)
} else {
  # Parallel-group-like model
  symptoms ~ biomarker + t + biomarker:t + (1 + t|participant_id)
}

# Always include time for period effects
# Use drug random slope when appropriate for research question
# Document carryover as experimental feature
```