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Frailty Cox model applied on maze test

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Outline

1. Maze test experiments, description and problematic
2. Conditional frailty Cox models
3. Application on real dataset
4. Conclusion

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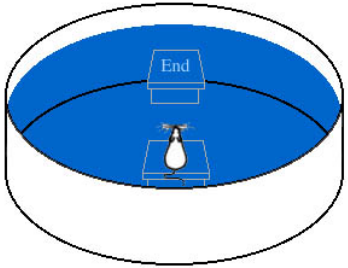
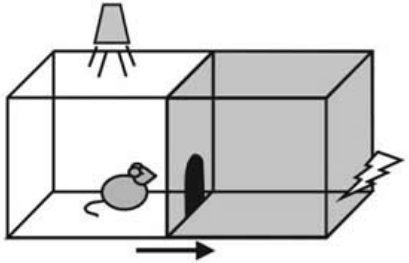
What is a maze test experiment?

Presentation of maze tests

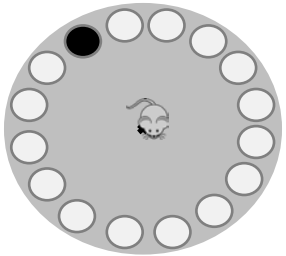
- **Objective: evaluate spatial learning and memory of rodents**
- **Measuring a latency time to reach an objective a goal: a reduction of time is indicative of a learning process**
  - Hidden platform in a pool (Morris Water Maze)
  - Enter a dark component (Passive Avoidance Test)
  - An escape tunnel (Barnes Maze test)



MWM

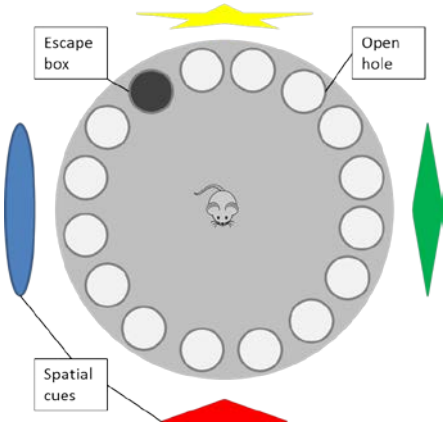


PAT



BM

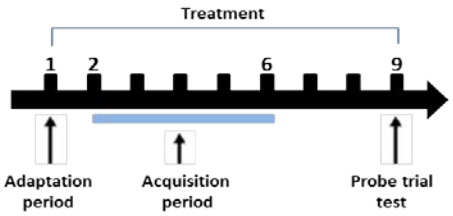
Barnes maze test



- **Event:** find the escape hole
- **Interested measure:** time to reach the escape box
- **Censored information :** end of the test at 180 seconds

Maze tests data

- **Study design**



  - **Adaptation period**: Habituation to the maze (performance not recorded)
  - **Acquisition period**: 5 days with 4 sessions per day for each animal
    - 20 sessions per animal
    - Several groups of animals, treated or not
  - **Probe trial**: memory of escape box location (time spent in area close to the escape box)

- **Acquisition period objectives**
  - Measure the learning performance in each group
  - Compare the performance between groups

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How to analyze maze tests data?

Advised approaches in the literature

Name	How does it work?	Aims
MARGINAL MODEL	• Estimate parameters making the (false) hypothesis of independence within individuals (Cox model) • Correct variance of estimations to take into account the correlation	• Improve the variance evaluation without modifying the estimate
CONDITIONAL FRAILTY MODEL	• Take into account the correlation between individuals directly in the model (Cox model with random effect term) • Estimate parameters conditionally to the random effect term	• Improve the estimate of parameters

Survival method - Frailty Cox model

- **Let T be the time to have the event and t a value of T**

  - Hazard function:

$$h(t) = \lim_{\Delta \to 0} \frac{\mathbf{P}(t \leqslant T \leq t + \Delta t \,|\, T \geq t)}{\Delta t}$$

- **Model:**

$$h(t|w_i, \mathbf{Z}_i) = \underbrace{h_0(t)\, exp(\beta' \mathbf{Z}_i)}_{\text{Cox model}} \underbrace{exp(w_i)}_{\text{Random effect}}$$

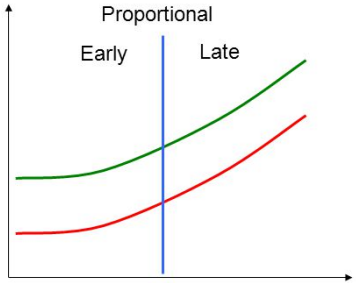
  - **Baseline hazard $h_0(t)$**: value if all Z (explanatory variables) do not have an effect
  - **Add a random term, w_i, to the Cox hazard function**
    - Let take into account repetitions of measurement for an animal

Hypotheses to be verified

- **Non informative censoring**
  - Fixed censoring is a particular case of random censoring considering a Dirac distribution

$$\delta(t) = \begin{cases} 1 \text{ if } t = C \\ 0 \text{ if } t \neq C \end{cases}$$

- **Proportional hazard hypothesis (PHH)**
  - Factor effect does not depend on time



- **Distribution of the random effect term**

	Distribution	Mean	Variance
Gamma	$exp(w_i) \sim G(1/\theta, 1/\theta)$	$E(exp(w_i)) = 1$	$V(exp(w_i)) = \theta$
Lognormal	$w_i \sim N(0, \theta)$	$E(w_i) = 0$	$V(w_i) = \theta$

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Real data application

Application on real dataset

- **Barnes Maze test**
  - **12 mice per group**
  - **5 days**
  - **4 sessions per day**

  } 20 measures per mouse

- **4 groups of treatments**
  - **C57BI6 VEH**: healthy and non treated mice
  - **APOE VEH**: pathologic and non treated mice
  - **APOE 10 MG**: pathologic and treated mice
  - **APOE 30 MG**: pathologic and treated mice

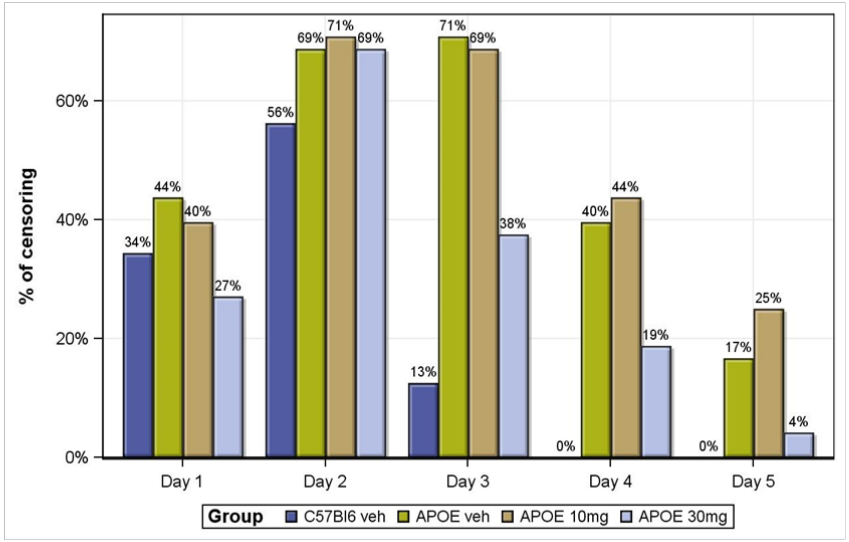
- **Objectives**
  - Study the learning in each group
  - Compare the learning between groups
    - Validate the pathology
    - Dose effect efficacy

Latency to find the platform / % of censoring

Latency to find the target hole (seconds): median [Q1;Q3]

Group	N per group	N	Day 1	Day 2	Day 3	Day 4	Day 5
C57Bl6 veh	8	32	116.5 [40.5;180]	180 [90;180]	64.5 [42.5;108.5]	22.5 [12;36]	15.5 [9.5;23]
APOE veh	12	48	149.5 [74;180]	180 [153.5;180]	180 [153;180]	140.5 [104;180]	100 [78;126]
APOE 10mg	12	48	140 [83.5;180]	180 [162;180]	180 [149;180]	146.5 [98;180]	97.5 [71;171.5]
APOE 30mg	12	48	94.5 [63;180]	180 [141.5;180]	117.5 [82;180]	76.5 [41.5;132]	58 [36;79]

180 is a censored value. If the target hole is not found after 3 minutes, the latency is recorded as 180 seconds

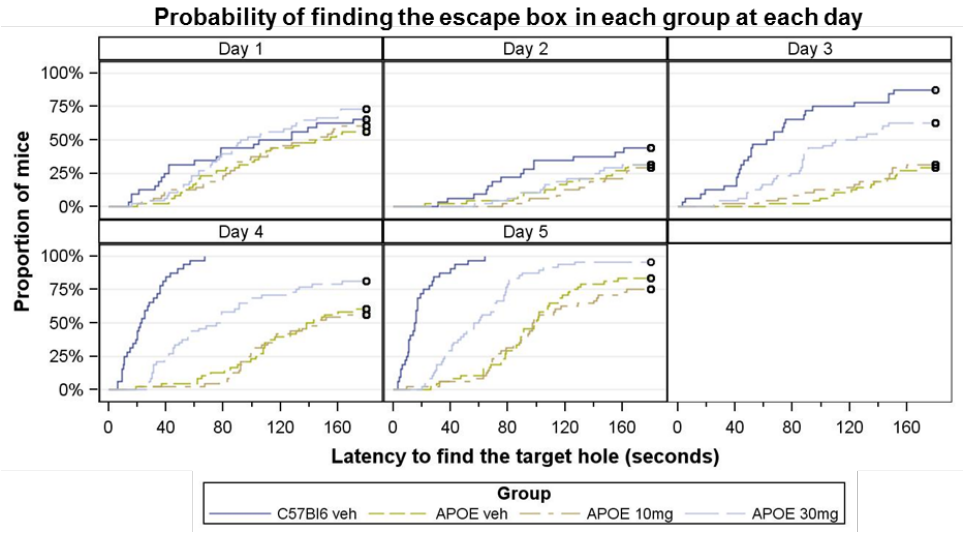


Censoring rate in each group and at each day

Frailty Cox model applied on maze test

Kaplan-Meier curves

- **Descriptive information about survival**
  - Graphical representation of probability to find the escape
- **Checking proportional hazard assumption**
  - Use graphics to assess proportional hazard assumption



Frailty model with SAS

- **Model:**

$$h(t|w_i, Day = X, Group_i = Y) =$$

$$h_0(t)\, exp(\beta_{DayX} \times \mathbf{1}_{Day=X} + \beta_{GroupY} \times \mathbf{1}_{Group=Y} + \beta_{DayXGroupY} \times \mathbf{1}_{Day=X}\mathbf{1}_{Group=Y})\, exp(w_i)$$

- **PHREG procedure**

```
PROC PHREG data=maze_test;
    class animal day(ref=first) group(ref="APOE VEH");
    model latency*censored(1) = group day group*day / ties=efron;
    random animal / dist=lognormal;
    hazardratio day / diff=ref;
    contrast "D5 vs D1 and CONTROL vs APOE VEH"
            group 0 0 0 day  0 0 0 0 group*day  0 0 0 1  0 0 0 0  0 0 0 0 / estimate = exp e;
RUN;
```

Hazard Ratios depending the objectives

- **Study of learning between day 5 and day 1 in group Y**

$$HR = HR(t|w_i, \text{Day 5 vs. Day 1, Group}_i = Y)$$

$$HR = \frac{h_0(t) \times exp(\beta_{GroupY} + \beta_{Day5} + \beta_{Day5GroupY}) \times exp(w_i)}{h_0(t) \times exp(\beta_{GroupY} + \underbrace{\beta_{Day1} + \beta_{Day1GroupY}}_{\substack{\text{Reference levels} \\ \beta = 0}}) \times exp(w_i)} = exp(\beta_{Day5} + \beta_{Day5GroupY})$$

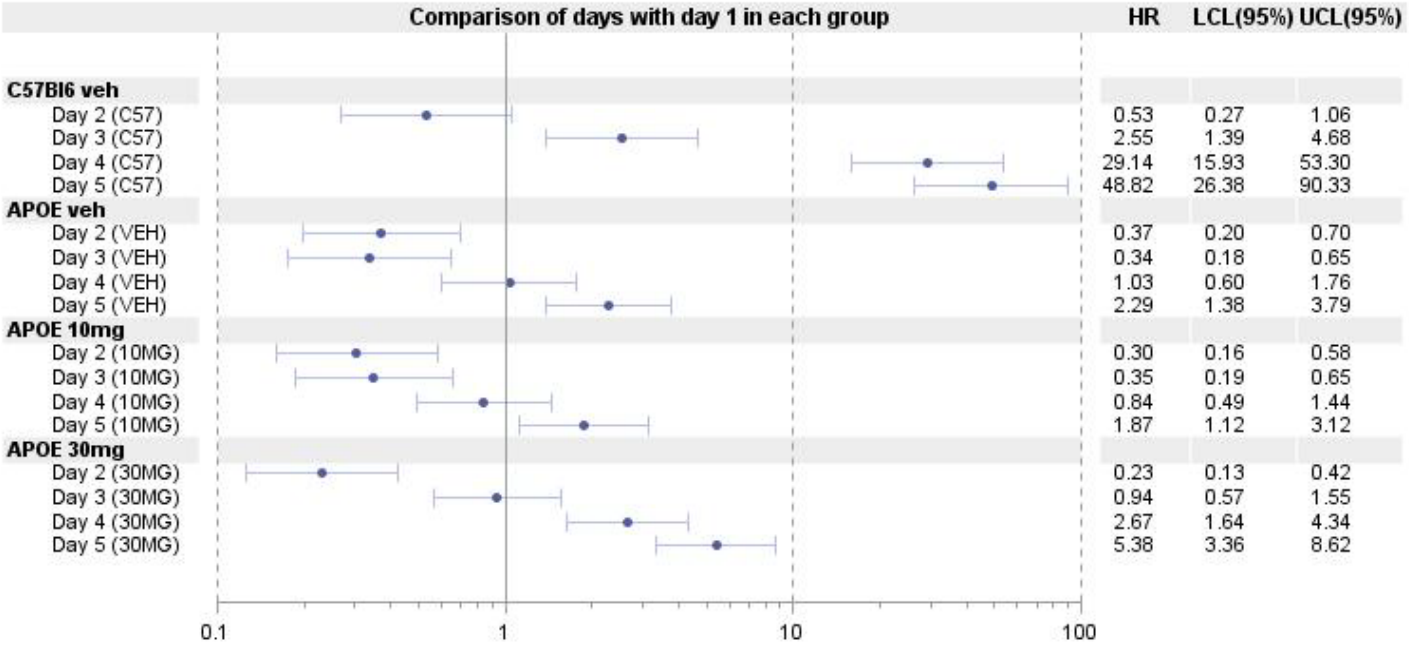
- **Comparison of day 5 vs. day 1 between Apoe vehicle and control group**

$$HR = \frac{HR(t|w_i, \text{Day 5 vs. Day 1, Group} = \text{CONTROL})}{HR(t|w_i, \text{Day 5 vs. Day 1, Group} = \text{APOE VEH})}$$

$$HR = \frac{exp(\beta_{Day5} + \beta_{Day5CONTROL})}{exp(\beta_{Day5} + \underbrace{\beta_{Day5APOEVEH}}_{\substack{\text{Reference level} \\ \beta = 0}})} = exp(\beta_{DAY5CONTROL})$$

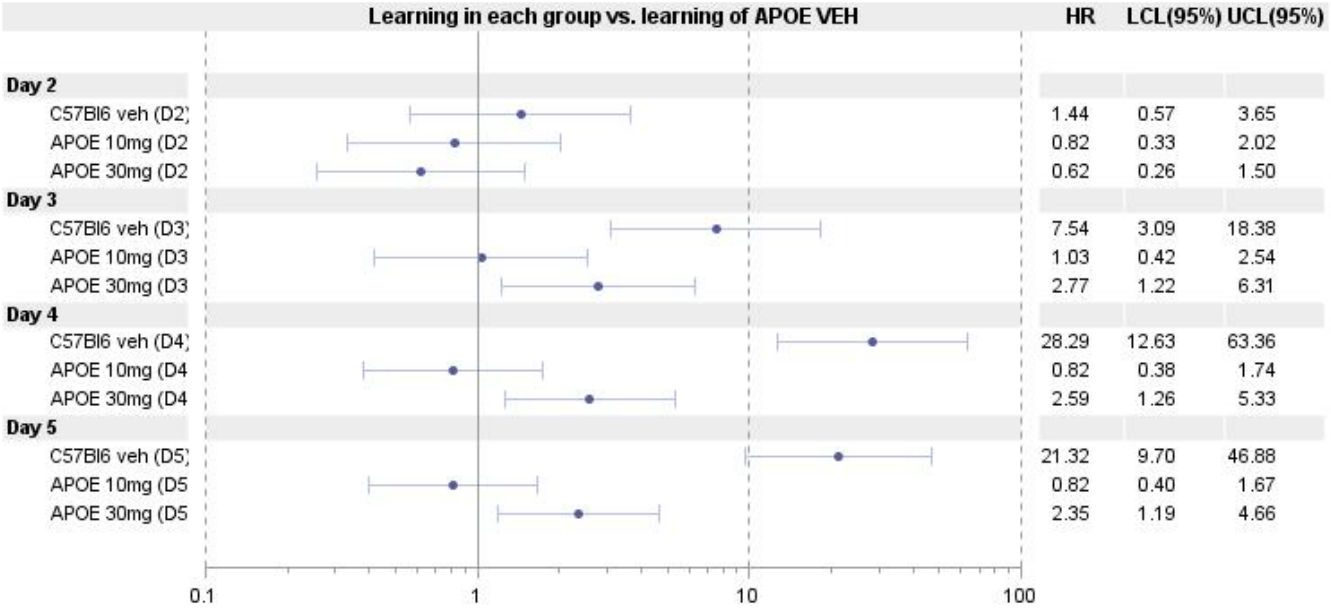
Study of learning in a group of treatment

- **Study of learning between day X and day 1 in each group**



Comparison of groups

- **Comparison of days vs. day 1 between APOE VEH and other groups**



Conclusion

- **Conditional frailty Cox model**
  - Consider both censoring and repetitions of tests
  - Analysis of results with hazard ratios
  - More powerful than Logrank or Anova-type analysis (simulation done internally)

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References

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  - KLEIN, John P. and MOESCHBERGER, Melvin L. Survival analysis: techniques for censored and truncated data. Springer Science & Business Media, 2005.
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  - HOUGAARD, Philip. Frailty models for survival data. Lifetime data analysis, 1995, vol. 1, no 3, p. 255-273
  - DUCHATEAU, Luc and JANSSEN, Paul. The frailty model. Springer Science & Business Media, 2007.
- **Proportional hazards assumption:**
  - XU, Ronghui and GAMST, Anthony. On proportional hazards assumption under the random effects models. Lifetime Data Analysis, 2007, vol. 13, no 3, p. 317-332.

Appendix: Interpretation of HR

- **HR(t, D5 vs. D1 in APOE VEH group) = 2,29 >1**
  - A mouse from the APOE group has a better potential to find the escape box at day 5 than the same mouse at day 1

- **Impossibility to quantify the difference!**
  - **HR is different than a risk ratio:**

$$HR(t, \mathbf{Z_1} \text{ vs. } \mathbf{Z_2}) = \frac{\lim_{\Delta \to 0^+} \frac{\mathbf{P}(t \leq T < t+\Delta t | T > t, \mathbf{Z_1})}{\Delta t}}{\lim_{\Delta \to 0^+} \frac{\mathbf{P}(t \leq T < t+\Delta t | T > t, \mathbf{Z_2})}{\Delta t}}$$

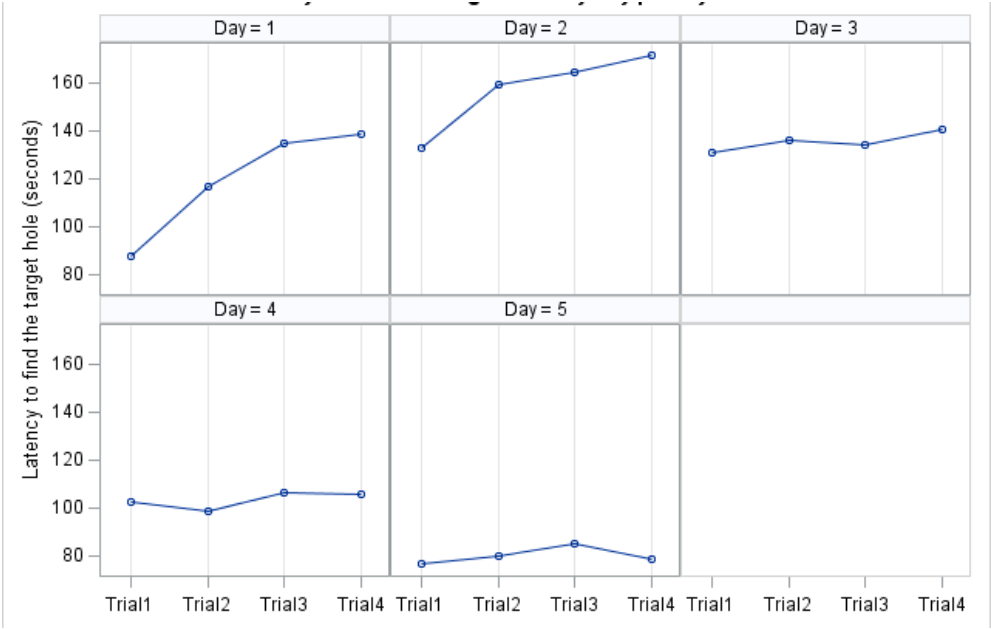
$$HR(t, \mathbf{Z_1} \text{ vs. } \mathbf{Z_2}) = \frac{h(t, \mathbf{Z_1})}{h(t, \mathbf{Z_2})}$$

$$RR(t, \mathbf{Z_1} \text{ vs. } \mathbf{Z_2}) = \frac{\mathbf{P}(T \leq t | \mathbf{Z_1})}{\mathbf{P}(T \leq t | \mathbf{Z_2})}$$

$$RR(t, \mathbf{Z_1} \text{ vs. } \mathbf{Z_2}) = \frac{1 - S(t, \mathbf{Z_1})}{1 - S(t, \mathbf{Z_2})}$$

$$RR(t, \mathbf{Z_1} \text{ vs. } \mathbf{Z_2}) = \frac{1 - exp(-\int_0^t h(u, \mathbf{Z_1}) du)}{1 - exp(-\int_0^t h(u, \mathbf{Z_2}) du)}$$

  - **RR is a ratio of probability that tends to 1 when t tend to infinity**
  - **HR is a ratio of instantaneous potential that is constant across time**

Session information

- **Do not use session information in the model**