A Practical Framework for Design and Analysis of Experiments with Interference Effects

Katherine Allen Moyer (NCSU)
Jon Stallrich (NCSU)
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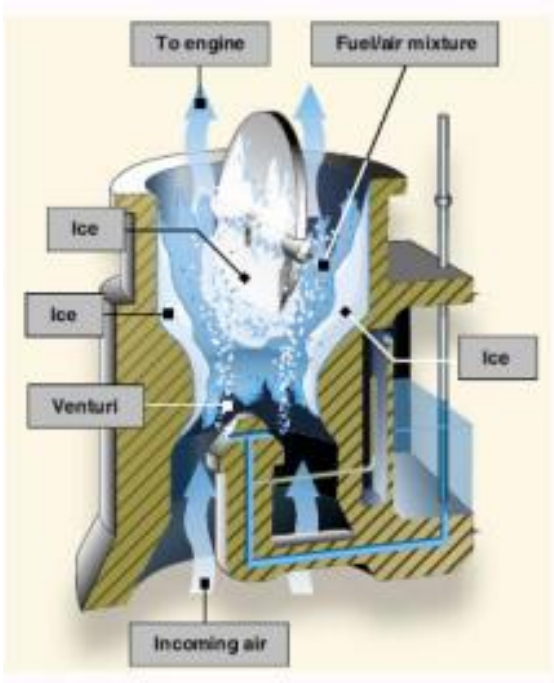
Carburetor Experiment

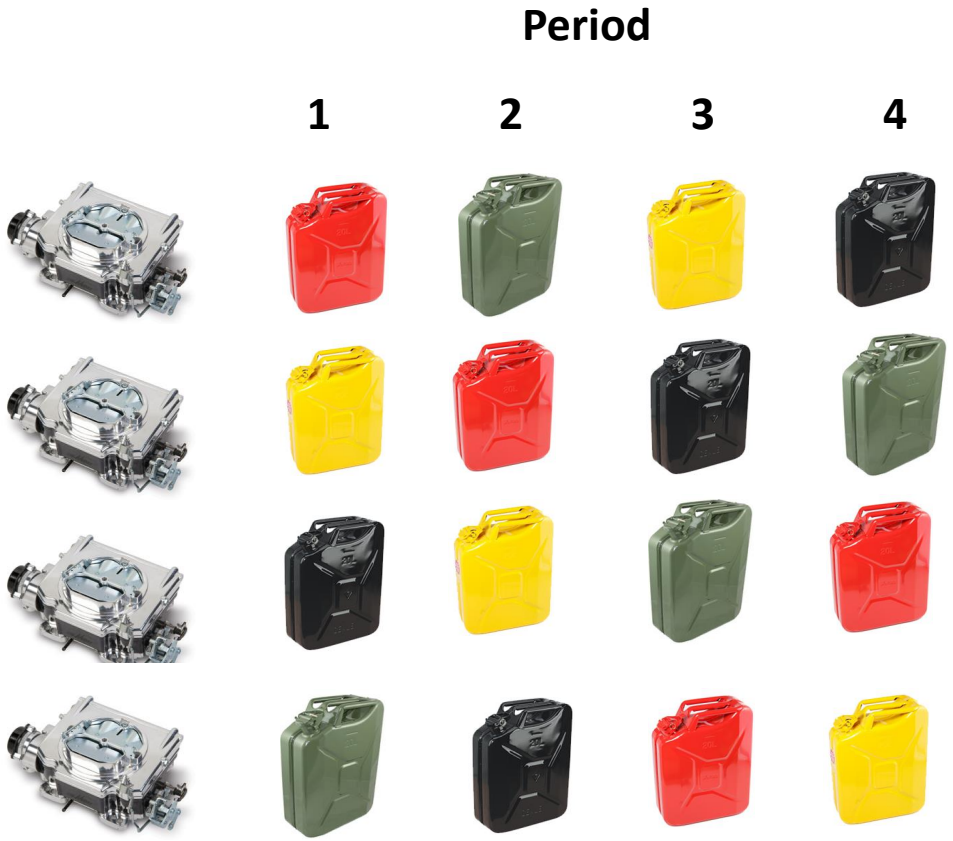


Goal: Compare four gasoline additives ability to prevent carburetor icing

Completely randomized design: carburetors assigned one treatment

Carburetor Experiment

Crossover experiment: carburetor gets all 4 treatments in some sequence, separated by some amount of time



- **Advantage:** Accounts for experimental error due to subject variation
- **Disadvantage:** Treatment's effect could spill over to future periods (**interference effect**)
- Interference also arises in designs with spatial structure adjacently over plots in space

Addressing interference effects

1. **Washout** – remove previous treatment's effect before applying next treatment
   - Require a certain period of time between applications
   - For carburetors, there may be a cleaning process

2. **Model interference effect** – each response includes a **direct effect** of current treatment and **residual effect** from previous treatment(s)
   - What residual effect structure do we pick?
   - How do we justify it?
   - How does it influence the design (chosen treatment sequences)

Washout Periods Model

$$Y_{ij} = \mu + \delta_i + \pi_j + \tau_{d[i,j]} + E_{ij}$$

- $i = 1, \ldots, n$ subjects; $j = 1, \ldots, p$ periods
  $d[i,j] \in \{1, \ldots, v\}$ treatment for i^{th} subject in the j^{th} period

- δ: subject effect
- π: period effect
- τ: direct treatment effect
- $E_{ij} \sim N(0, \sigma^2)$

Design Representation

1	4	2	3
2	1	3	4
3	2	4	1
4	3	1	2

First-Order Residual Effects Model

$$Y_{ij} = \mu + \delta_i + \pi_j + \tau_{d[i,j]} + \boldsymbol{\gamma_{d[i,j-1]}} + E_{ij}$$

- γ : first-order residual effect
- $\gamma_{d[i,0]}$ = 0 (no residual effect in the first period)
- **Highlighted Cell:** Response influenced by τ_4 and γ_1

- Treatment has no residual effect after one period

1	4	2	3
2	1	3	4
3	2	4	1
4	3	1	2

Variations of residual effect model

- Second or higher order residual effects

$$\gamma_{d[i,j-1]} + \lambda_{d[i,j-2]}$$

- Residual effects decay **proportionally** to direct effect

$$\gamma_{d[i,j-1]} = \boldsymbol{\lambda}\tau_{d[i,j-1]}$$

  where $\boldsymbol{\lambda}$ is the proportionality parameter

- **Interactions** between residual effects, periods, subjects

- Authors such as Bose and Dey (2009), Cheng and Wu (1980), and Kempton, Ferris, and David (2000), have studied optimal designs under different models

Optimal designs for crossover experiments

- Optimal design theory starts by specifying
  - Number of available subjects
  - **Fixed application and measurement times**
  - A residual effect structure
  - Analysis focuses on estimating treatment contrasts

- Design = set of recommended sequences

- Design on the right is **optimal for first-order model** because each treatment follows every other treatment same number of times

1	4	2	3
2	1	3	4
3	2	4	1
4	3	1	2

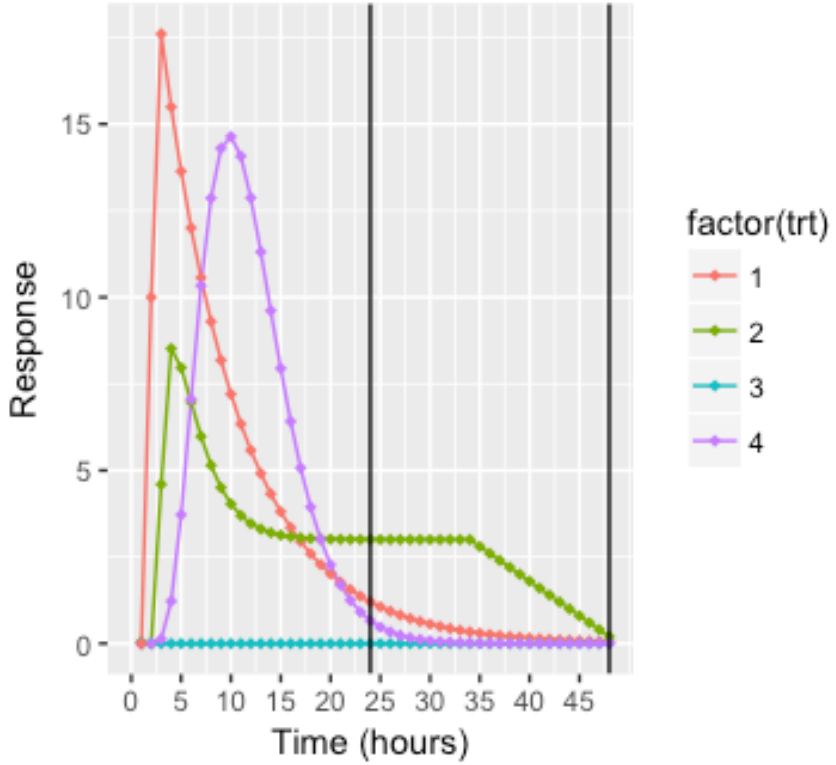
Planning crossover experiments

- Important questions before this stage:
  - How many treatments do we assign per subject?
  - When do we apply treatments?
  - When do we take measurements after application?
  - How many measurements per treatment application?

- Current literature has **one measurement per application**, taken at **roughly the same time** post application (Jones and Kenward (2014), Senn (2002))

Dynamic treatment effects

- All residual effects assume the **treatment effect decays**
  - Subject will eventually return to its initial state
- **Dynamic treatment effect:** effect of the treatment depends on time follows its application
  - Assume no interactions for now
- Visualization of treatment effects:
  - Time = time since application
  - What does a direct effect mean?



Dynamic treatment effects

- First-order crossover model where **measurements taken at the same time post-application, t_0**, works well provided

1. Direct effect of interest coincides with $\tau(t_0)$ for all treatments
2. $\tau(t)$ decays to 0 for t occurring after the subsequent period

- **Upshot:** The times we **apply treatments** and **take measurements** are important design questions and could significantly impact the resulting analysis

Simulation Study

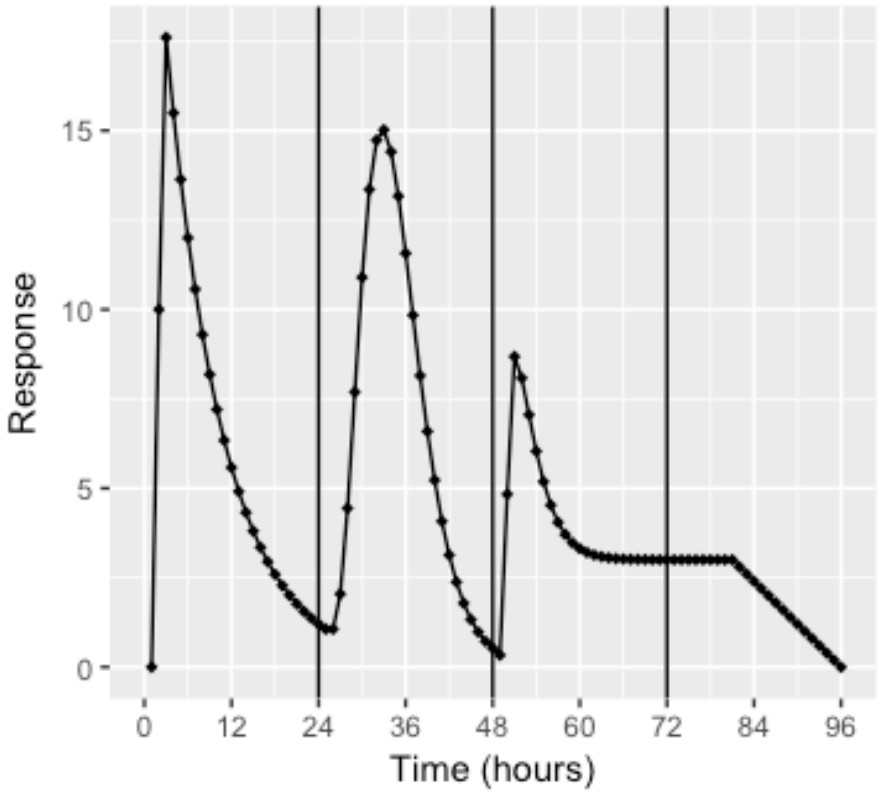
- Replication the following design three times (12 subjects)

1	4	2	3
2	1	3	4
3	2	4	1
4	3	1	2

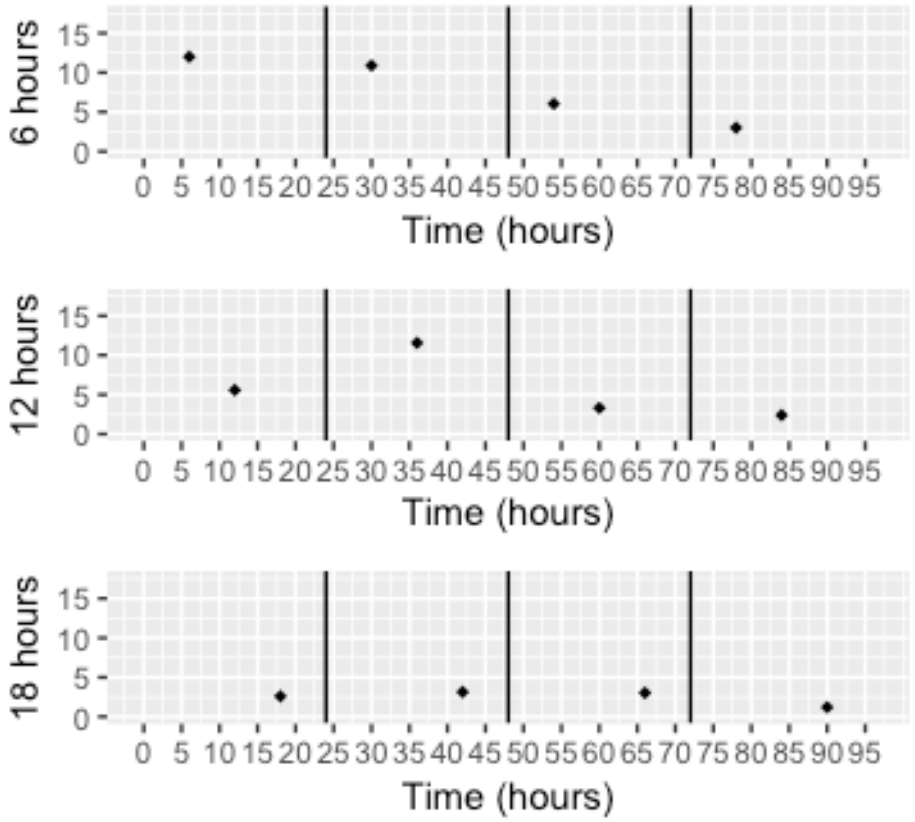
- Use earlier dynamic treatment effects with only one measurement taken post-application
  - **Fixed** measurement time, t_0, across design, set $\boldsymbol{t_0 \in \{3, 6, \ldots, 18\}}$
  - Measurement times **random in window around $\boldsymbol{t_0 = 8}$**, changes for each period

- Compare estimated $\tau_i - \tau_1$ using first-order model

Simulation Study (Fixed t_0)



How the treatment sequence | 1 | 4 | 2 | 3 | works over time



Single measurements taken at different times from the treatment effect curves on left

Simulation Study Results (Fixed t_0)

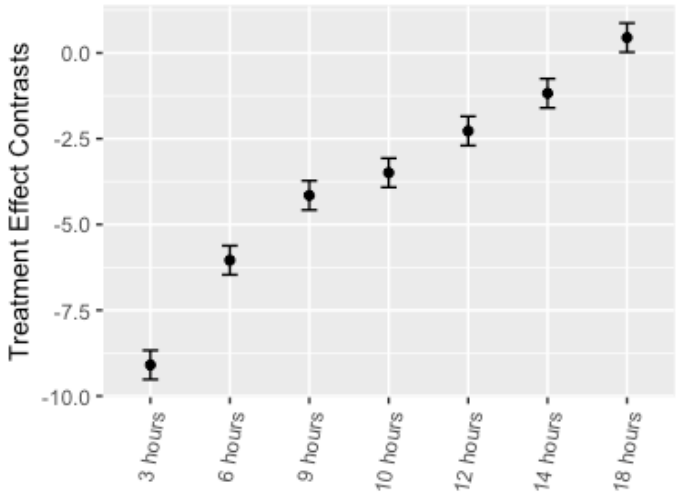


Figure 4: Contrast for $\tau_2 - \tau_1$

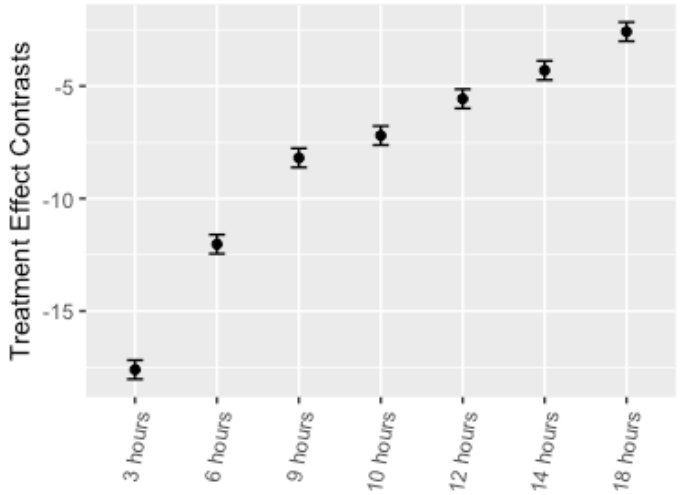


Figure 5: Contrast for $\tau_3 - \tau_1$

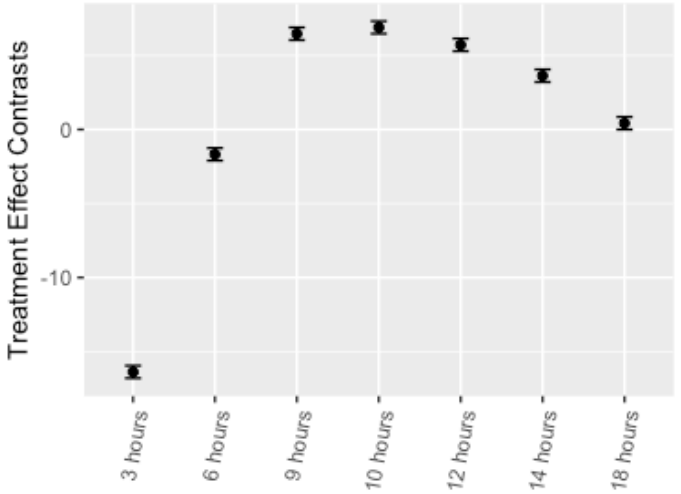


Figure 6: Contrast for $\tau_4 - \tau_1$

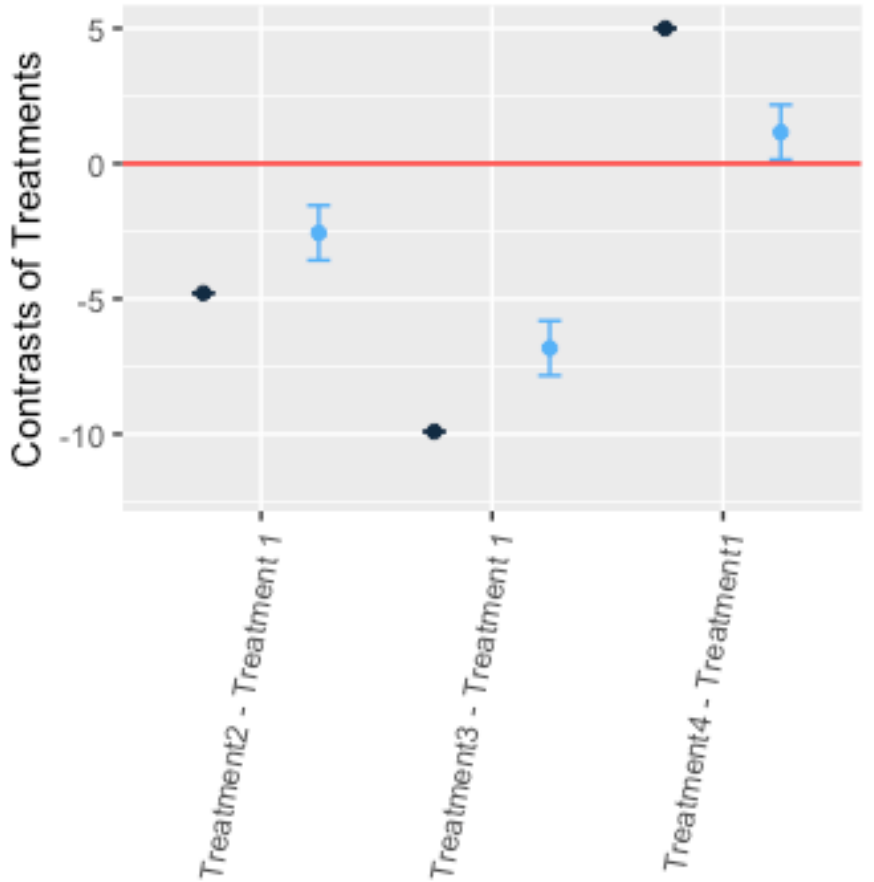
Means over 1000 replications of a simulation, bars are for standard errors.

Definition of direct effects heavily depend on t_0

Simulation Study Results ($t_0 \in [6, 10]$)

- Model incorrectly assumes consistent measurement times
- Leads to muted treatment effects and larger standard errors
- **Need a model that can incorporate more informative measurement times**

Black dots represent true difference at hour 8
Blue dots represent differences using traditional first-order crossover model



Capturing Dynamic Treatment Effect Curves

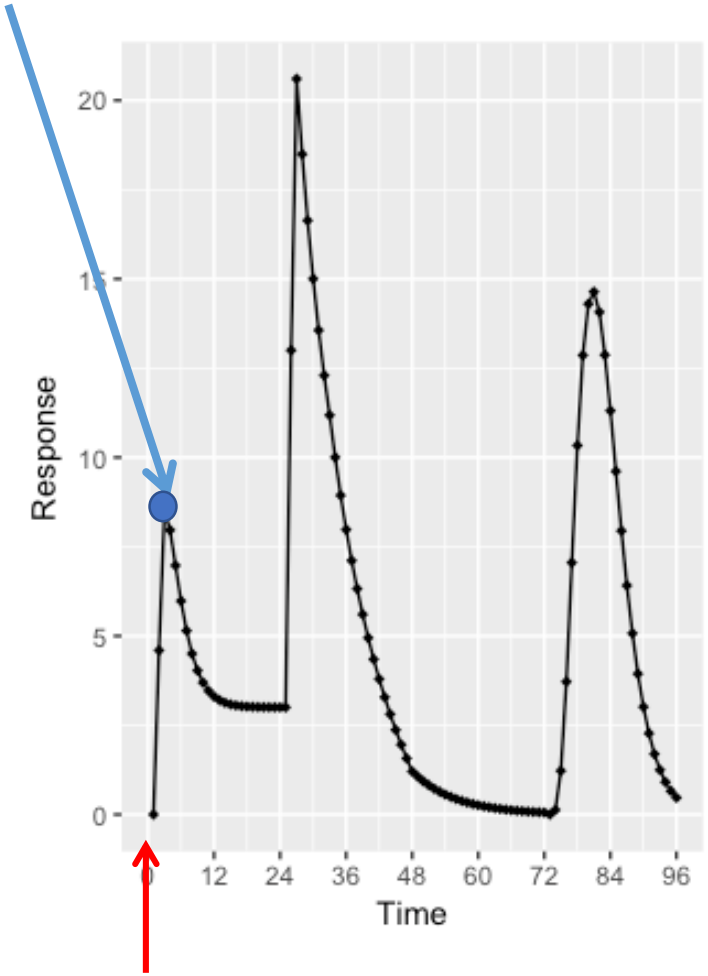
Measurement at $t = 6$ has effect $\tau_2(t - t_{A2}) = \tau_2(6)$

If we could sample at many time points, what model would we use?

Each measurement affected by one or more effect curves

Key: Depends on the time since that treatment was applied

Need to record:
t = absolute time value in [0,96]
t_{Ah} = time treatment *h* was applied



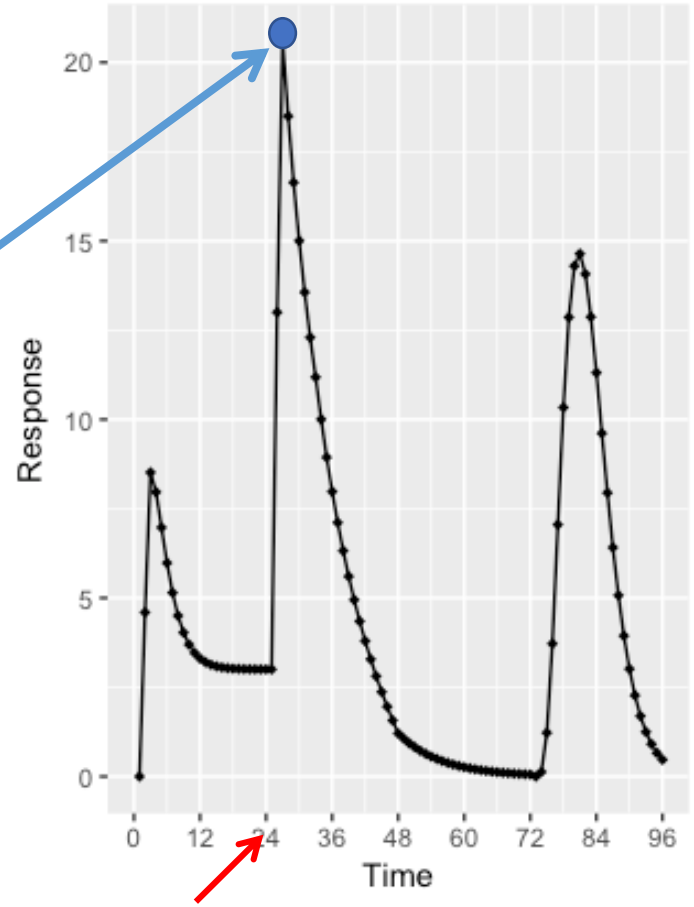
Treatment 2 applied, $t_{A2} = 0$

Capturing Dynamic Treatment Effect Curves

Assuming treatment effects are additive

Treatment 1 has $t_{A1} = 24$

Measurement at t = 28 affected by:
τ_2(28-0) + τ_1(28-24) = $\boldsymbol{\tau_2(28) + \tau_1(4)}$



Treatment 1 applied, $t_{A1} = 0$

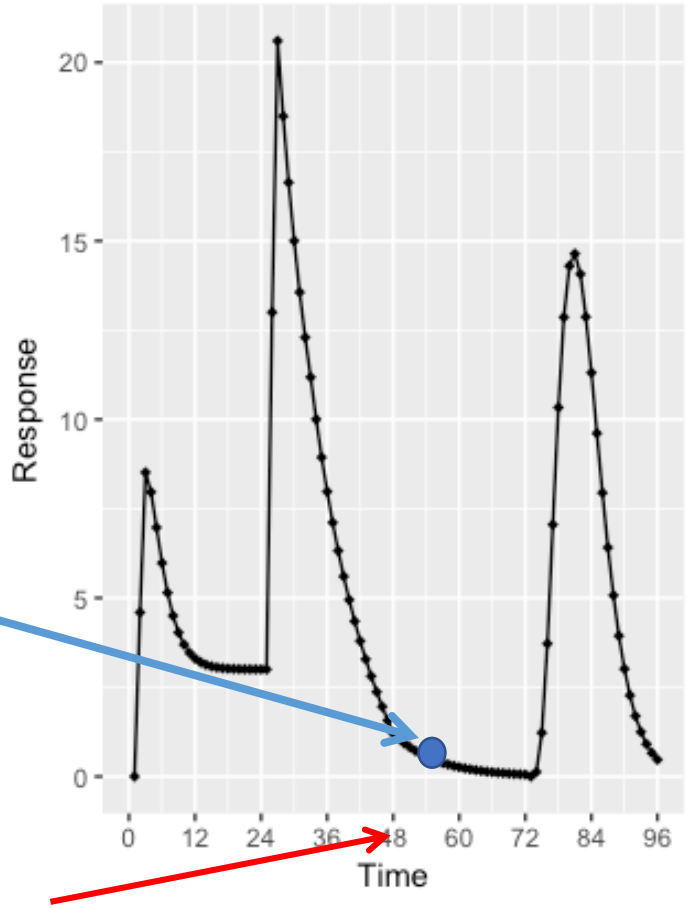
Capturing Dynamic Treatment Effect Curves

Treatment 3 has $t_{A3} = 48$

Measurement at t = 52 affected by:

τ_2(52-0) + τ_1(52-24)+ τ_1(52-48) =

$$\boldsymbol{\tau_2(52) + \tau_1(28) + \tau_3(4) \approx \tau_1(28) + \tau_3(4)}$$



Treatment 3 applied, $t_{A3} = 0$

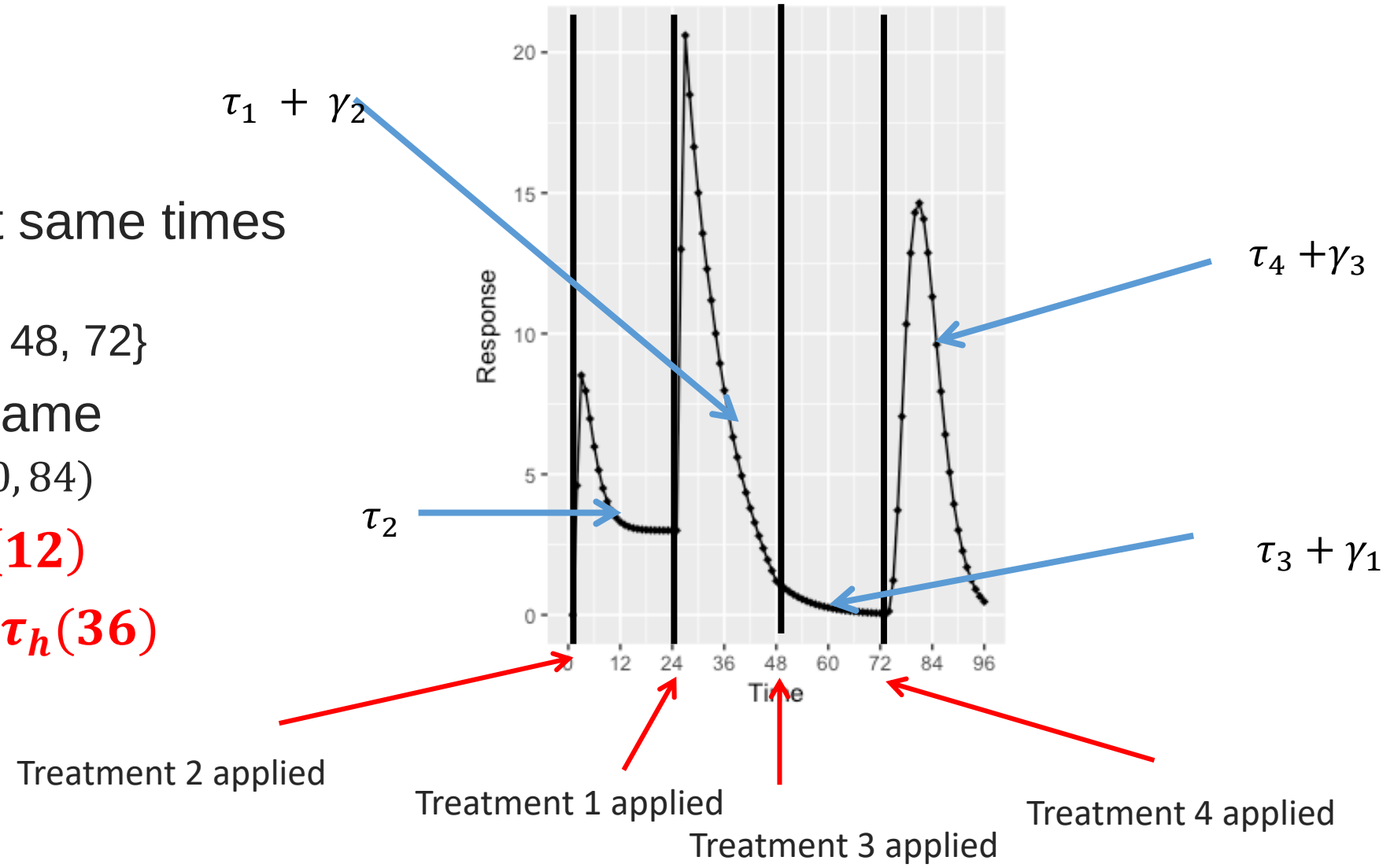
A More Flexible Framework

$$Y_{im_i} = \mu + \delta_i + \sum_{h=1}^{v} \tau_h(t_{im_i} - t_{Ah}^i) + E_{im_i}$$

- Assume no overall time/period effect and each treatment applied once for each subject
- Subject *i* has
  - Application times: $\boldsymbol{t_{A1}^i, t_{A2}^i, \ldots, t_{Av}^i}$
  - Total of $m_i \in \{1, .., M_i\}$ measurements at times $\boldsymbol{t_{i1}, t_{i2}, \ldots, t_{iM_i}}$
- Assume $\boldsymbol{\tau_h(t) = 0}$ **when** $\boldsymbol{t \leq 0}$ (so if treatment hasn't been applied yet it drops from model)

Flexible Framework Applied to Traditional Model

- Treatments applied at same times but in different orders
  - Permutation of {0, 24, 48, 72}
- Measurement times same
  - $(t_1, \ldots, t_4) = (12, 36, 60, 84)$
- Direct effect: $\boldsymbol{\tau_h = \tau_h(12)}$
- Residual effect: $\boldsymbol{\gamma_h = \tau_h(36)}$



Extending current designs and analyses

- **Big Question:** Have flexibility in the t_{Ah} and t_{im_i}?

- **Design:**
  - What aspects of the treatment curves are you interested in?
  - How many treatments can you apply to a subject?
  - How many measurements can you take?
  - **What structure do you need in the above times?**

- **Analysis:** When were treatments applied and responses measured?

Practical Example: Two Stage Design

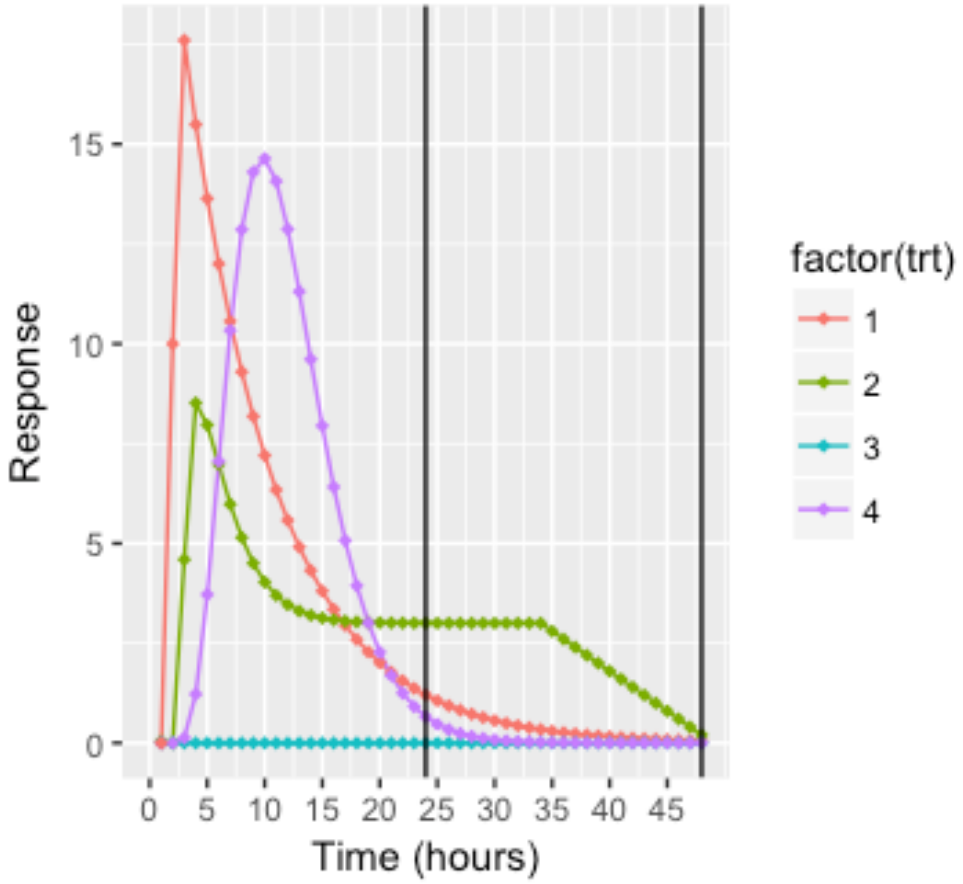
Stage 1

- One treatment is randomized to each unit
- Many measurements for each subject initially
- **Benefit:** Gives detailed, initial estimate of τ_h curves
- **Usage:** Estimates can identify peak effects and decay time
  - Peaks = direct effects
  - Decay times tell us how long we need between applications and measurements to washout

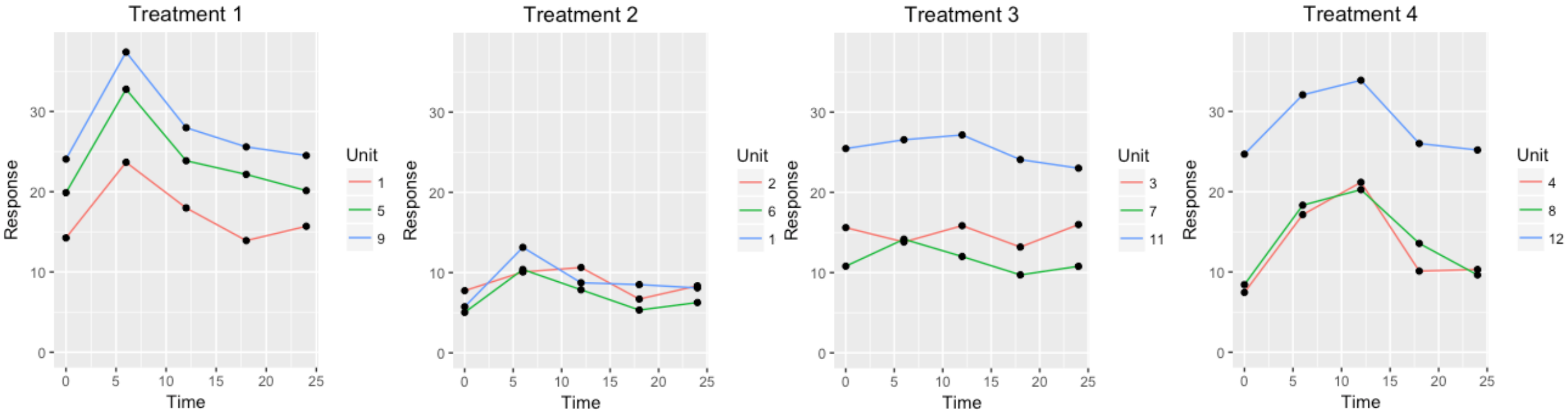
Stage 2: Use stage 1 information to determine application and measurement times

Two Stage Demonstration: Stage 1

- CRD with 12 subjects and 4 treatments
- Measurements taken at times 0, 6, 12, 18, and 24
- **Goal:** obtain information about the effect curves and when effect is no longer active
- If more information required, perform crossover design as Stage 2

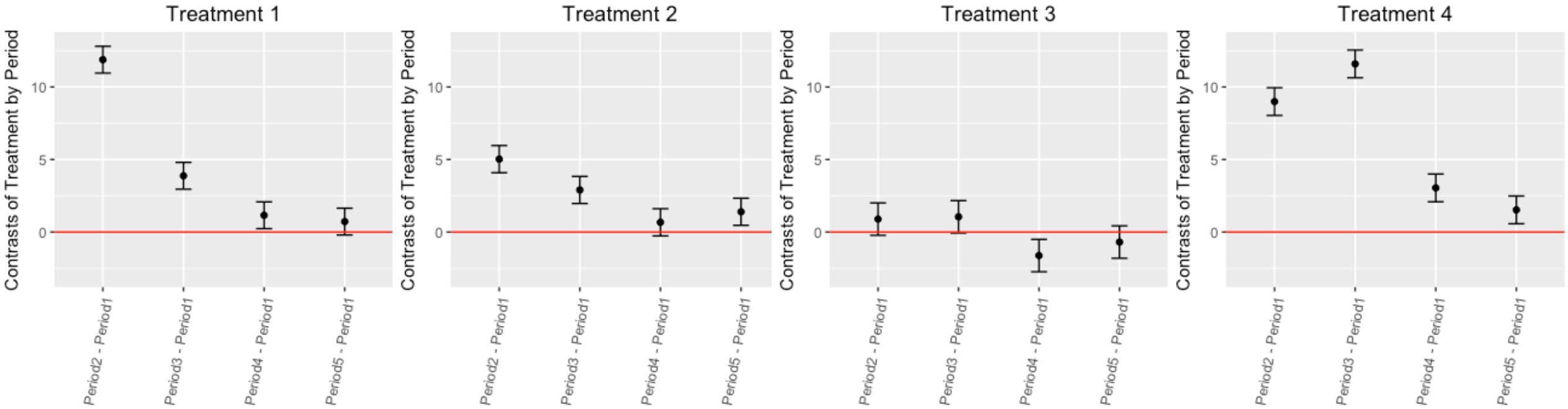


Visual Assessment of Stage 1 Results



Each line represents a different subject

Statistical Assessment of Stage 1 Results



Looking for time where the treatment is **most efficacious** and time when **unit returns to baseline**

Contrasts compare measurements taken at baseline ($t = 0$) with measurements taken farther along the treatment curve

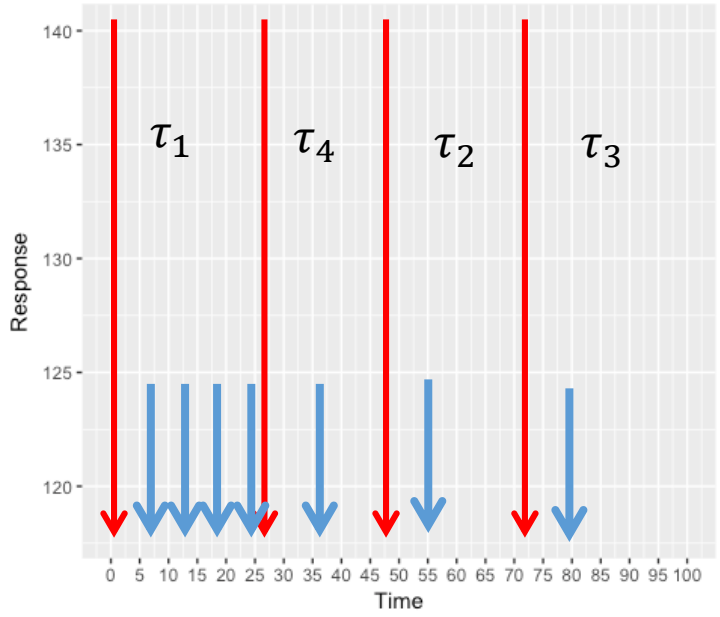
Two Stage Design - Stage 2

- Use information from Stage 1 to design follow-up experiment
  - Each subject receives other three treatments
  - Measurements taken at a **different times** for each treatment, to capture max($\boldsymbol{\tau_i}$), the desired direct effect
  - Use information on when treatment is out of unit's system for application times

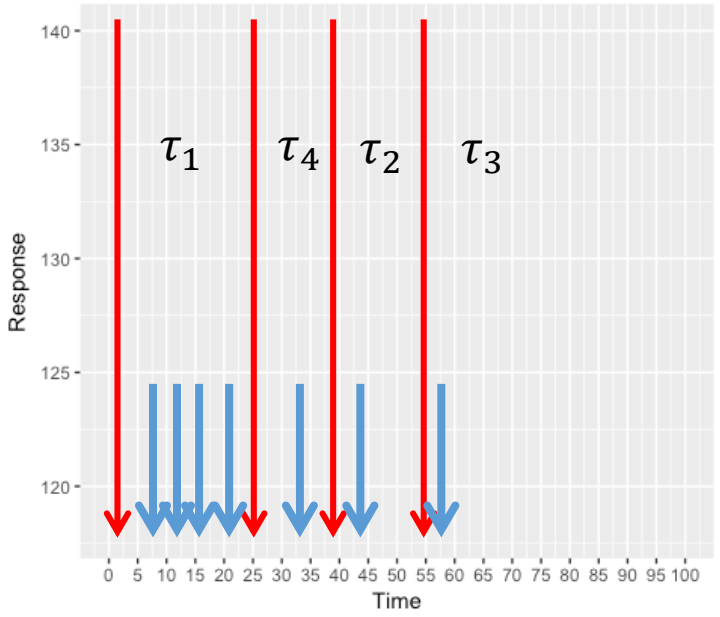
- Compare two potential designs for Stage 2:
  1. **Washout design:** enough time to allow effects to decay
  2. **Residual design:** Treatments not given time to washout and flexible residual effect was added to the model

Two Stage Design - Stage 2

Washout Design Example



Residual Design Example

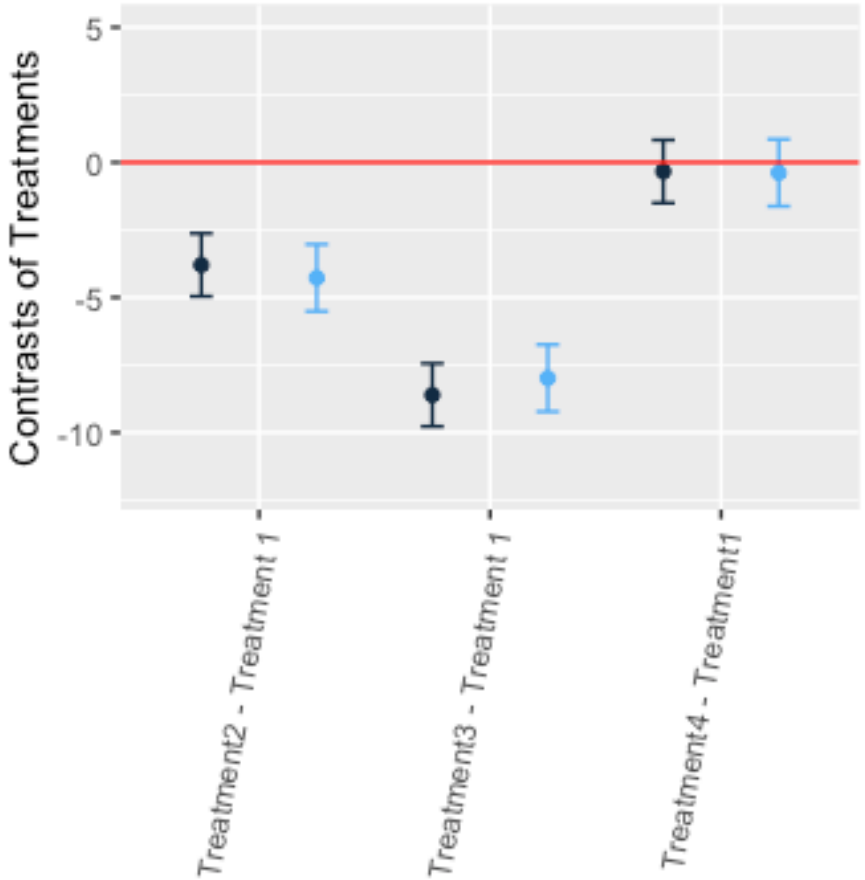


Two Stage Design – Some Results

Black: Washout design estimates

Light Blue: Residual design estimates using flexible residual effect

Results are similar! Stage 1 information means that washout may be unnecessary!



Moving Forward

- Design search algorithm that selects application and measurement times
- Implement flexible analysis corresponding to these designs or to traditional crossover designs when time is more variable than originally thought
- Apply to problems with multi-directional interference effects (spatial plot)

References

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