Prédiction d'événements récurrents en survie

Développement de méthode d'apprentissage et application en oncologie

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En collaboration Cifre avec les laboratoires Pierre Fabre

Outline

1. Motivating clinical data
Motivating clinical context Recurrent events analysis Objectives

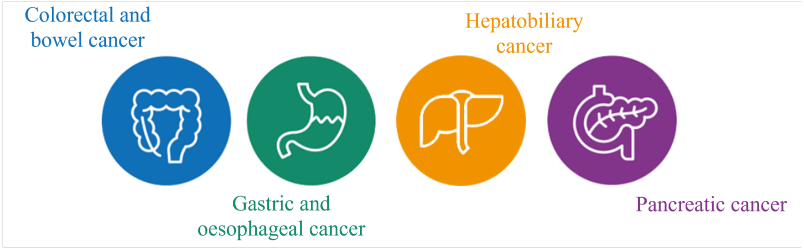
2. Combining statistical inference and ensemble machine learning
The RecForest algorithm Performance evaluation Variable importance To wrap-up

3. Transparent use of survival ML algorithms
Rationale Interpretability for survival ML algorithms

4. Conclusion

01
Motivating clinical data

Digestive Cancer in France



Key Facts

- Among the most frequent cancers, affecting over 70,000 patients annually
- The second leading cause of cancer-related deaths in France
- Surgery is the primary treatment strategy

Public Health Concerns

- What are the outcomes after the initial cancer surgery?
- What is the risk of complications or mortality post-surgery?
- Which factors contribute to readmissions?

Real-World Evidence in Healthcare

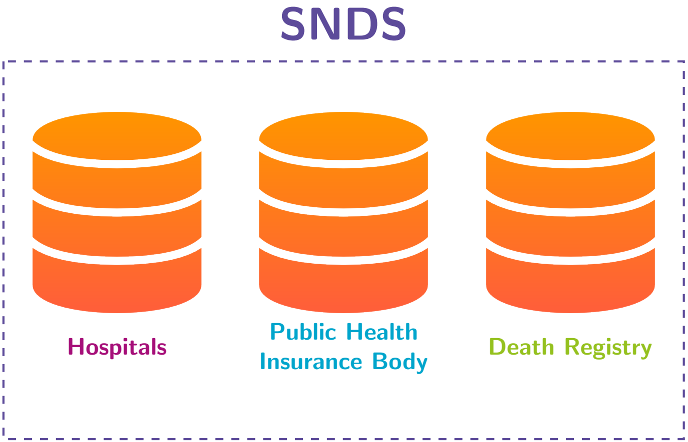
Traditional Research Data Sources

- **Randomized Controlled Trials (RCTs)** are the gold standard for generating healthcare evidence 📘 Hariton & Locascio (2018)
- **Cohorts and Registries** enable prospective collection of data on specific populations 📘 Porta (2014)

Real-World Data

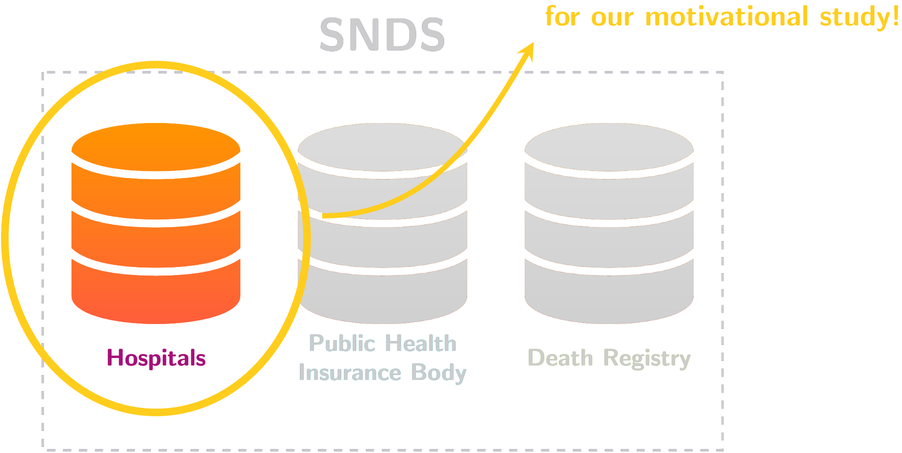
- **Electronic Health Records (EHRs)** contain detailed patient histories, diagnoses, treatments, and outcomes 📘 Gunter & Terry (2005)
- Claims Databases provide billing and reimbursement info, including diagnostic codes, procedures, and prescriptions 📘 Cadarette & Wong (2015)

Claims Databases in France



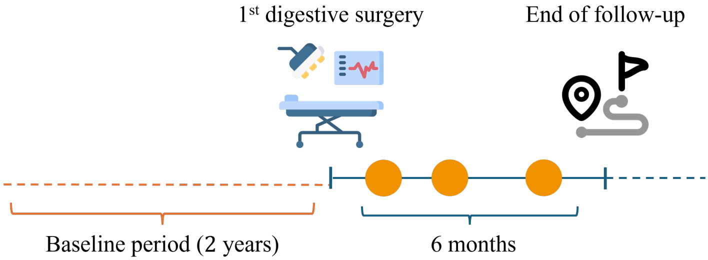
SNDS: Système national des données de santé

Claims Databases in France



SNDS: Système national des données de santé

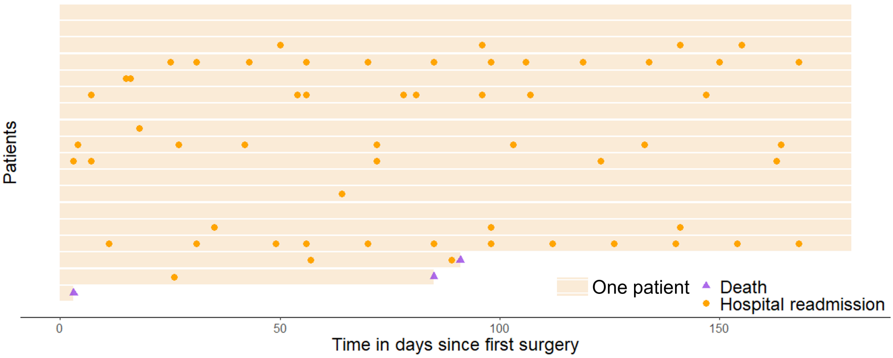
Claims Databases in France – our motivational study



- **P**opulation – adult patients who have undergone digestive surgery (colorectal surgery, small bowel surgery, hepatobiliary surgery, pancreatic surgery, oesogastric surgery)
- **I**ntervention – first digestive surgery between January 2020 and December 2022
- **C**omparator – Not for our study
- **O**utcome – Cumulative number of hospital readmissions over time in a 6-month window

What our data is made of

Subsample of 17/255,732 patients extracted



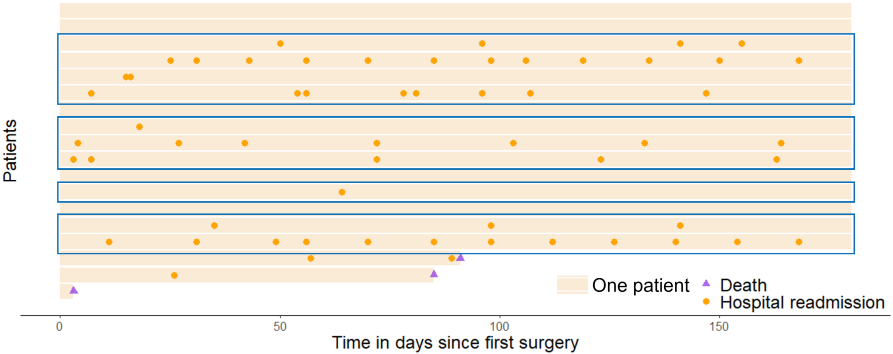
What our data is made of

Subsample of 17/255,732 patients extracted

Patients with **no readmissions** over time

What our data is made of

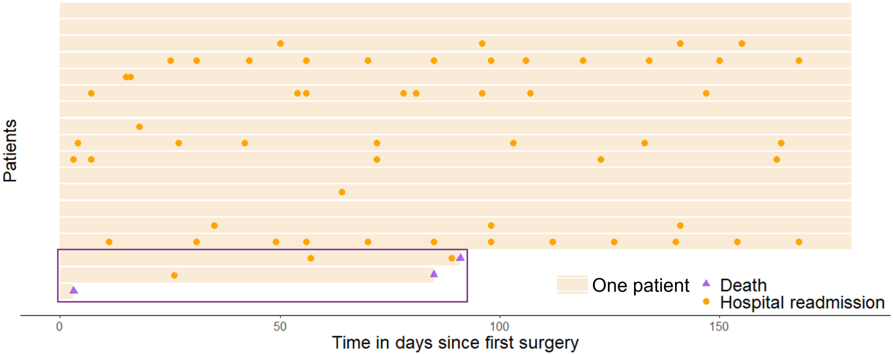
Subsample of 17/255,732 patients extracted



Patients with **one or more readmissions** over time

What our data is made of

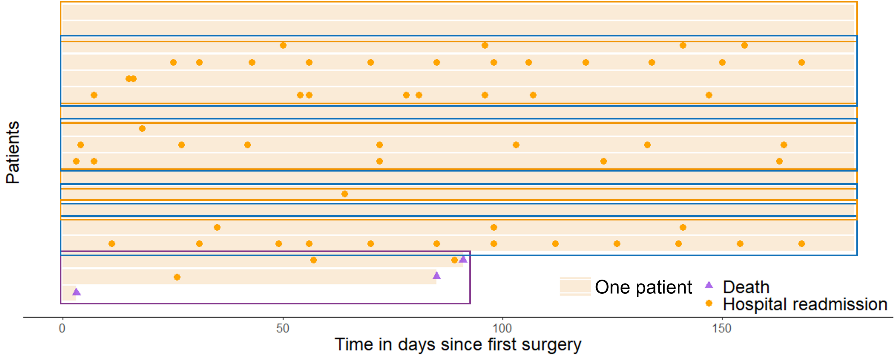
Subsample of 17/255,732 patients extracted



Patients who died during follow-up

What our data is made of

Subsample of 17/255,732 patients extracted



How to analyze multiple hospital readmissions over time for each patient?

What options do we have?

- Focus on the presence of at least one readmission?
  - **Classification** problem, Solution: classifier, **No consideration of multiple events**

- Focus on the number of readmissions at 6 months?
  - **Regression** problem, Solution: regressor, **No consideration of time**

- Focus on time to first hospital readmission?
  - **Survival** problem, Solution: Survival analysis, **No consideration of subsequent events**

- **Focus on time to recurrent readmission**
  - **Survival** problem, Solution: Survival analysis for **recurrent events**

Recurrent events

Definition

Stochastic processes that generate events of the same type repeatedly over time.

No event → First event → Second event →

Censoring

When the **exact** time of an event is **not fully observed** for some subjects **within the study period**

Scientific questions for appropriate endpoints

- A Does the intervention decrease the event number over the study period?
- B How many events does the intervention prevent, on average?
- C What is the intervention effect on the number of subsequent events amongst patients with a preceding event?

1. Cumulative number of events
2. Rate of events
3. Times to successive events
4. Times between successive events

ICH E9 (2019), Schmidli (2023), Wei (2023)

Non-parametric approach

The **Mean Cumulative Function** is the marginal expected number of events in $[0, t]$:

$$\mu(t) = \mathbb{E}[N(t)]$$

MCF Estimator:

total number of events observed over $[t, t + \Delta t)$

$$\hat{\mu}(t) = \int_0^t d\hat{\mu}(u)\, du = \int_0^t \frac{\sum_{i=1}^n Y_i(t) dN_i(t)}{\sum_{i=1}^n Y_i(t)}$$

total number at risk over $[t, t + \Delta t)$

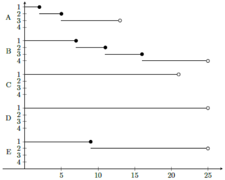
Cook & Lawless (1997)

Modeling strategies

Conditional models

Andersen & Gill (1982), Prentice, Williams & Peterson (1981)

- **Focus: Intensity** – instantaneous probability of observing any event in a small time period $[t; t+)$
- **Time scale: counting process**

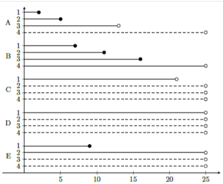


- Dependence structure between recurrent events by **full specification** of the recurrent event process

Marginal models

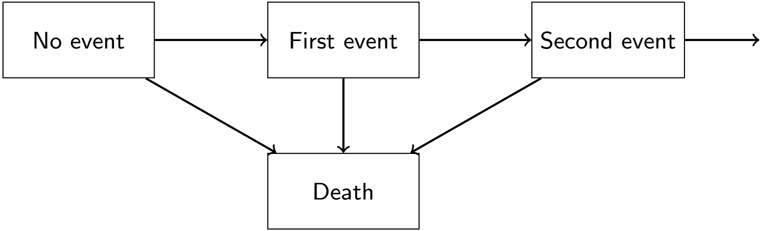
Wei, Lin & Weissfeld (1989), Lee, Wei & Amato (1992)

- **Focus: Marginal features** – marginal distribution of times to the first, second, third, ... event
- **Time scale: total time**



- Dependence structure between successive events may **remain unspecified**

Non-informative censoring ?



= with a **terminal** event

With a Terminal Event

MCF Non-parametric Estimator:

increment
at time u

$$\hat{\mu}(t) = \int_0^t \hat{S}(u-) \frac{\sum_i Y_i(u) dN_i(u)}{\sum_i Y_i(u)}$$

Kaplan-Meier estimator
of survival just before u

Modeling:

$$\mu(t|X) = \begin{cases} \mu_0(t) \cdot \exp(\beta^T X) & \text{if } X \text{ is time-independent} \\ \int_0^t \exp(\beta^T X(s))\, d\mu_0(s) & \text{if } X \text{ is time-dependent} \end{cases}$$

Ghosh & Lin (2000, 2002)

Raising questions – from the statistician's perspective

Key challenges

- How to manage situations with **high-dimensional data**?
- How to handle **multicollinearity** amongst variables?
- How to avoid **overfitting** and ensure reliable **generalization** to new data?

Current insights

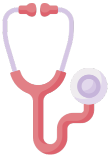
Machine learning (ML) and survival counterparts
However, no ML algorithm *specifically designed* for recurrent events in a survival framework

Murris (2023)

Raising questions – from the user's perspective

"Machine learning is frequently referred to as a black box – data goes in, decisions come out, but the processes between input and output are opaque." The Lancet editorial (2018)

Clinician



Why a treatment is recommended for the patient at hand?

Researcher

Data-induced hypothesis Discovery!

Patient

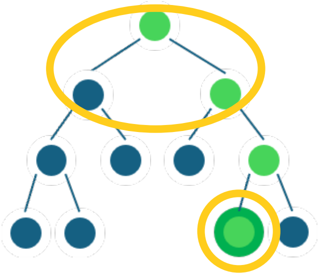
Informed consent
Life-style changes

Objectives

1. Sharpen recurrent events modeling with machine learning
2. Explore conditions for understanding survival machine learning

02
Combining statistical inference and ensemble machine learning

Growing Trees



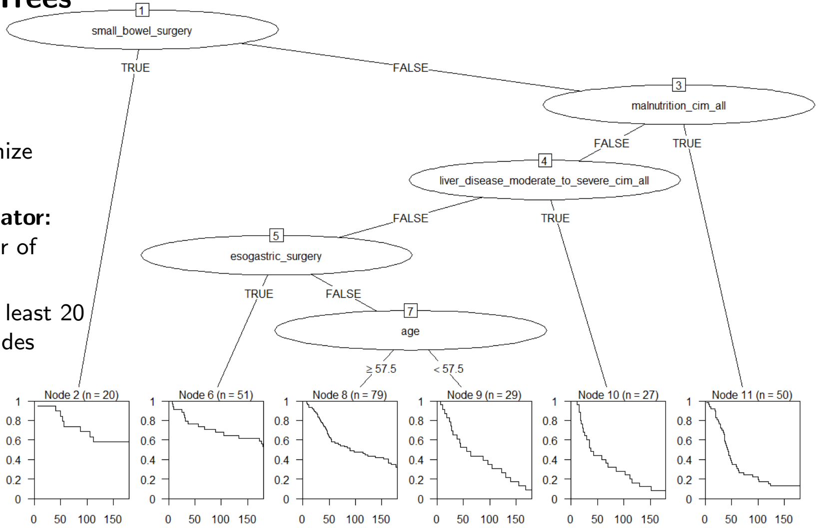
Key Components

- **Splitting Rule:** Identifies the optimal way to partition data at each node.
- **Terminal Node Estimator:** Selects the most suitable estimator to summarize final nodes.
- **Pruning Strategy:** Applies techniques to refine and simplify the tree structure.

Breiman (1996)

Growing Survival Trees

- **Splitting Rule:** Maximize Logrank test statistic
- **Terminal Node Estimator:** Kaplan-Meier estimator of survival function
- **Pruning Strategy:** At least 20 subjects in terminal nodes



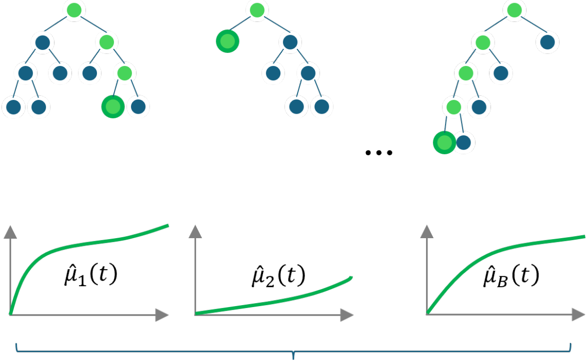
📘 Ishwaran (2008)

Growing Survival Trees with Recurrent Events

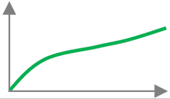
	Without a Terminal Event	**With** a Terminal Event
Splitting Rule	**Maximize the Test Statistic**	
At each node, $m \in \mathbb{N}$ predictors are randomly selected	Pseudo-score test	Wald test from Ghosh-Lin model
Terminal Node Estimator	**MCF Estimator** $\hat{\mu}_b(t\|\mathbf{x})$	
For tree b	$\int_0^t \frac{dN_b(u)}{Y_b(u)}$	$\int_0^t \hat{S}_b(u) \frac{\sum_i Y_{b,i}(u) dN_{b,i}(u)}{\sum_i Y_{b,i}(u)}$
Pruning Strategy	**A Minimal Number of Events and/or Individuals**	

Murris (2024)

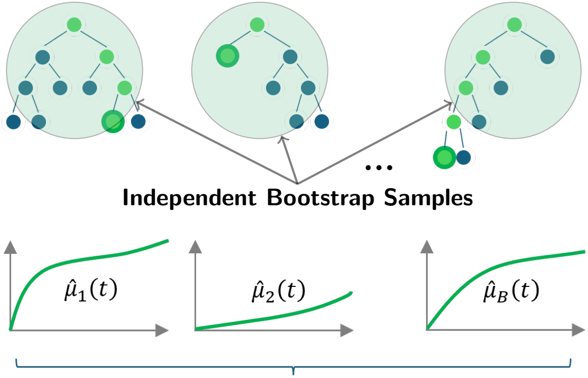
Aggregating to build random forests – RecForest



$$\widehat{\mathrm{M}}(t|\mathbf{x}) = \frac{1}{B}\sum_{b=1}^{B} \hat{\mu}_b(t|\mathbf{x})$$



Aggregating to build random forests – RecForest



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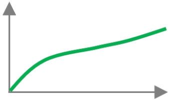
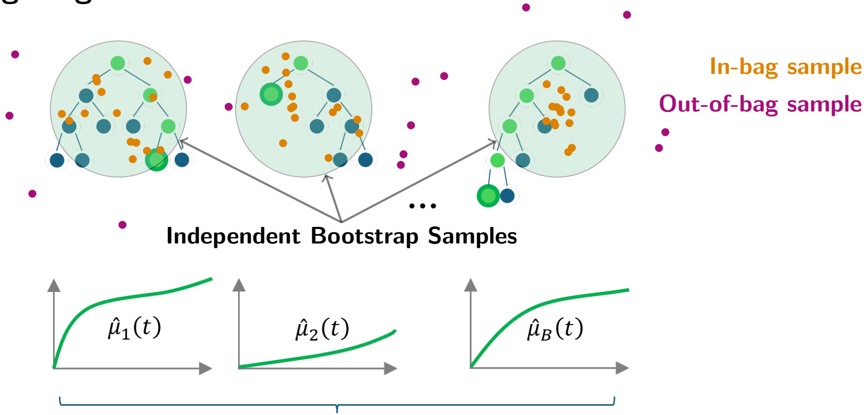


Aggregating to build random forests – RecForest



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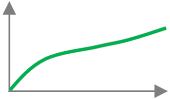
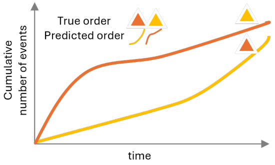


Performance evaluation – (a) The concordance index

- C-index widely used as a performance metric
  Harrell (1982)
- Extension needed to take into account subsequent event occurrences Kim (2018)



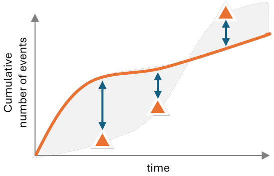
New C-index based on event **occurrence rate** Murris (2024)

$$\hat{\mathbb{C}}_{\text{rec}} = \frac{\sum_{i=1}^{n} \sum_{j=1}^{n} \mathbb{1}_{r_i > r_j} \times \mathbb{1}_{\hat{r}_i > \hat{r}_j}}{\sum_{i=1}^{n} \sum_{j=1}^{n} \mathbb{1}_{r_i > r_j}}$$

with $r_i = \frac{N_i(T_i)}{T_i}$ and $\hat{r}_i = \frac{\hat{\mu}(T_i|\mathbf{x}_i)}{T_i}$ the observed and predicted event occurrence rates, respectively.

Performance evaluation – (b) The mean square error

- No MSE metric for recurrent events until very lately Bouaziz (2024)
- We adapted it for an ensemble framework



For each tree b,

$$\widehat{MSE}_b(t, \hat{\mu}_b) = \frac{1}{n} \sum_{i=1}^{n} \left(\int_0^t \frac{dN_i(u)}{\hat{G}_c(u|\mathbf{x})} - \hat{\mu}_b(t|\mathbf{x}) \right)^2$$

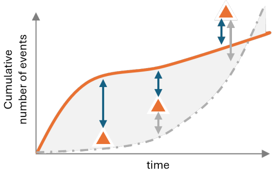
Where $\hat{G}_c(u|\mathbf{x}) = 1 - \hat{G}(u - |\mathbf{x})$ is an estimator of $G_c(u|\mathbf{x}) = 1 - G(u - |\mathbf{x})$, the conditional cumulative distribution function of the censoring variable C given $\mathbf{x}$.

Therefore:

$$\widehat{MSE}(t, \hat{M}) = \frac{1}{B} \sum_{b=1}^{B} \widehat{MSE}_b(t, \hat{\mu}_b)$$

Performance evaluation – (c) The score

But ✋
Two different models may lead to similar MSE values over time.



Need for a score to represent the prediction gain compared to a reference estimator $\hat{\mu}_0$ and we define for each tree b

$$Score_b(t, \hat{\mu}_b, \hat{\mu}_{b,0}) = \widehat{MSE}_b(t, \hat{\mu}_{b,0}) - \widehat{MSE}_b(t, \hat{\mu}_b)$$

Therefore:

$$Score(t, \hat{M}) = \frac{1}{B} \sum_{b=1}^{B} Score_b(t, \hat{\mu}_b, \hat{\mu}_{b,0})$$

Performance evaluation – Integrated counterparts

But ✋
There is a need for the estimation of the expectation of single-time MSE and derived score over time (e.g. hyperparameter tuning, generalized metric, etc.)

$$\begin{cases} \widehat{IMSE}(\tau_1, \tau_2, \hat{M}) & = \frac{1}{\tau_2 - \tau_1} \int_{\tau_1}^{\tau_2} \widehat{MSE}(t, \hat{M}) dt \\ IScore(\tau_1, \tau_2, \hat{M}) & = \frac{1}{\tau_2 - \tau_1} \int_{\tau_1}^{\tau_2} Score(t, \hat{M}) dt \end{cases}$$

With $\tau_1 = 0$ and τ_2 the maximum event time on the original sample.

Importance of Variables

Input: Trained model $\hat{f}$, variable matrix X, target vector y

1. Estimate the original model error err_{OOB} from a chosen evaluation metric
2. For each feature $j \in \{1, \ldots, p\}$ do:
   - Generate feature matrix X^{perm} by permuting feature j in the data X ← *This breaks the association between j and y*
   - Estimate error $\widehat{err}_{OOB}^{X^{\text{perm}}}$ based on the predictions of the permuted data
   - Calculate permutation variable importance over B trees as:

$$VImp(j) = \frac{1}{B} \sum_{b=1}^{B} (\widehat{err}_{OOB}^{X^{\text{perm}}} - err_{OOB})$$

Output: Importance scores for all variables

Application to French Digestive Cancer Data

Table: Performances

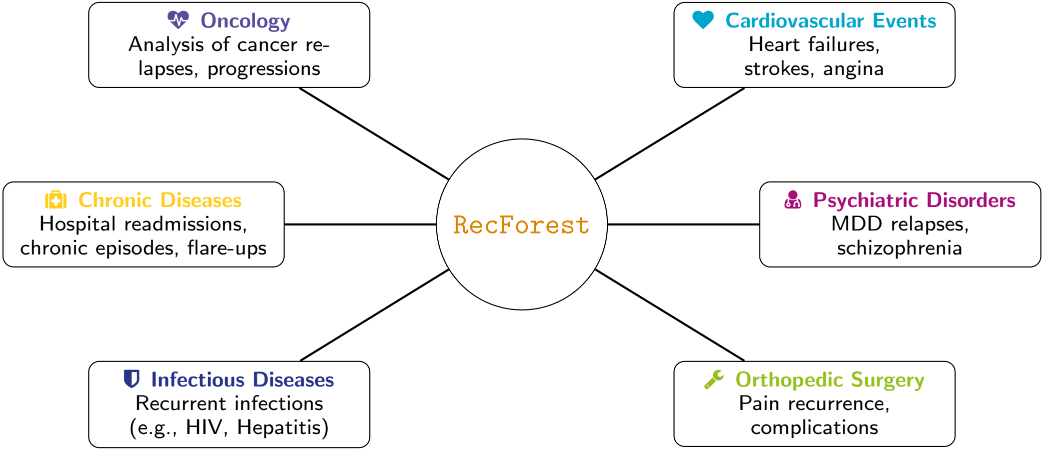
	C-index ↑	IMSE ↓	IScore ↑
`RecForest`	0.72	1,398.04	409.32
Np estimator	0.52	3,773.21	ref.

Importance of Variables

Demographics, ICD-10 codes, Procedures, Comorbidity indices, Surgery types

- **Most important**: $\%V_{\text{imp}} \geq 4\%$
- **Moderately important**: $1\% \leq \%V_{\text{imp}} < 4\%$
- **Least important**: $\%V_{\text{imp}} < 1\%$

Multiple Medical Applications of RecForest

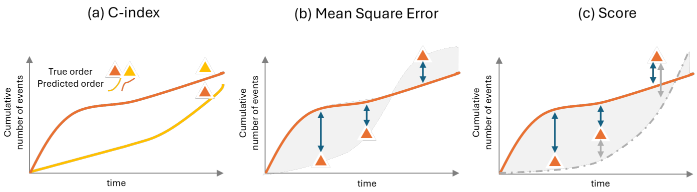


To Wrap-Up – Key Takeaways

RecForest

- **Non-Parametric** when no terminal event
- **High-Dimensional Data**
- **Robust to Multicollinearity**
- **Variable Importance**

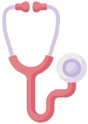
3 metrics for performance evaluation



- A **powerful and flexible tool** for recurrent events analysis in **many medical fields**
- Allows for potential **extensions**, e.g. tree-based boosting techniques

03
Transparent use of survival ML algorithms

Why?



Users need

- **Transparency**: Better understand *how* the model makes predictions
- **AI-based decision-making risk understanding**: *Assessment*, *management* and *quantification*
- **Bias handling**: Ensure the model doesn't learn *unintended biases*
- **Scientific discovery**: Gain *insights* and uncover *new knowledge* from the model

Liao (2020), Markus (2021), Farah & Murris (2023)

What?

Model explainability

- Intrinsically understandable model

OR

- Non-understandable model complemented with understandable and faithful explanations

Explanation interpretability

- Unambiguous explanation

AND

- Avoid cognitive overload to foster understanding

Markus (2021)

What?

Model explainability

- Intrinsically understandable model

OR

- Non-understandable model complemented with understandable and faithful explanations

Explanation interpretability

- Unambiguous explanation

AND

- Avoid cognitive overload to foster understanding

Interpretability methods

Markus (2021)

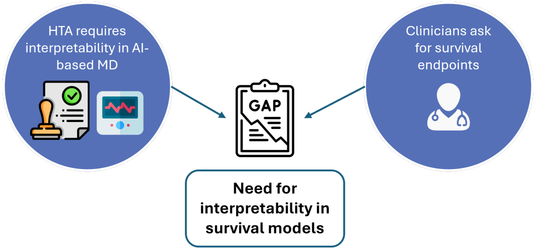
How?

Interpretability methods from the literature

- Global feature importance: Identifies impactful features at the population scale
- Local feature importance: Focuses on features at the most granular scale
- Model-agnostic method: Applicable regardless of the assessed model
- Post-hoc method: Applied on top of model inference

Guidotti (2019), Miller (2019), Ali (2023)

Gap identified in survival problems



HTA: Health Technology Assessment; MD: Medical Device.

Widely adopted interpretability methods:

- LIME and SHAP
- Over **6,000** citations in PubMed.

However, for survival problems:

- SurvLIME and SurvSHAP are natural extensions
- Only **4** citations in PubMed*.

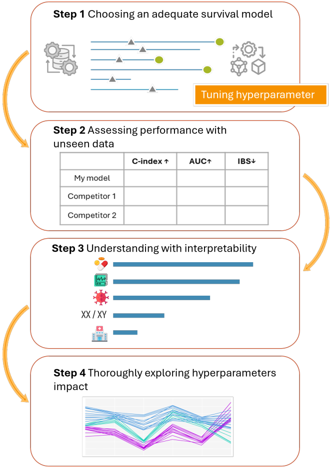
*While *'survival machine learning'* gets 10,745 hits since 2020

Ribeiro (2016), Lundberg & Lee (2017), Kovalev (2020), Krzyziński (2023)

A Comprehensive Tutorial for Interpretability in Survival ML

Our 4-Step Approach

1. **Model Selection and Tuning:** Choose and fine-tune a survival model adapted to data characteristics
2. **Model Evaluation:** Ensure accuracy and reliability with metrics such as C-index, AUC, and IBS
3. **Interpretability Methods:** Explore advanced tools like `SurvLIME` and `SurvSHAP`
4. **Impact of Hyperparameters:** Demonstrate how hyperparameters influence model efficiency and complexity



Murris (2024b)

04
Conclusion

To wrap-up

1 Sharpen recurrent events modeling with machine learning

- *Identified a gap* in handling both recurrent event data and statistical learning Murris (2023)
- Developed `RecForest`: An extension of the Random Survival Forests algorithm to handle recurrent events, *with or without a terminal event* Murris (2024)
  - Refine the splitting rule and terminal node estimation
  - Provide appropriate metrics and error evaluation methods
  - Adjust variable importance calculations accordingly

2 Explore conditions for understanding survival machine learning

- Assessed *evaluation criteria of ML algorithms* by Health Technology Assessment bodies Farah & Murris (2024)
- Developed **ready-to-use tools** to consider interpretability methods for survival problems Murris (2024b)

Take home messages

From the statistician's perspective

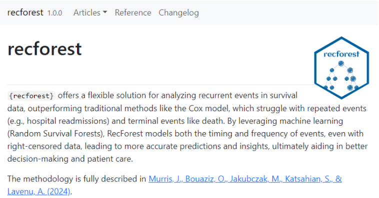
From the user's perspective

What is the **research question**?

Give attention to **recurrent events** analysis!

Care about **transparency**, **explainability** and **interpretability**

Next Steps



recforest 1.0.0 Articles Reference Changelog

recforest

`{recforest}` offers a flexible solution for analyzing recurrent events in survival data, outperforming traditional methods like the Cox model, which struggle with repeated events (e.g., hospital readmissions) and terminal events like death. By leveraging machine learning (Random Survival Forests), RecForest models both the timing and frequency of events, even with right-censored data, leading to more accurate predictions and insights, ultimately aiding in better decision-making and patient care.

The methodology is fully described in Murris, J., Bouaziz, O., Jakubczak, M., Katsahian, S., & Lavenu, A. (2024).

`RecForest` **development:**
R package in progress!
Made possible by Guillaume D (Pierre Fabre)

Application on French Hospital Data:
Our study on post-operative readmissions in digestive cancer is on track
In collaboration with Stylianos T (AP-HP) and Pierre Fabre

Tree-based model-specific interpretability method for survival outcomes:
Project shaping up, submitted for ENSAE work
Kudos to Lucas D (Inria) for handing over

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Merci

Appendix I – Modeling recurrent events, conditional models

- **Poisson models:**

$$\alpha_{j(j+1)}(t) = \alpha_0(t) \cdot r(\beta, X(t)) \quad \text{or} \quad \alpha_{j(j+1)}(t) = \alpha_0 \cdot r(\beta, X)$$

  with β as the regression coefficient and $r(\beta, X)$ the relative risk function.

- **AG model:**

$$\alpha_{j(j+1)}(t) = \alpha_0(t) \cdot r(\beta, X(t))$$

- **PWP-CP model:**

$$\alpha_{j(j+1)}(t) = \alpha_0(t) \cdot r(\beta, X(t))$$

- **PWP-GT model:**

$$\alpha_{j(j+1)}(t) = \alpha_0(t) \cdot r(t - T_{N(t-)}, \beta, X(t))$$

- **NB models:**

$$\alpha_{j(j+1)}(t \mid U) = U \cdot \alpha_0(t) \cdot r(\beta, X(t)) \quad \text{or} \quad \alpha_{j(j+1)}(t \mid U) = U \cdot \alpha_0 \cdot r(\beta, X)$$

  where U is a gamma-distributed random effect.

Appendix II – Theoretical MSE Criterion with Known Censoring Distribution

We introduce a theoretical criterion that would be available if the censoring distribution was known. For some function $\mu \in \mathcal{M}$, let:

$$MSE(t, \mu) = \mathbb{E}\left[\left(\int_0^t \frac{dN(u)}{G_c(u \mid \bar{X}(u))} - \mu(t \mid \bar{X}(t))\right)^2\right] \tag{1}$$

The crucial idea behind this comes from the fact that:

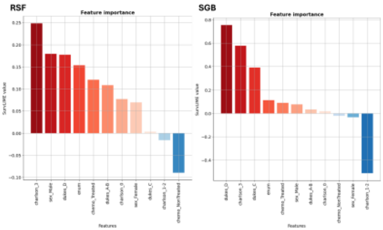
$$\mathbb{E}\left[\int_0^t \frac{dN(u)}{G_c(u \mid \bar{X}(u))}\right] = \mathbb{E}[\mu^*(t \mid \bar{X}(t))] \tag{2}$$

demonstrated in Bouaziz (2024)

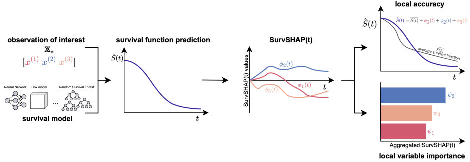
Appendix III – SurvLIME and SurvSHAP

SurvLIME

- Local explanation method for survival models
- Perturbs the input data and fits a simple interpretable model (e.g., linear regression) to approximate the model's behavior around a specific instance.



SurvSHAP



- Global and local interpretability method based on Shapley values
- Calculates the contribution of each feature to the prediction by considering all possible feature combinations