Bayesian survival analysis of the French Childhood Cancer Survivor Study using mixture distribution

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MICS - Biomathematics
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Introduction:

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- Progressive, irreversible, and sometimes fatal treatment-related cardiovascular effects may appear years later[6].
- Heart failure is one of the most important late effects after treatment for cancer in childhood[3].

Problem statement:

The main goal of this study is to leverage the Bayesian analysis tools as well as the insight given by the FCCSS[1] to:

- Identify the distribution of the survival time in the FCCSS
- Predict the risk of appearance of CD[2] using clinical data

[1] French Childhood Cancer Survivor Study `https://fccss.fr/`

[2] Cardiac Disease

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Cohort Constitution:

Figure: French Childhood Cancer Survivor Study[1]

- Cohort Size: 7670 survivors
- Treatment Period: 1946 - 2000
- Cancer Types: Common childhood solid cancers
- Treatment Centers: Five different cancer centers in France
- Age at Treatment: < 21 years

The database:

- **ctr, numcent**: Patient identifiers.
- **Pathologie_cardiaque_3_new**: Indication if the patient got diagnosed with grade 3 or above CD.
- **survival_time_years**: Duration between the start of the treatment and the diagnosis of the CD.
- **ALKYL, ANTHRA, VINCA, ANIM, ANTIB, Chimio_groupe_autre**: Chemotherapy groups.
- **Age_at_diagnosis**: Age at cancer diagnosis.
- **Mean_dose_to_heart**: Mean dose of radiotherapy administered to the heart.

Censorship:

- Discard the instances of missing information.

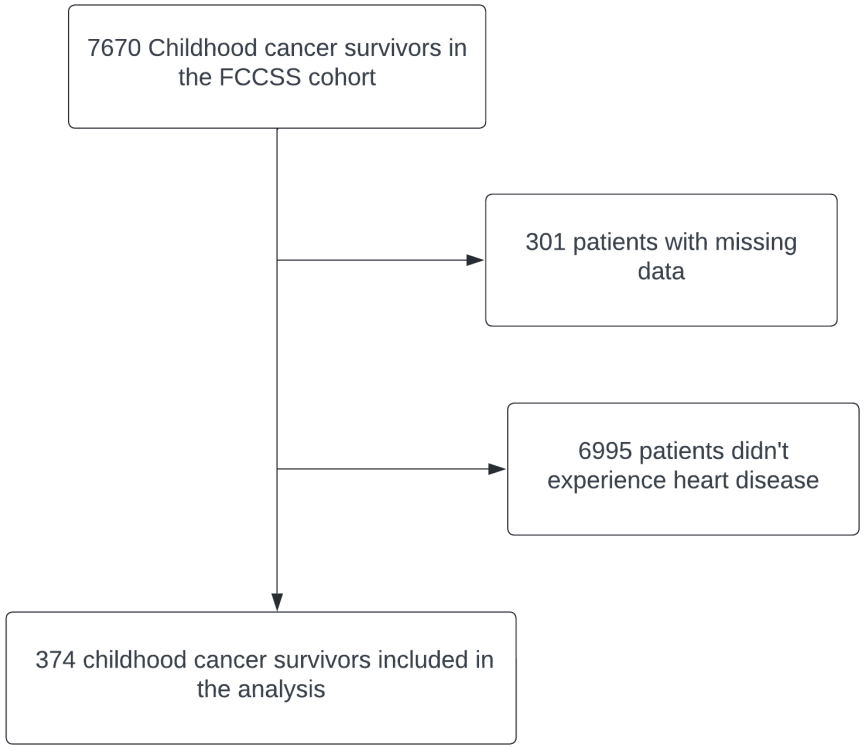

Figure: Flow chart of the FCCSS

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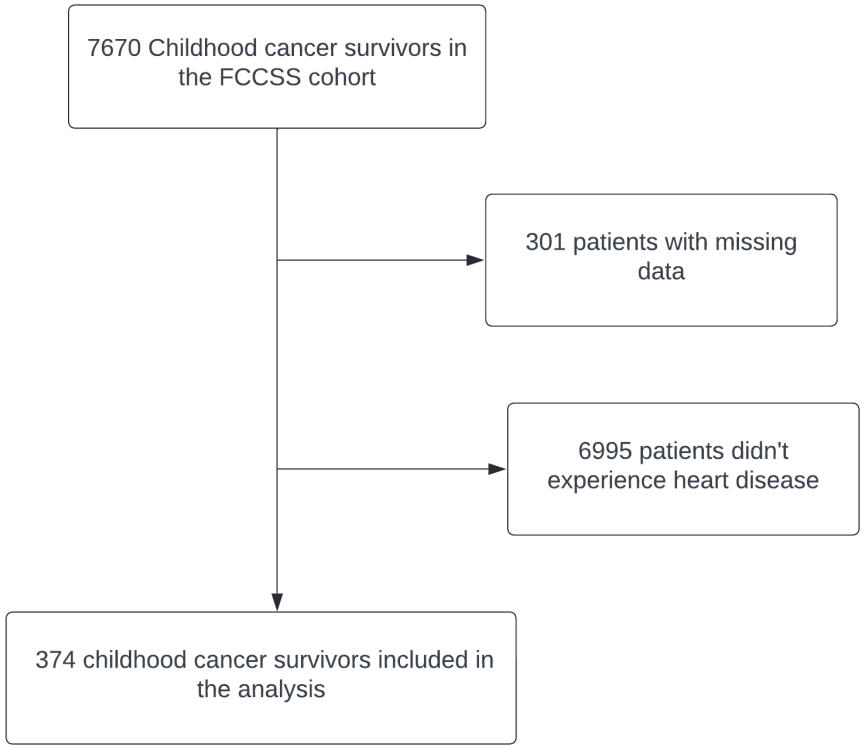

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Summary of the survival time:

Min	1st Qu.	Median	Mean	3rd Qu.	Max
0.06	15.39	23.63	23.68	32.59	65.37

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- The maximum recorded survival time in our dataset is 65.37 units, portraying the upper bound of observed temporal extents.

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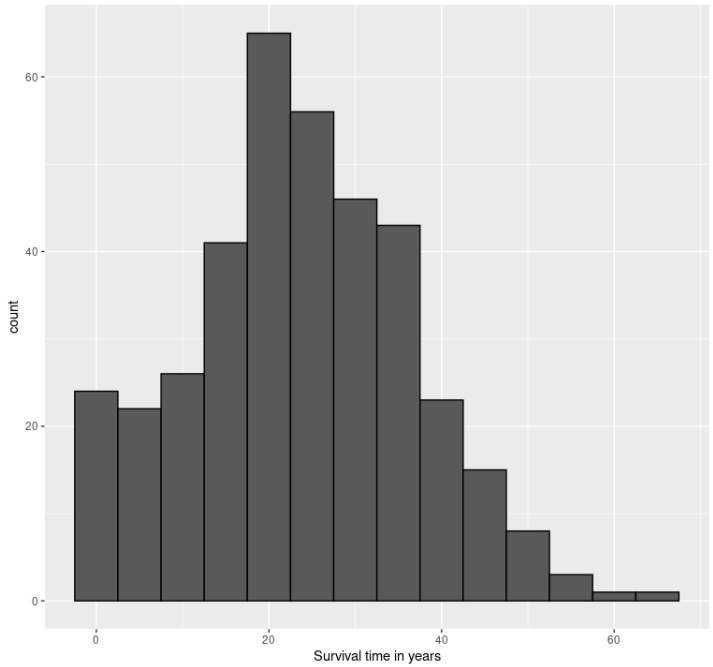
Bimodal mixture distribution



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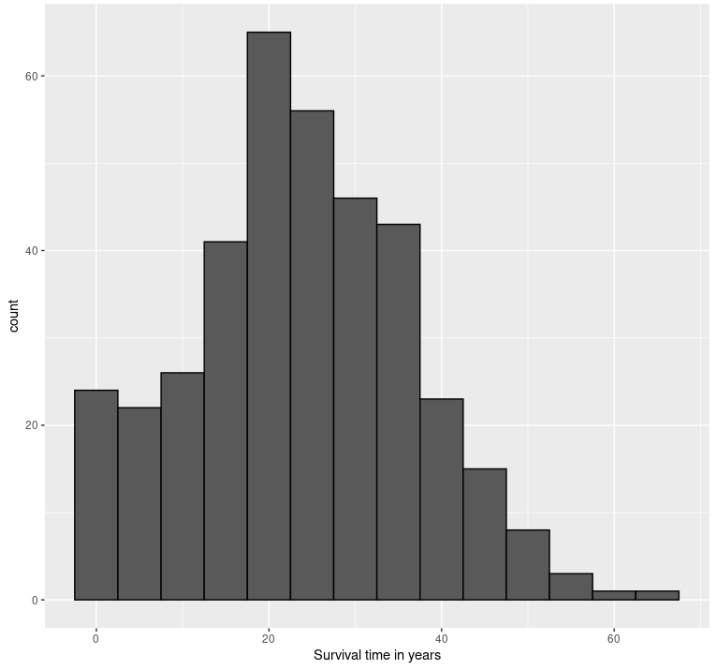

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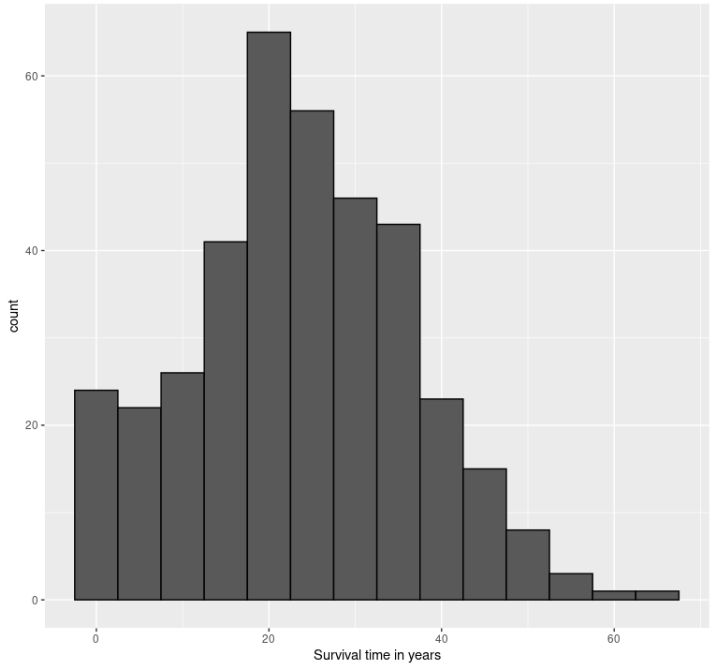

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Using a mixture model in order to account for multimodality

- The support of the survival time is $\mathbf{]0, +\infty[}$
- The distribution seems **heavy tailed**
- The distribution looks **right skewed**

This insight guides us to use Log-normal components for the mixture

$$T|\mu_1, \sigma_1, \mu_2, \sigma_2, p \sim p\mathcal{LN}(\mu_1, \sigma_1) + (1-p)\mathcal{LN}(\mu_2, \sigma_2)$$

Reparametrization of the mixture:

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$$\mu_1 = \mu - \sigma\ \phi\ .\left(\frac{\sqrt{1-p}}{\sqrt{p}}\right); \qquad \mu_2 = \mu + \sigma\ \phi\ .\left(\frac{\sqrt{p}}{\sqrt{1-p}}\right)$$

$$\sigma_1 = \sigma\left(\frac{\eta_1}{\sqrt{p}}\right); \qquad \sigma_2 = \sigma\left(\frac{\eta_2}{\sqrt{1-p}}\right)$$

$$\text{where } \eta_1^2 + \eta_2^2 + \phi^2 = 1$$

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$$\mu \sim \mathcal{N}(\bar{\beta}, \bar{\sigma}) \qquad \bar{\beta} = \frac{1}{N}\sum^{N} Z_i \quad \bar{\sigma}^2 = \frac{1}{N-1}\sum^{N}(Z_i - \bar{\beta})^2$$

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  - **Prediction:**

$$\mu = \mu_{X\beta} = In\left(\sum \beta_i X_i\right) \qquad \boldsymbol{\beta} \mid X, \hat{\beta}, \mathbf{c} \sim \mathcal{N}_k\left(\hat{\beta}, \mathbf{c}(X^\top X)^{-1}\right)$$

Posterior distribution

To compute each posterior and update our priors we apply Bayes's theorem:

$$\pi(\theta_i \mid X_1, \ldots, X_n) = \frac{\pi(X_1, \ldots, X_n \mid \theta_i)\pi(\theta_i)}{\pi(X_1, \ldots, X_n)}$$

$$= \frac{\ell(\theta \mid X_1, \ldots, X_n)\pi(\theta_i)}{\int \ell(\theta \mid X_1, \ldots, X_n)\pi(\theta)\mathrm{d}\theta}$$

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In light of these computational challenges, Markov chain Monte Carlo(MCMC) methods are the tool of choice.

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Gibbs sampler:

- Gibbs sampler relies on easier conditional sampling.
- The kernel of the Markov chain is the conditional distribution.

1. Initialize the Markov Chain $\mathrm{x}^{(0)} = \left(x_1^{(0)}, \ldots, x_p^{(0)}\right)$
2. For $t = 1, \ldots, T$ update $x^{(t)}$ as follows:
   1. $x_1^{(t)}$ according to $\pi_1\left(x_1 \mid x_2^{(t-1)}, \ldots, x_p^{(t-1)}\right)$
   2. $x_2^{(t)}$ according to $\pi_2\left(x_2 \mid x_1^{(t)}, x_3^{(t-1)}, \ldots, x_p^{(t-1)}\right)$

   $\vdots$

   $x_p^{(t)}$ according to $\pi_p\left(x_p \mid x_1^{(t)}, \ldots, x_{p-1}^{(t)}\right)$

Metropolis-Hastings sampler:

- Enables sampling from complex distributions.
- Proposing samples and accepting them based on a defined scheme.

1. Initialize the Markov Chain with an arbitrary starting value $x^{(0)}$
2. For $t = 1, \ldots, T$ update $x^{(t)}$ as follows:
   1. Given $x^{(t-1)}$, generate $\tilde{x} \sim q\left(x^{(t-1)}, x\right)$
   2. Compute

$$\rho\left(x^{(t-1)}, \tilde{x}\right) = \min\left(\frac{\pi(\tilde{x})/q\left(x^{(t-1)}, \tilde{x}\right)}{\pi\left(x^{(t-1)}\right)/q\left(\tilde{x}, x^{(t-1)}\right)}, 1\right).$$

   3. With probability $\rho\left(x^{(t-1)}, \tilde{x}\right)$, accept $\tilde{x}$ and set $x^{(t)} = \tilde{x}$; otherwise reject $\tilde{x}$ and set $x^{(t)} = x^{(t-1)}$

Metropolis within Gibbs

$$\pi(\theta_i \mid X_1, \ldots, X_n) = \frac{\ell(\theta \mid X_1, \ldots, X_n)\pi(\theta_i)}{\int \ell(\theta \mid X_1, \ldots, X_n)\pi(\theta)\mathrm{d}\theta}$$

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The objective at hand involves the integration of a Metropolis-Hastings algorithm within a Gibbs sampler to effectively estimate the parameters of the mixture model

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The MH blocks of the algorithm are similar in structure therefore we will only go in depth in the sampling of the mixture weights p and perform a comprehensive study on that.

- We start by simulating control data

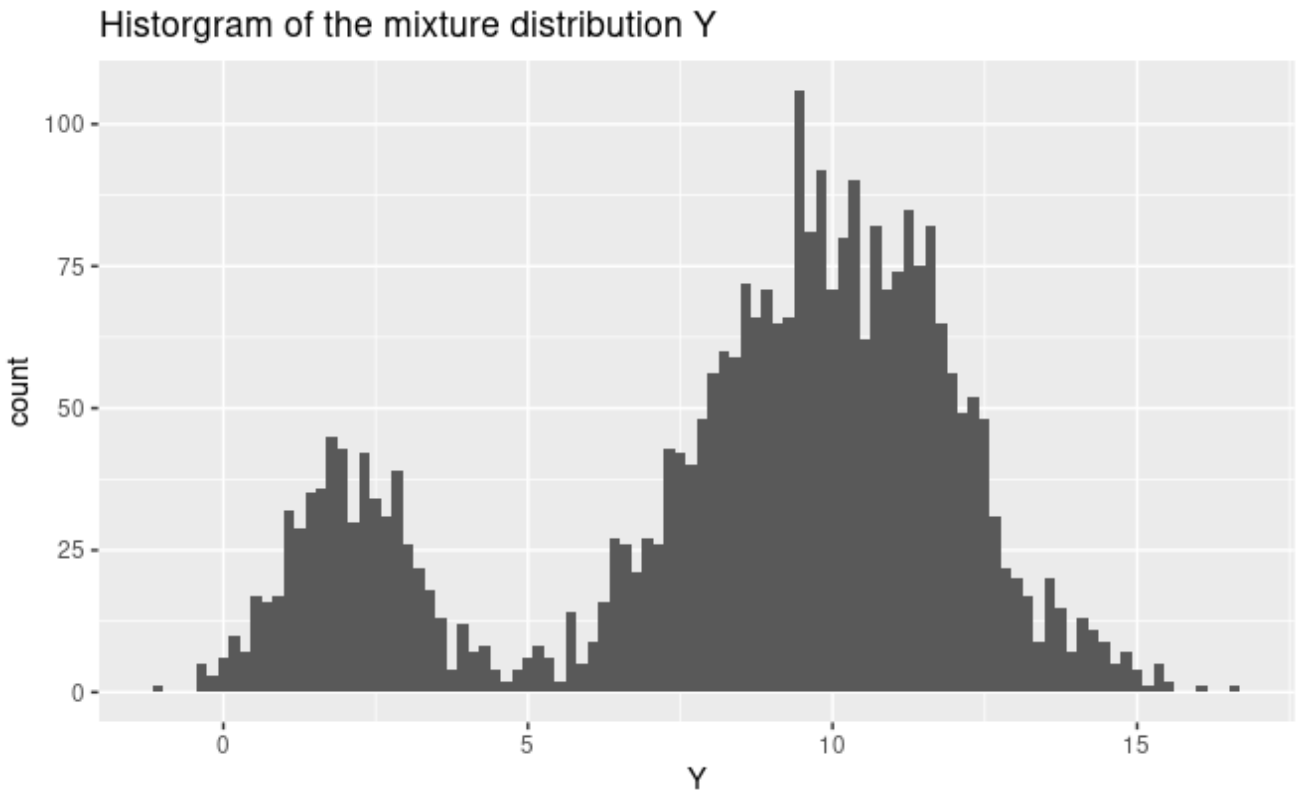
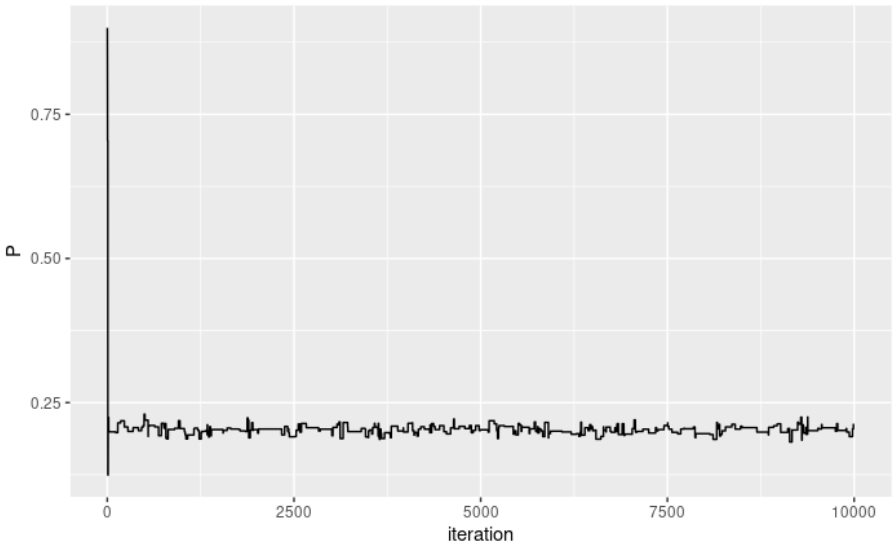
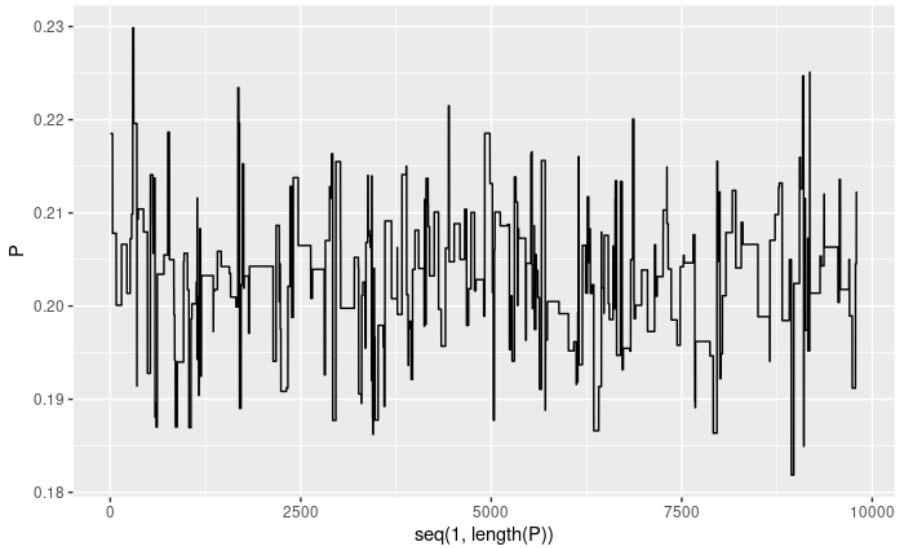


Figure: Histogram of simulated mixture $Y \sim 0.2\mathcal{N}(2,1) + 0.8\mathcal{N}(10,2)$

Output:



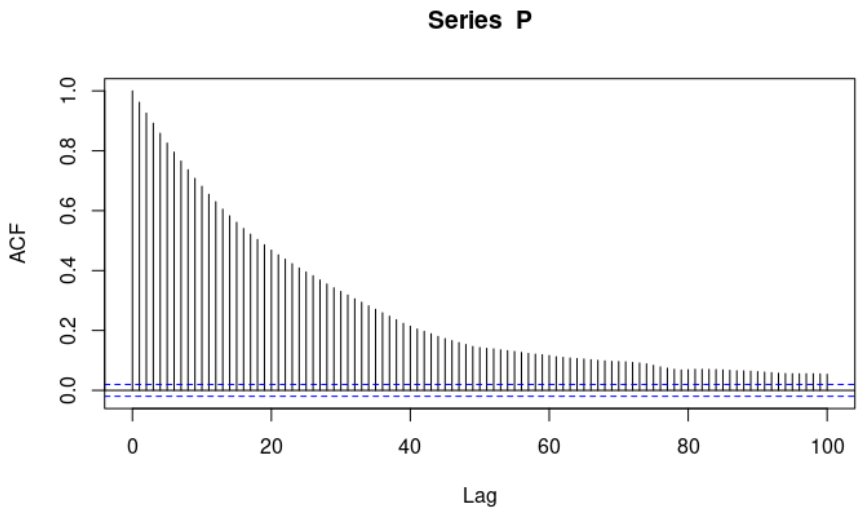
(a) Output Markov chain



(b) Truncated Markov chain

- The Markov chain seems to reach its stationnary state in less than 10 iterations
- We discard the few iterations at the beginning to account for the burn-in phase

Stationarity: autocorrelation analysis



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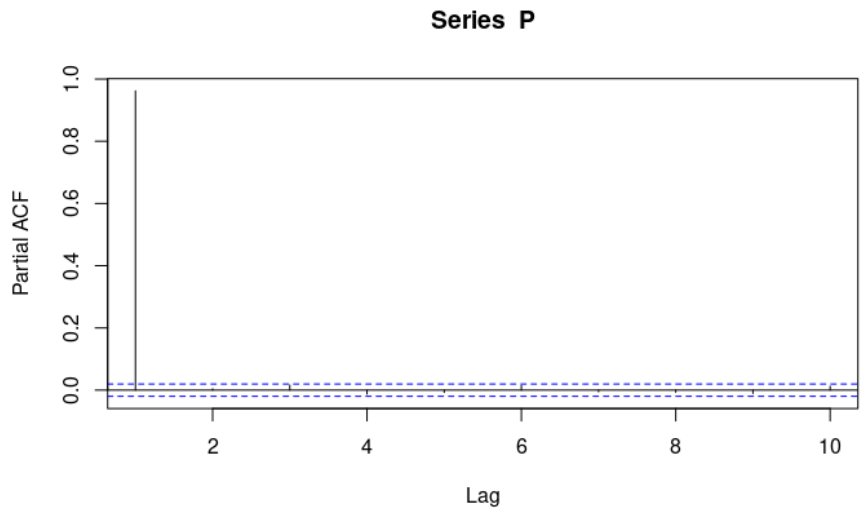

(b) PACF

- **ACF:** Exponential decay as lag increases

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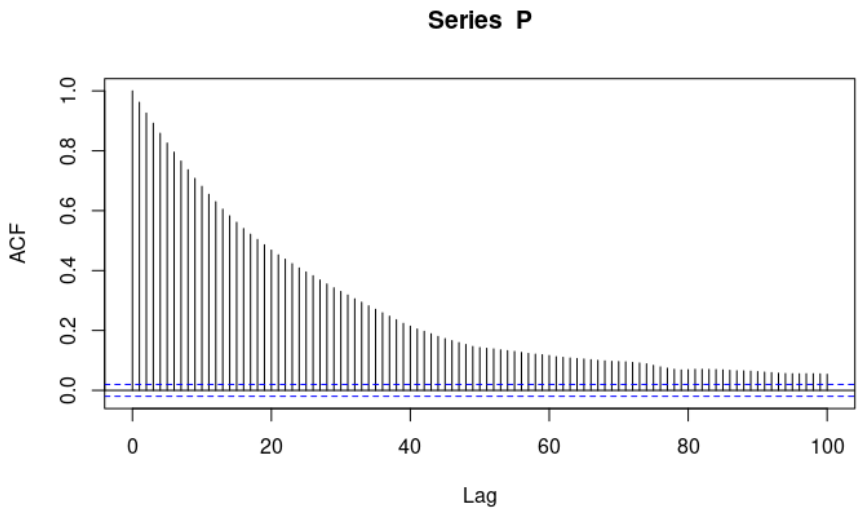

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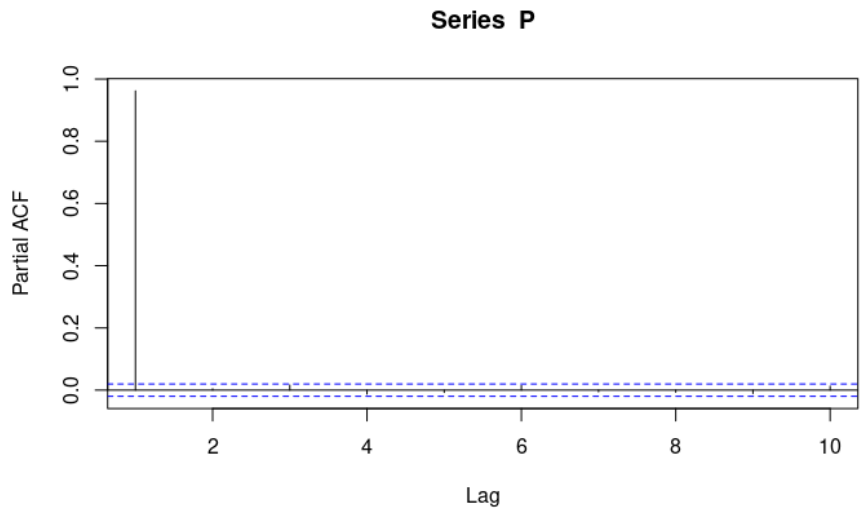

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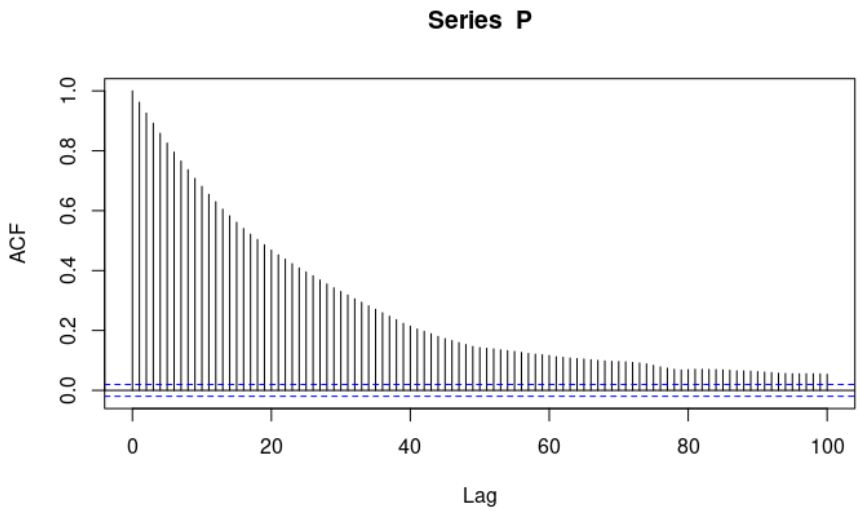

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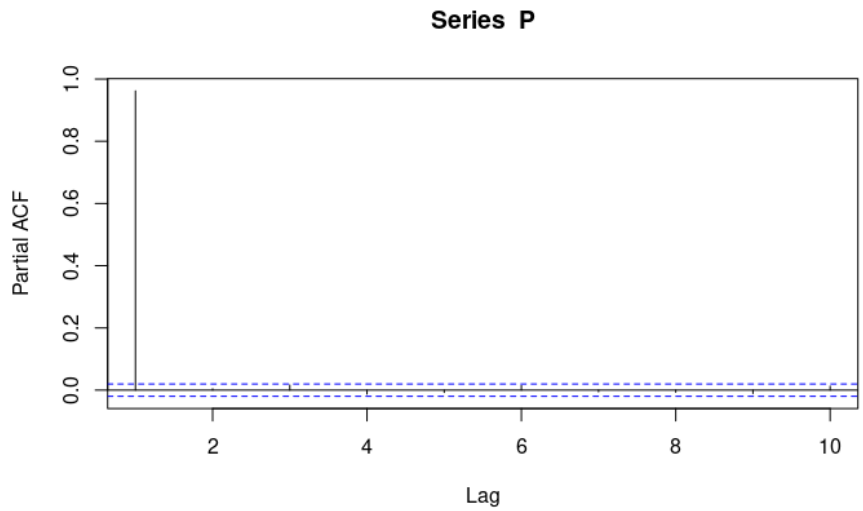

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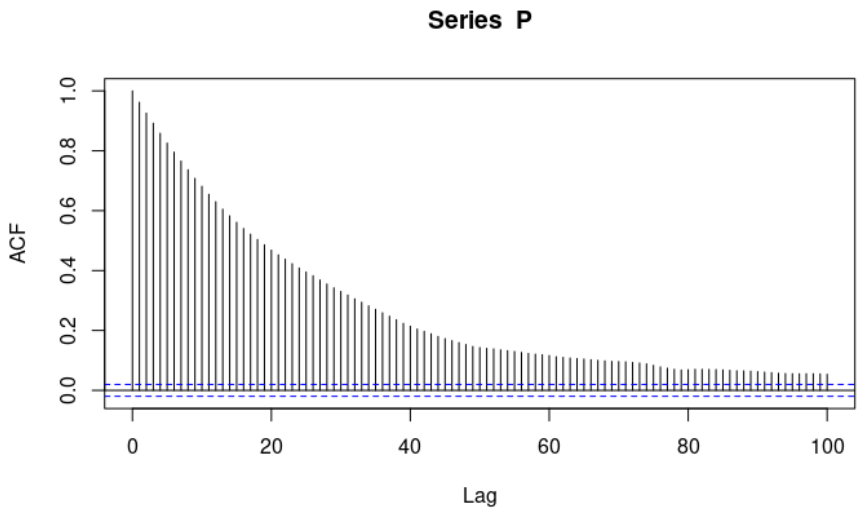

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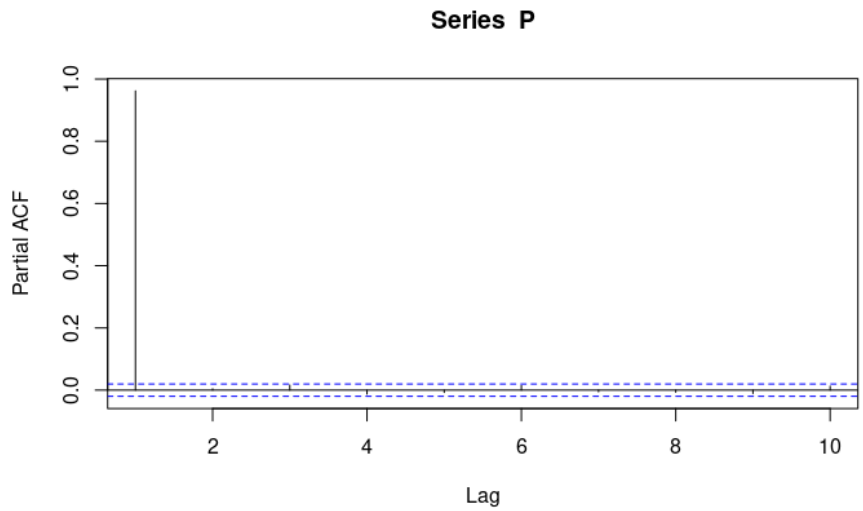

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  $\Longrightarrow$ Direct linkage between the current state and its predecessor

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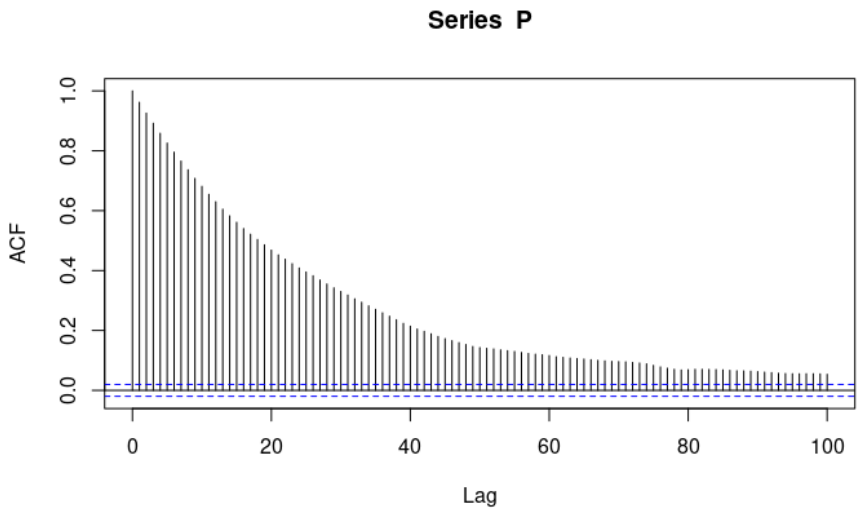

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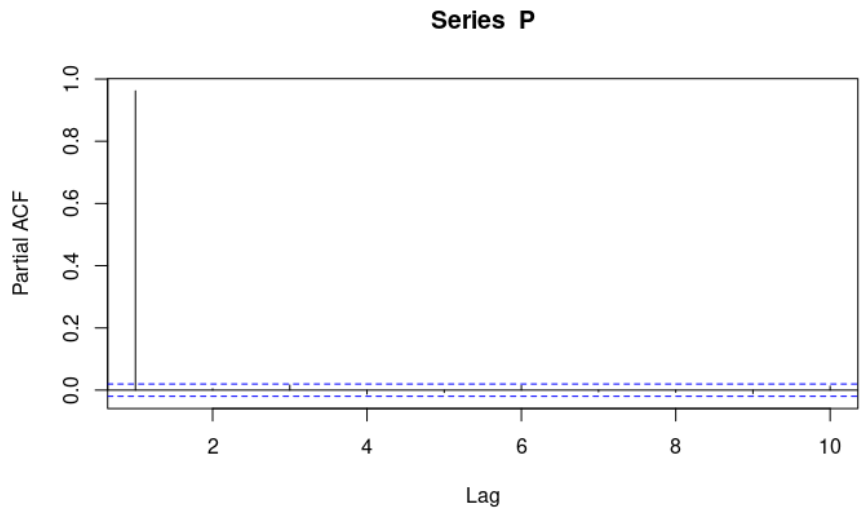

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The ACF and PACF provide **strong evidence for stationarity**

Stationarity: statistical tests

Test	$\mathcal{H}_0$	p-value
KPSS Test	stationnary	0.08026
Augmented Dickey-Fuller	Non stationnary	$<$0.01
Philips-Perron Unit Root test	Non stationnary	$<$0.01

Table: Stationarity tests results

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- The alignment of the results of the 3 tests provides strong evidence for the convergence of the Markov chain to its stationnary distribution.

Estimation of p

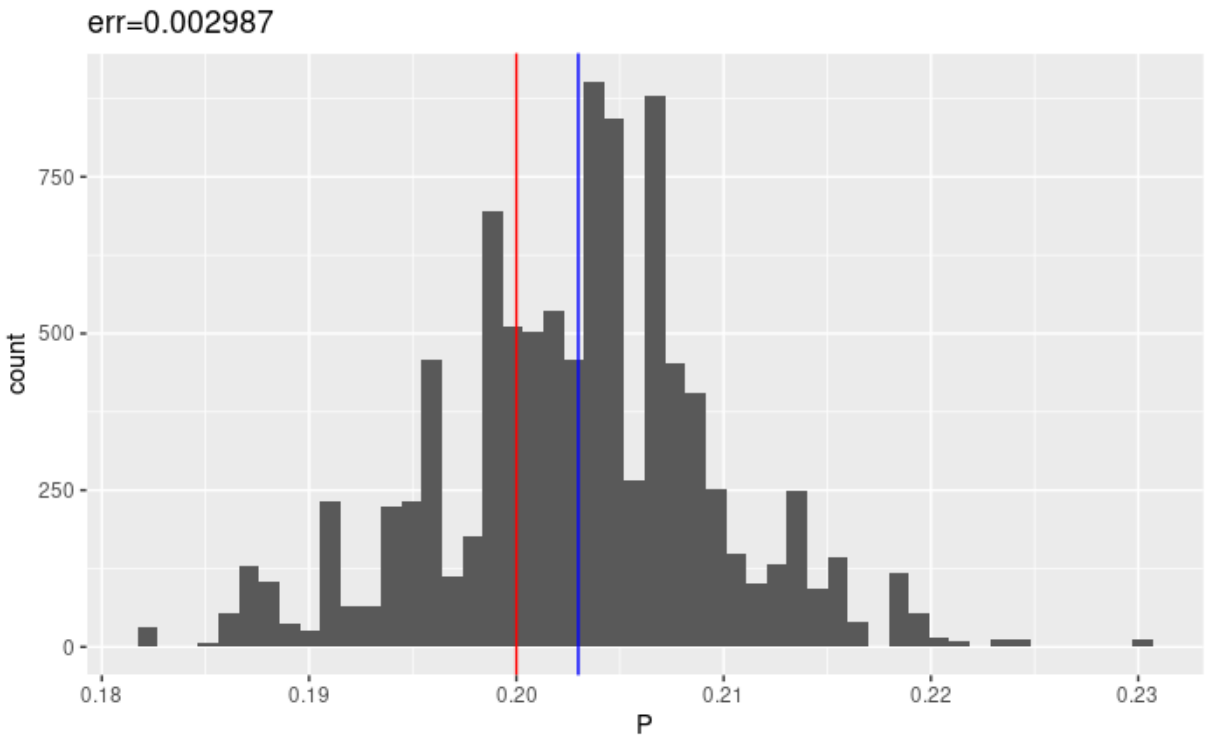


Figure: Histogram of the generated samples for p

- The Bayesian mean estimator(blue) is very close from the exact value(red) $|p - p_{est}| = 0.0029$
- the sampler seems to have very low acceptance since its exploration is only restricted to a narrow interval

Effect of the variance on the acceptance

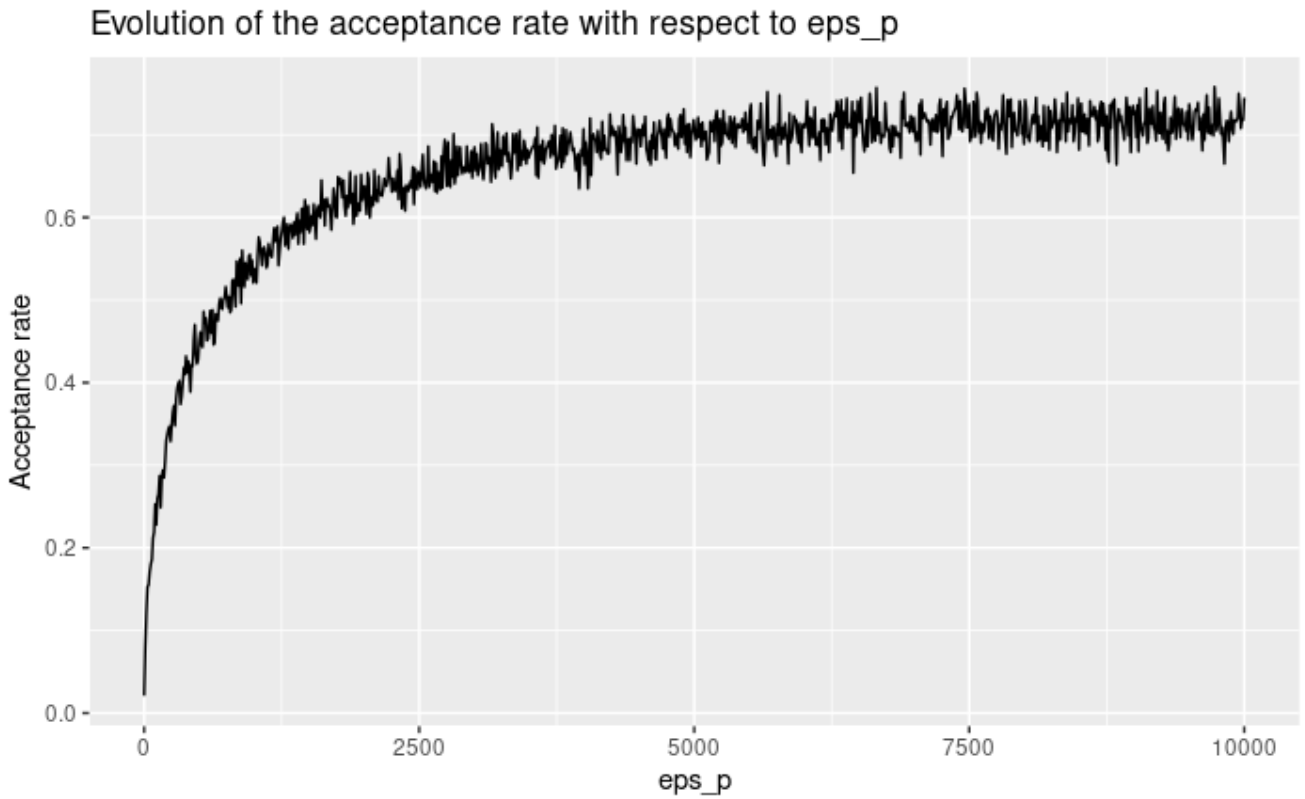


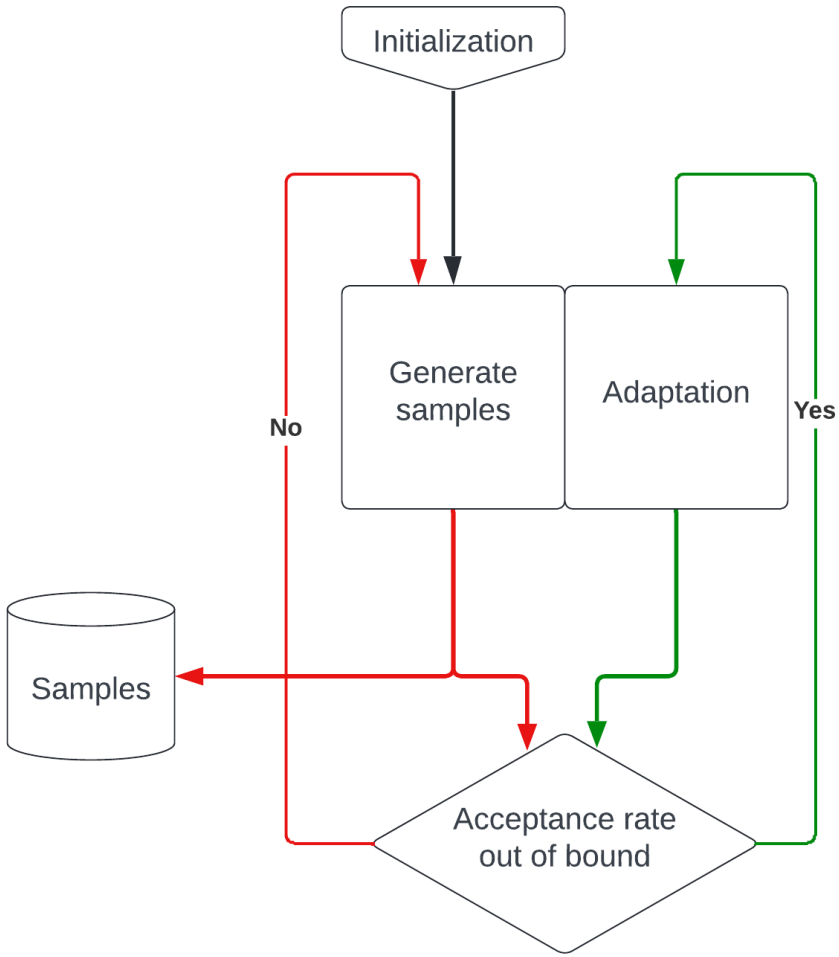
Figure: Evolution of the acceptance rate with the variance of the proposal

- The increase in variance in the proposal enduces an increase in the acceptance rate.

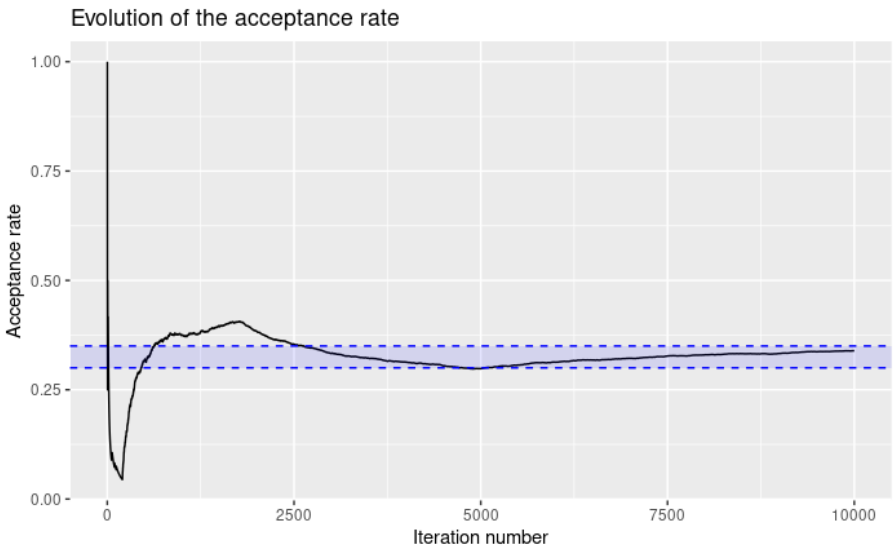
Variance adaptation:

- Too high acceptance means inefficient domain exploration
- Too low acceptance means not enough domain exploration

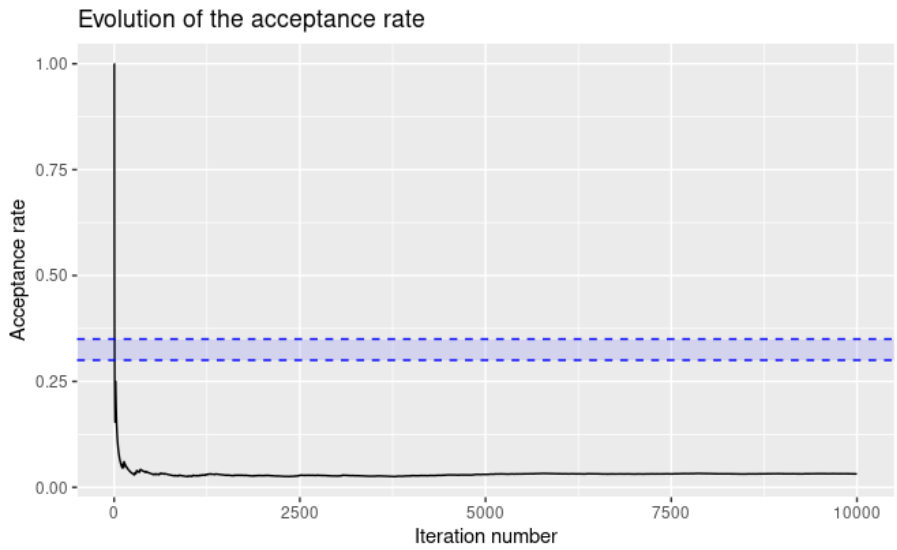
In practice we want the acceptance rate to be between 0.3 and 0.35



Adaptation results



(a) Acceptance rate with adaptation



(b) Acceptance rate without adaptation

- The adaptation scheme works well and ensures that the acceptance is between $0.35 - 0.4$

Results on simulated data

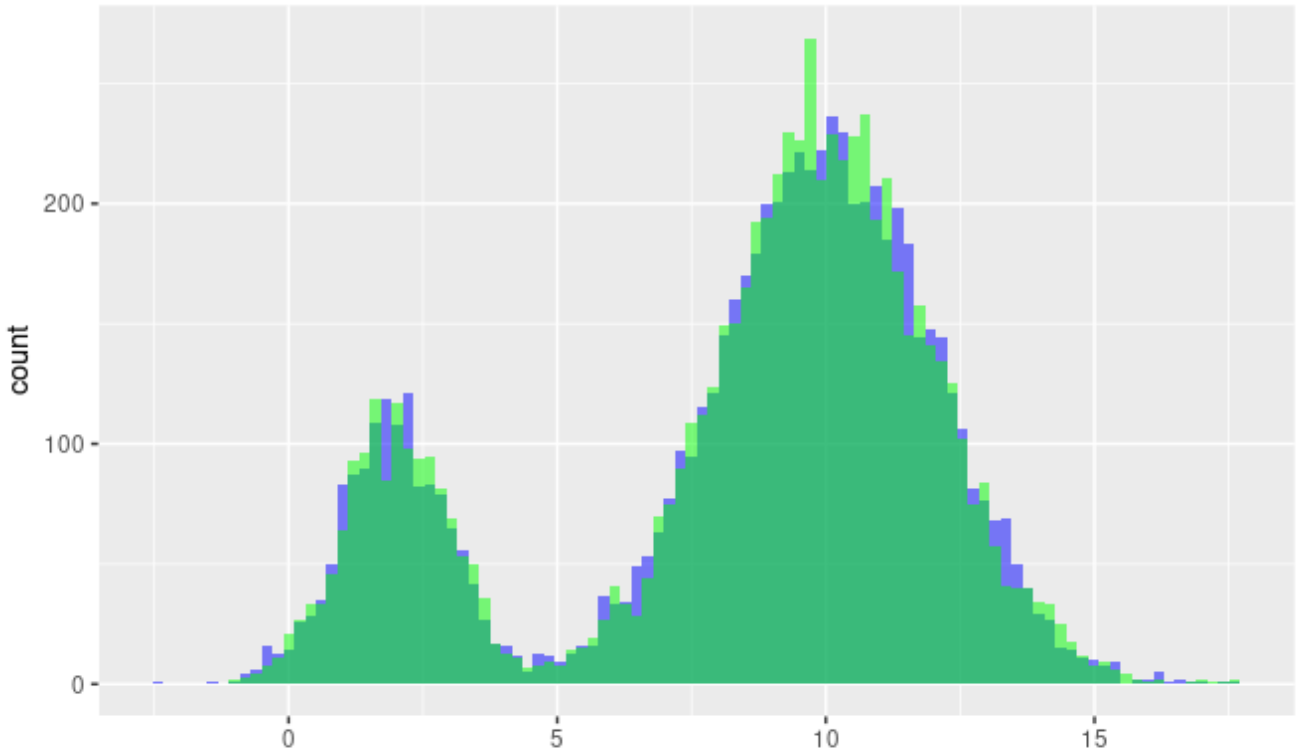
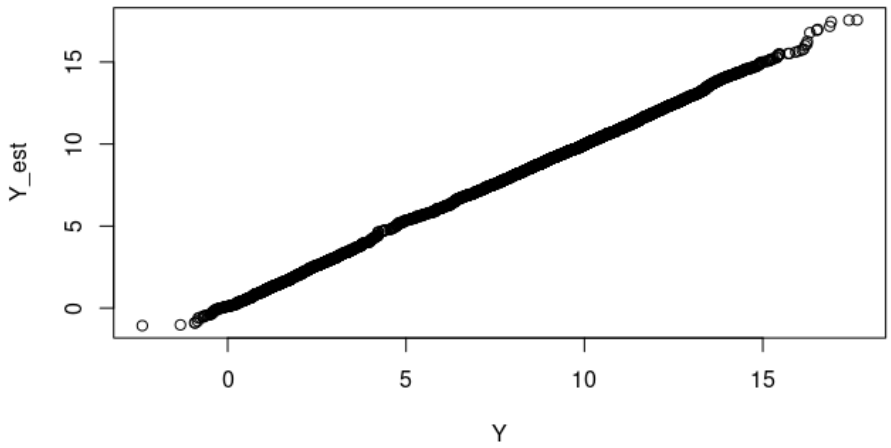


Figure: Histograms of the original (Blue) and simulated (Green) samples

We perform the Kolmogorov-Smirnov test with null hypothesis that the two samples come from the same distribution and get p-value$= 0,55$.

- The test confirms that the two samples are from the same distribution



- The quantiles are aligned in the Q-Q plot which indicates that the two samples come from the same distribution

Results on the FCCSS

$\hat{p}$	$\hat{\sigma}$	$\hat{\mu}$	$\hat{\varphi}$	$\hat{\eta_1}$	$\hat{\eta_2}$
0.107	0.516	3.322	0.643	0.529	0.551

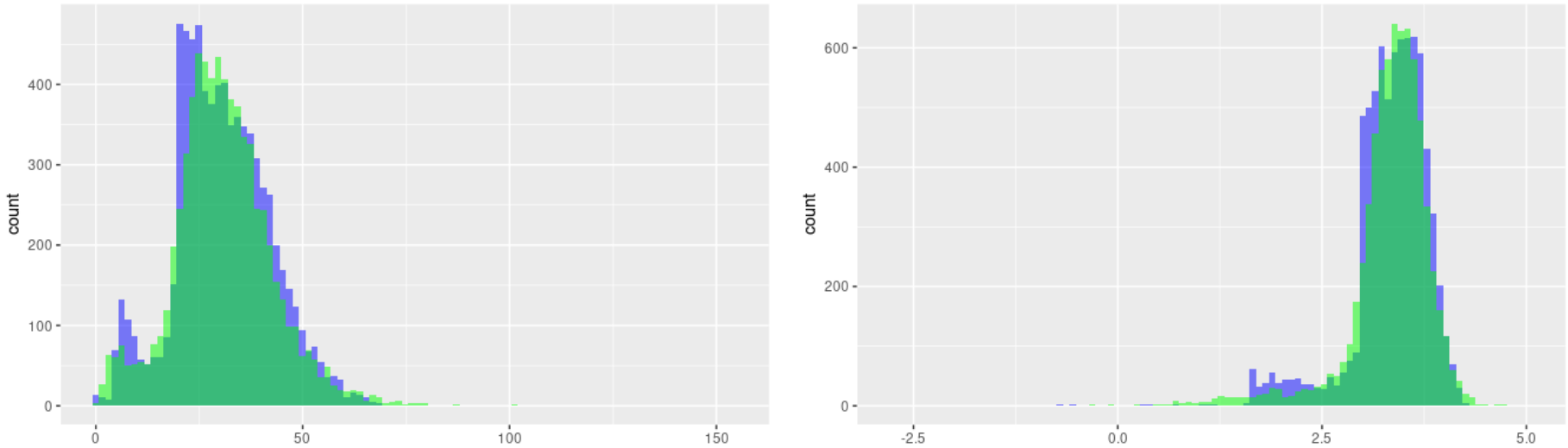
Table: Bayes mean estimators obtained using our algorithm

We used the `Ultimixt`[5] package as a benchmark for our results. The package offers a wide variety of tools to manipulate Gaussian mixture models and got the the following estimates

$\hat{p}$	$\hat{\sigma}$	$\hat{\mu}$	$\hat{\varphi}$	$\hat{\eta_1}$	$\hat{\eta_2}$
0.108	0.519	3.326	0.532	0.532	0.551

Table: Bayes mean estimators using the `Ultimixt` package

Results on the FCCSS



(a) Survival time

(b) Log transformation

- The model fails to detect the first mode of the distribution.
- The model could be improved by using more than two components in the mixture

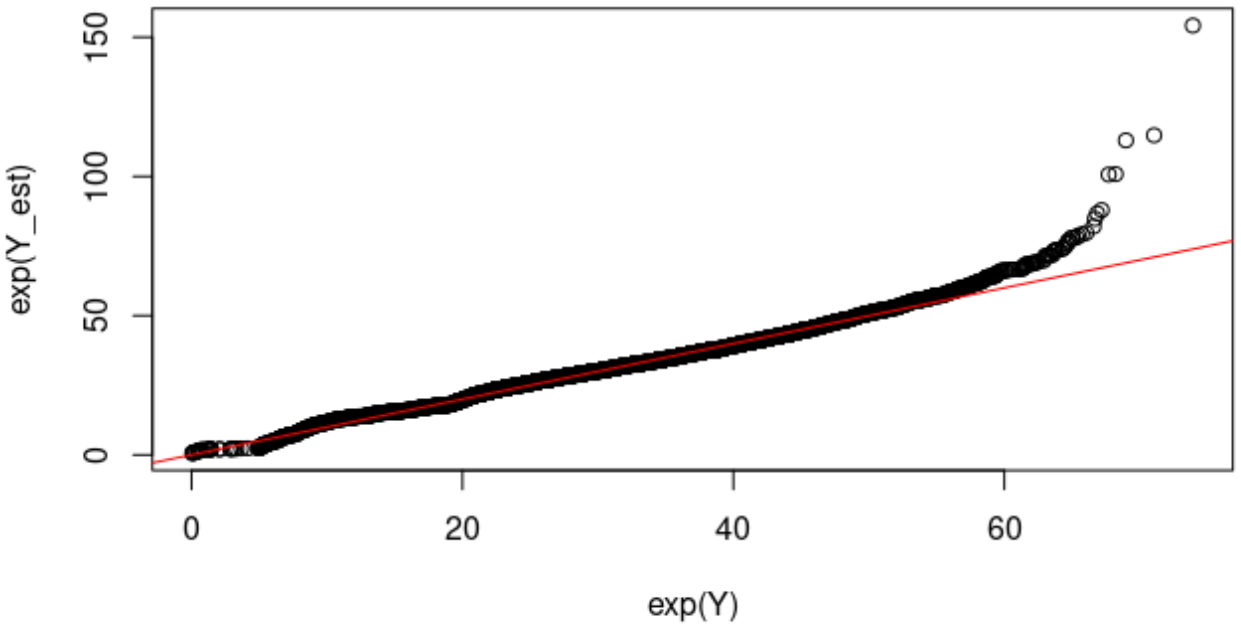
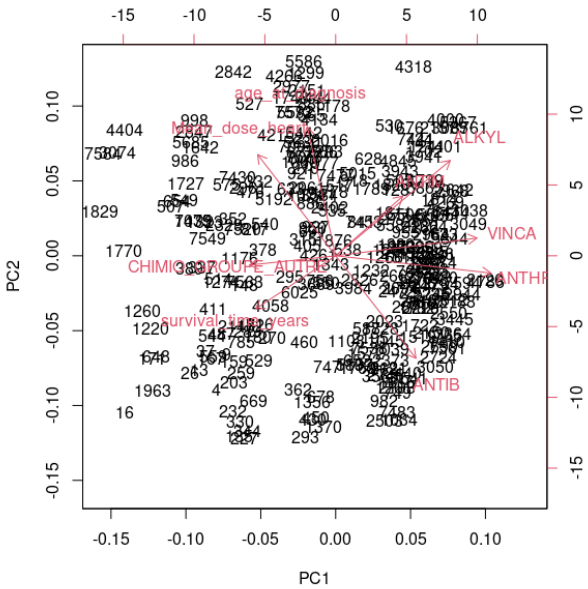
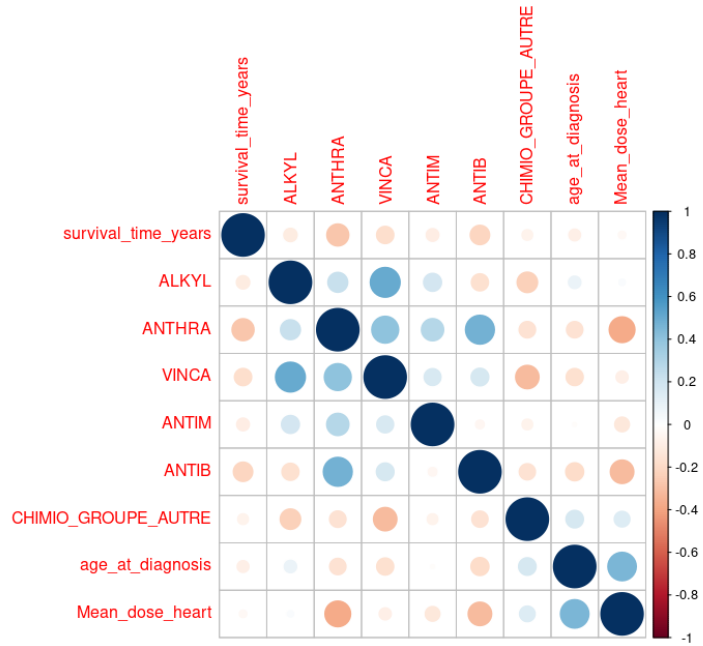


Figure: Q-Q plot of the FCCSS survival time against the simulated survival time

Predictive model for the survival time in the FCCSS



(a) PCA biplot



(b) Correlation matrix

- Weak correlation observed survival time and other variables, including mean dose of radiotherapy to the heart $\Longrightarrow$ Suggests non linearity
- Notable correlation between survival time and 'ANTHRA' and 'ANTIB'.
- Emphasis on studying the impact of chemotherapy dosage as it appears to play a significant role on the survival time.

Predictive model for the survival time in the FCCSS

- The linear model for survival time prediction is not suitable and does not grasp its complexity.
- More exploration of the FCCSS is needed to capture the underlying dynamics and provide better modeling.
- We failed to adapt our implementation of the Bayesian predictor to account for this complexity however we got a fully implemented linear predictor that is still to be tested and validated .

Contributions and perspectives:

At this point, the project is still in its starting phase and we succeeded in:

- Modeling the survival time
- Implementing MCMC methods to identify the survival time's distribution
- Reject the linear model as potential candidate for the survival time

The project as whole is still an ongoing work and further contributions are yet to be made:

- Integration of the linear model estimation in the `Ultimixt` package
- Confrontation of the state of the art survival analysis tools to our Bayesian approach

Thank you for your attention.

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