

1. Organize data

Outcome: Y_{ijk} , i =subject, j =period, k =week

Covariates: ijk treatment, period, week, sequence, viral load, age, gender,

2. Three period Cross-over design

6 sequences, we assume only carry over one period

| | μ_A | $\mu_B + \rho_A$ | $\mu_C + \rho_B$ | Remaining effect | |
|-----|---------|------------------|------------------|------------------|----------|
| (1) | A | B | C | ρ_A | ρ_B |
| (2) | C | A | B | ρ_C | ρ_A |
| (3) | B | C | A | ρ_B | ρ_C |
| (4) | B | A | C | ρ_B | ρ_A |
| (5) | A | C | B | ρ_A | ρ_C |
| (6) | C | B | A | ρ_C | ρ_B |

Notice that $((1)+(4))-((2)+(5))=2(\rho_B-\rho_C)$

$$H_0: \rho_A = \rho_B = \rho_C \Leftrightarrow H_0: \rho_{AB} = \rho_{AC} = \rho_{BC}$$

Generate 3 new sequence indicators:

AB, CA, BC

$$\text{Sequence 2} = \begin{cases} 0, & \text{if } seq = ABC \text{ or } BAC \\ 1, & \text{if } seq = CAB \text{ or } ACB \\ 2, & \text{if } seq = BCA \text{ or } CBA \end{cases}$$

3. Time variable:

If you care about one pill is safer than another, only cumulate the 4 weeks in the period;
If you want to know about specific week, need use week as time variable.

Treat week as categorical vs continuous?

Categorical: model nonlinear trend

Continuous: linear trend

You can plot before model it.

4. Adverse events: often rare events, may not converge.

To solve :

- 1) sum over 4 weeks or code =1 if adverse events occurred at least in one week;
- 2) use penalized logistic

Use mixed effects model for this project.