

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

$\text{Bin}(7, p)$

Binomial
~~continuous~~

Adhere :

fix : p , drug, period

random : $b_{0i} + c_{0ij}$

$$Y_{ijk} = \dots + b_{0i} + c_{0ij}$$

Handwritten notes:

- $AE_{ij} = \left(\sum_{k=1}^4 AE_{ik} \right) / 4$
- Fix: $seq_i = 1$
- $drug_{ij} = A$
- period $j = 2$
- $r_{and} : b_{0i}$
- $AE \cdot \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \end{pmatrix}$
- $p_b \cdot \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \end{pmatrix}$
- $p_A \cdot \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \end{pmatrix}$

← EDA
Week

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.