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Modelling the desensitization in hyperimmunised patients awaiting for kidney transplant

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Table of contents

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I - Introduction

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A) Context

- **Human Leukocyte Antigen (HLA) antibodies :** make the distinction between self and non-self cells
- **anti-HLA antibodies :** neutralize and destroy non-self cells

- Hyperimmunised patients :
  - high proportion of anti-HLA antibodies
    → more likely to reject transplantation

- Desensitivisation protocol :
  - decrease the number of anti-HLA antibodies
  - long and heavy for patients

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B) Objectives

- Very different immune profiles with great variability :
  - HLA modelling as a function of covariates
  - Define optimized strategy of desensitization for patient
  - Create an R shiny application : visualize antibodies and the immune system complexity

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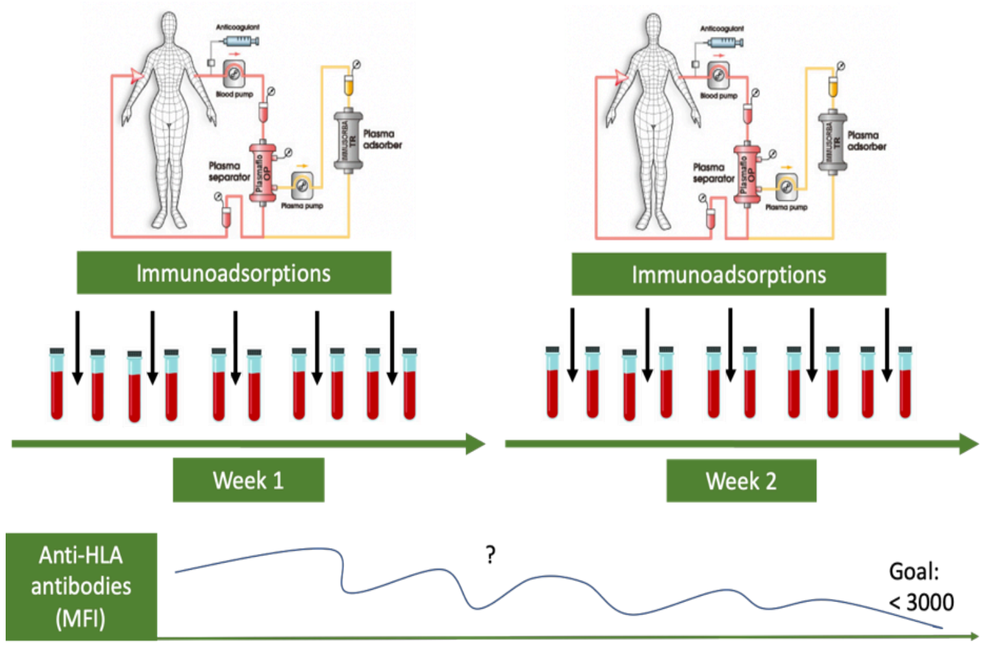
II - Data overview

A) Protocol

- 10 patients
- 10 desimmunisation session (immunoabsorptions) :
  - 2 weeks, 5 days per week
  - 2 samples : before and after the session
  - Quantification of MFI : Mean Fluorescence Intensity, way of measuring anti-HLA presence in patients bodies
  - Goal : MFI under the 3000 threshold



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B) Data description

- Longitudinal data: 20 samples for each of the 10 patients.
- Statistical unit: a hyperimmunised patient waiting for a kidney transplant.
- Outcome variable: `MFI Classe I` and `MFI Classe II`

Variables	Min	Median	Mean	Max
MFI Classe I	136.0	2998.0	4985.82	20241
MFI Classe II	311.5	5637.5	8493.65	21307

B) Data description

- 8 selected covariates : `Time`, `Durée de la séance (min)`, `Volume plasma traité`, `Poids (kg)`, `Taille (cm)`, `Sexe`, `Grossesses`, `Greffe antérieure`.

Variables	Min	Median	Mean	Max
Durée de la seance (min)	115	185.0	189.7	340.0
Volume plasma traite	4040	5855.5	5805.5	8000.0
Poids (kg)	45	61.0	59.9	81.4
Taille (cm)	156	160.5	163.3	185.0

Sexe	Number
F	7
H	3

Greffe antérieure	Number
0	4
1	4
2	2

Grossesses	Number
0	1
1	2
2	2
3	1
4	1

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III - Methodology

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A) Statistical model

- Based on pharmacometrics models :
  - pharmacokinetics (PK) models
  - pharmacodynamics (PD) models

- Tools : Monolix@lixoft (implimented PK/PD models) and R (lixoftConnectors, PKPDsin, nlmeODE packages)

- Interests :
  - non-linear curves
  - repeated measurements
  - explain the variability between patients

  → Non-linear mixed effects model

A) Statistical model

- Non-linear mixed effects models :

$$y_i = f(\phi_i, \upsilon_i) + \epsilon_i \quad , \quad i = 1, \ldots, M$$

  - M : number of patients
  - f : non-linear function
  - $\phi_i = A_i\beta + Bb_i$: group specific parameters vector
    - β : a vector of fixed effects
    - b_i : a vectir of random effects associated with patient i
  - υ_i : covariate vector
  - ϵ_i random variable describing residual error

- Parameters to estimate : variance of random effects b_i , covariate vector υ_i and variance of residual error ϵ_i

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B) Strategy

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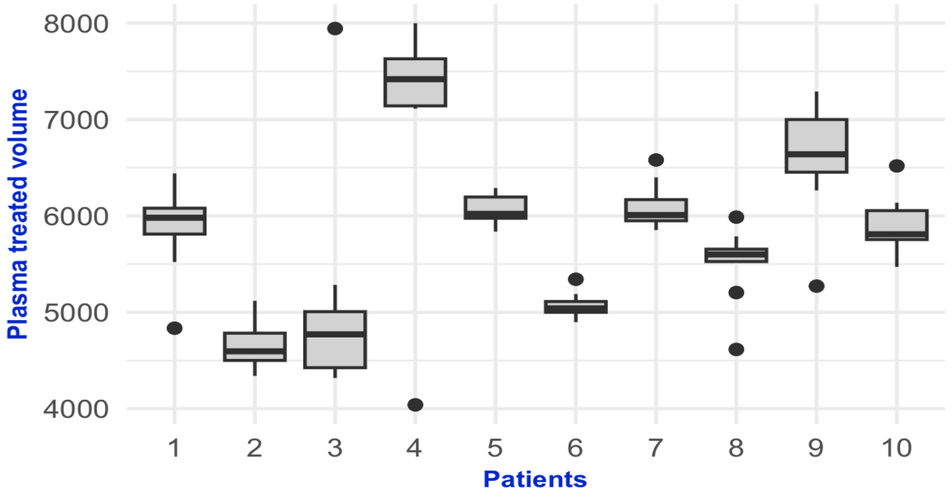
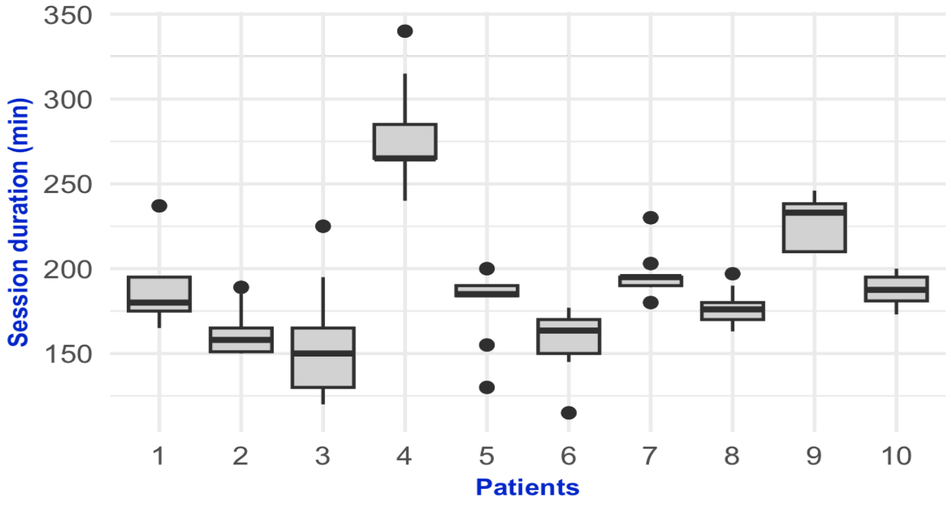
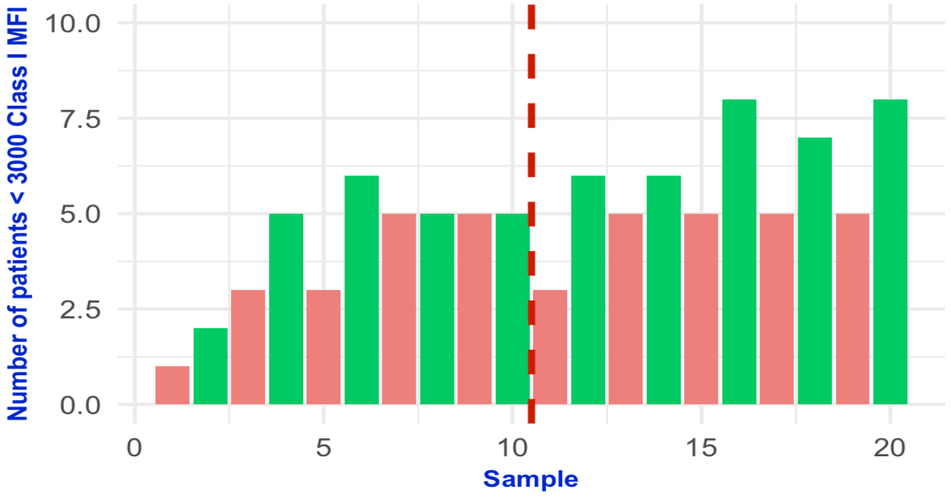
1. Data management

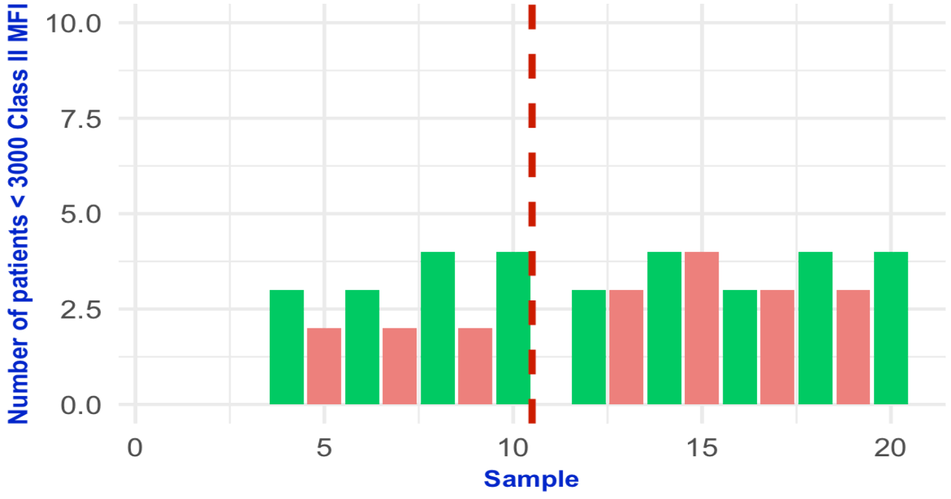
- Base file : Excel file
- What we want : csv file for easier work later
- How : 1st R program to rectify and structure data
- NA values handling : replaced by the mean value of the patient
- Seance duration recalculation : check the hand written value
- Adding delta MFI calcul

2. Descriptive statistics

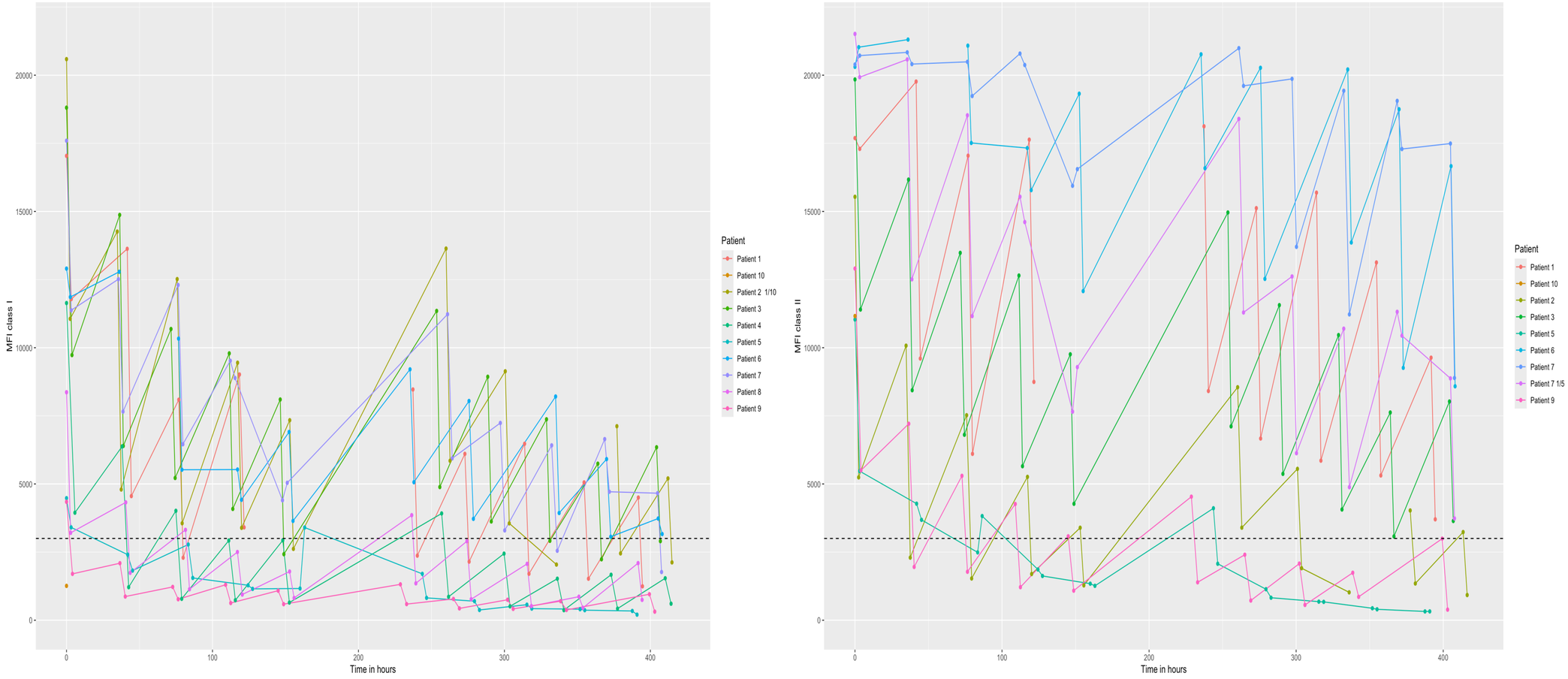








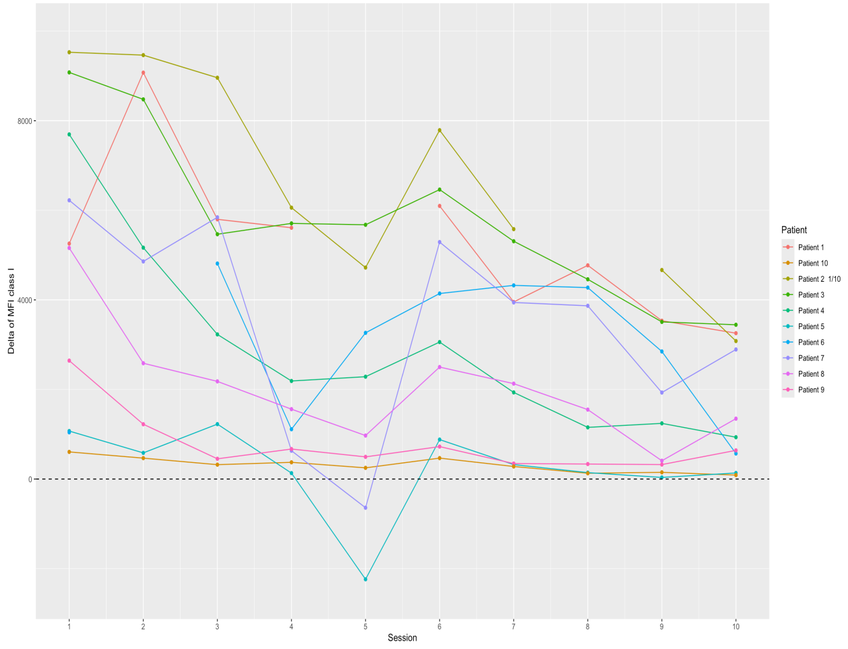
3. MFI visualisation

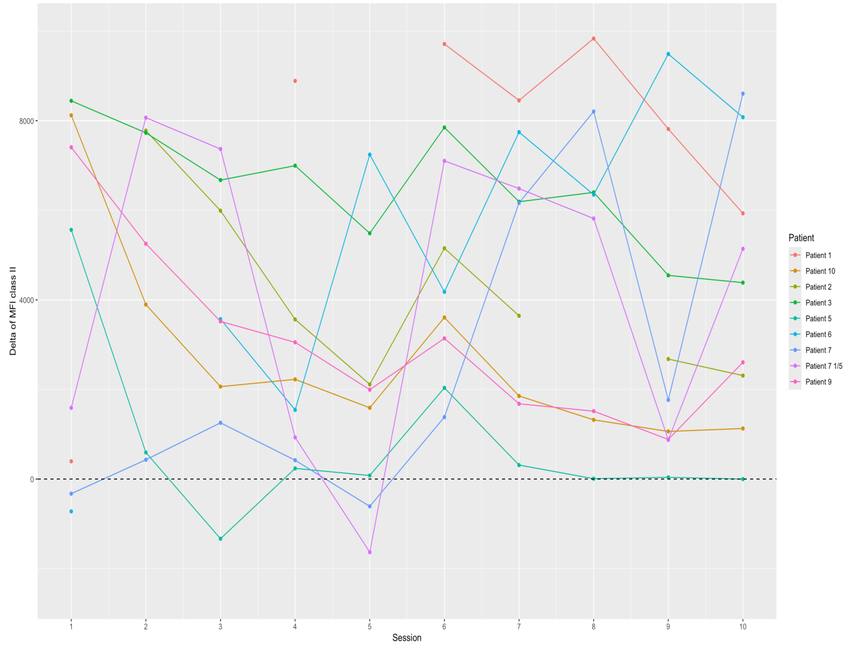


Gap half way through the treatment because of weekend break.

Some patients reach the 3000 threshold quickly.

- Delta of MFI : difference of MFI between the beginning and the end of a session.
- Visualisation of the delta of MFI





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4. Modelling

- Step 1 : function and covariates choice
- Step 2 : parameters estimation
- Step 3 : validation of the model
- Step 4 : simulation

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5. Shiny App

- Objective : visualize all the different anti-HLA
  - Because of the great variability
    - Difficulties in visualising the different models

- Several stages :
  - Defining the client’s needs and expectations
  - Creating a mock-up
  - Development of the shiny application

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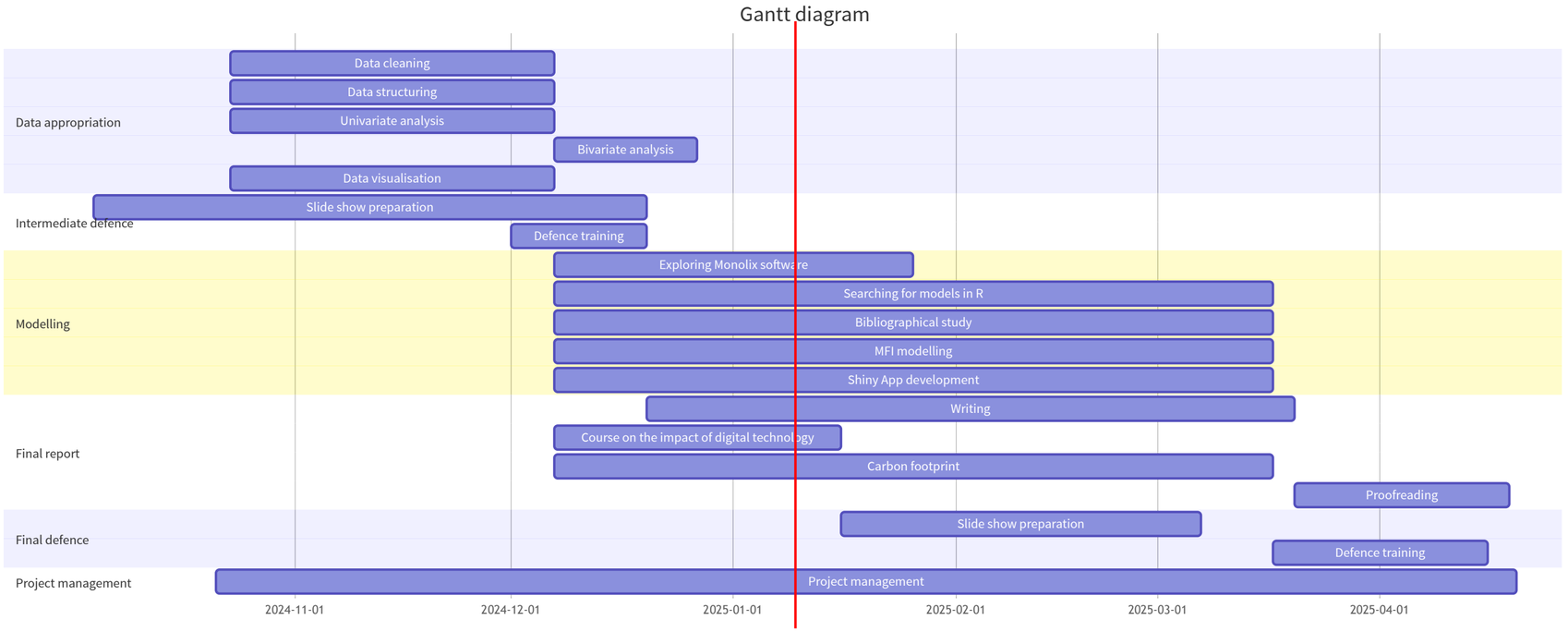
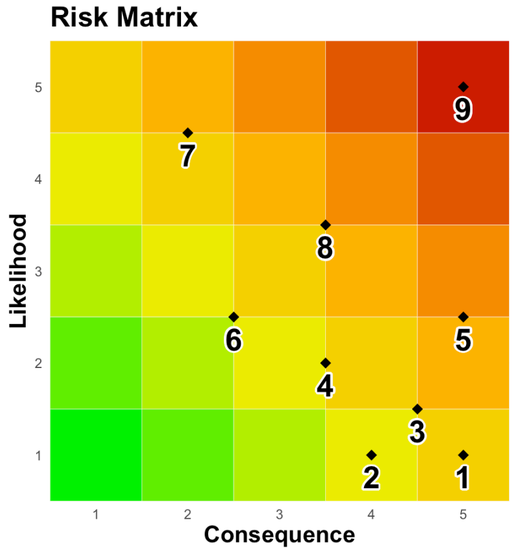
IV - Future plan

A) Schedule overview



B) Possible scenarios



Numbers	Tags
1	Non functional study
2	Legal issues (plagiarism)
3	Team conflicts
4	Files' loss
5	Response fail
6	Wrong files' versions
7	Missing students
8	Delayed schedule
9	Changing in backers' needs

Scenarios	Data management	Model choice	Model optimisation	Protocol optimisation	Needs charter	App mock-up	App development
Best	✓	✓	✓	✓	✓	✓	✓
Worst	✓	✓	✗	✗	✓	✓	✗
Most likely	✓	✓	✓	?	✓	✓	✗