The Patient Path: a first approach

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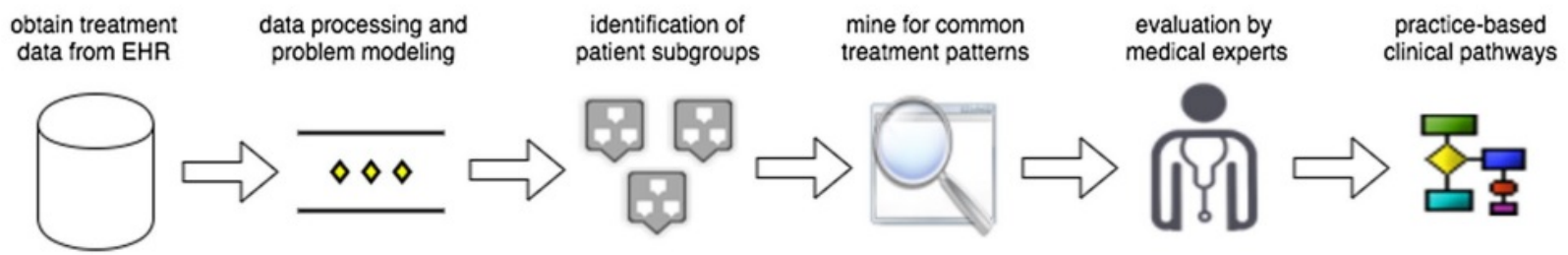
Collaboration between mathematicians and physicians

Patients pathways motivations

$\rightsquigarrow$ The aging of the population.
$\rightsquigarrow$ The increase in chronic diseases and patients suffering from multi-morbidity.
$\rightsquigarrow$ Financial resources and human constraints.
$\rightsquigarrow$ A considerable proportion of patients who do not receive appropriate evidence-based care because of unwarranted variation.

The quality of care patients is organised in a suboptimal way.

Main goal


obtain treatment data from EHR
data processing and problem modeling
identification of patient subgroups
mine for common treatment patterns
evaluation by medical experts
practice-based clinical pathways

Example: pre and post-surgery measures

Dataset: diagnoses, medical acts, UFs, authorization,...

Measures

ID_INTERVENTION	PARAMETRE	VALEUR	ID_UNITE	DATE_MESURE
661121	FcECG	116	3	03/02/2018 05:45
661121	FcECG	111	3	03/02/2018 05:45
661121	FcECG	109	3	03/02/2018 05:46
661121	FcECG	114	3	03/02/2018 05:47
661121	FcECG	103	3	03/02/2018 05:47
661121	FcECG	109	3	03/02/2018 05:48
661121	FcECG	104	3	03/02/2018 05:48
661121	FcECG	108	3	03/02/2018 05:48
661121	FcECG	106	3	03/02/2018 05:49

Patients

ID_PATIENT	DATE_NAISSANCE	SEXE
291743	1943-08-17	F
160413	1964-10-07	F
212991	1963-03-06	F
196615	1994-07-30	F
298214	1948-07-31	M
181364	1966-05-22	F
203297	1982-10-23	F
243583	1974-02-20	F
273458	1982-02-28	F

Procedures

ID_PATIENT	ID_INTERVENTION	POIDS	TAILLE	IMC	ASA	URGENCE	SERVICE_NM	SERVICE	DATE_INTERVENTION	ID_SEJOUR
4	347816	NA	NA	NA	1	0	46	Chir PÃ©diatrique	14/05/2011 08:20	66127
4	379043	39	159	15,4	2	0	46	Chir PÃ©diatrique	03/12/2011 09:03	90892
7	659230	64	157	25,9	2	0	14202	Bloc spe 1280	08/02/2016 08:05	310497
16	333480	90	152	38,9	2	0	44	CMCA	22/02/2011 09:21	54772
20	555366	67	180	20,6	1	0	32	ORL	05/08/2014 08:10	226258
21	288766	77	178	24,3	2	0	31	Bloc Commun	18/06/2010 12:31	22008
21	330430	NA	NA	NA	1	0	49	Traumatologie	12/02/2011 08:04	52301

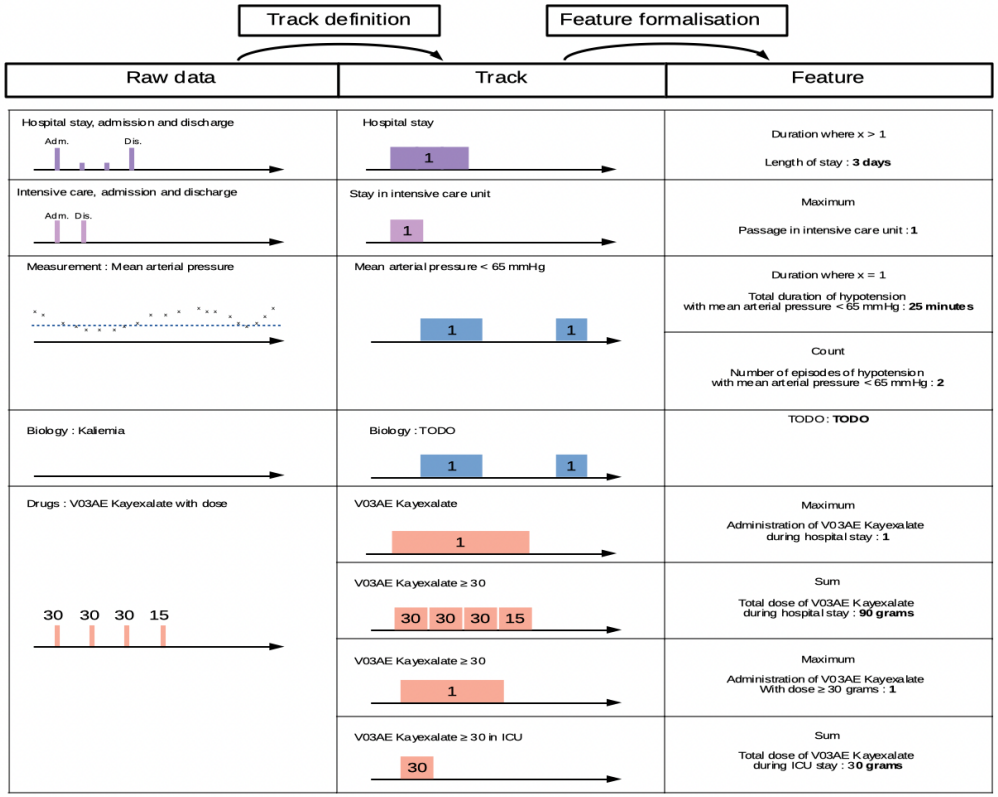
Stays

LIB_MODE_ENTREE	LIB_MODE_SORTIE	DATE_ENTREE_SEJOUR	DATE_SORTIE_SEJOUR	ID_SEJOUR
Domicile urgences	Domicile	2016-05-11	2016-05-12	326816
Domicile urgences	Mutation mco	2012-07-31	2012-08-03	122966
		NA	NA	256870
		NA	NA	29320
Domicile	Mutation mco	2010-02-21	2010-03-13	8746
		NA	NA	299
Domicile urgences	Mutation mco	2010-01-07	2010-01-13	2587
Domicile urgences	Mutation mco	2009-12-10	2010-01-07	1186

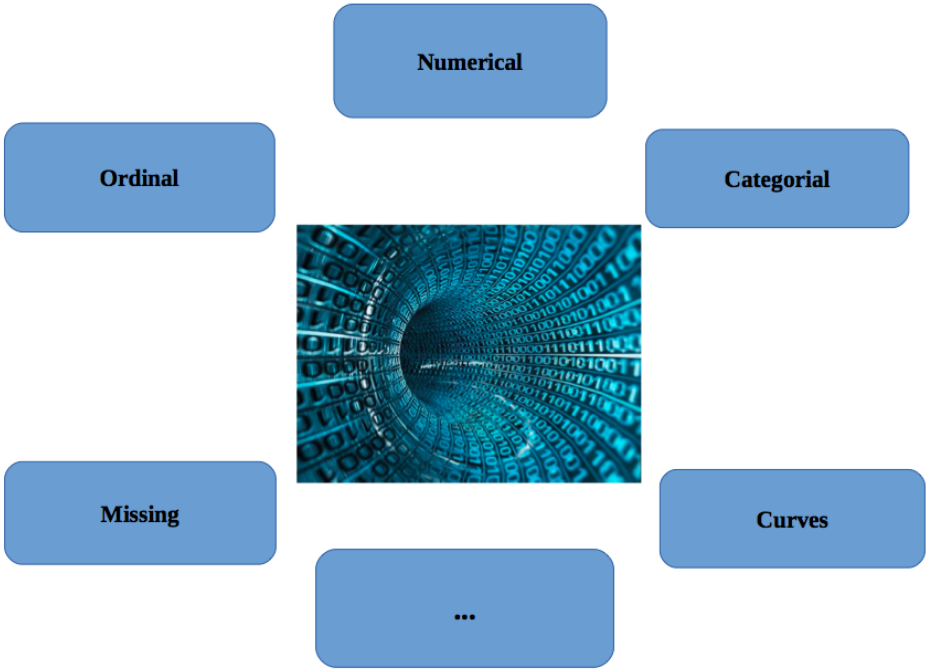
Data from diverse sources

- Data supplemented by those from the EDS of the Lille University Hospital; and from the National Health Data Hub (SNDS, Health Data Hub)
- Routine data of more than 1.5 million patients over the last 12 years
- From a software collecting medical acts, diagnoses, drug administration, the results of medical biology, visits to the care units (and the severity of the unit), vital signs, the evaluation scales, and all the textual data

Data Extraction

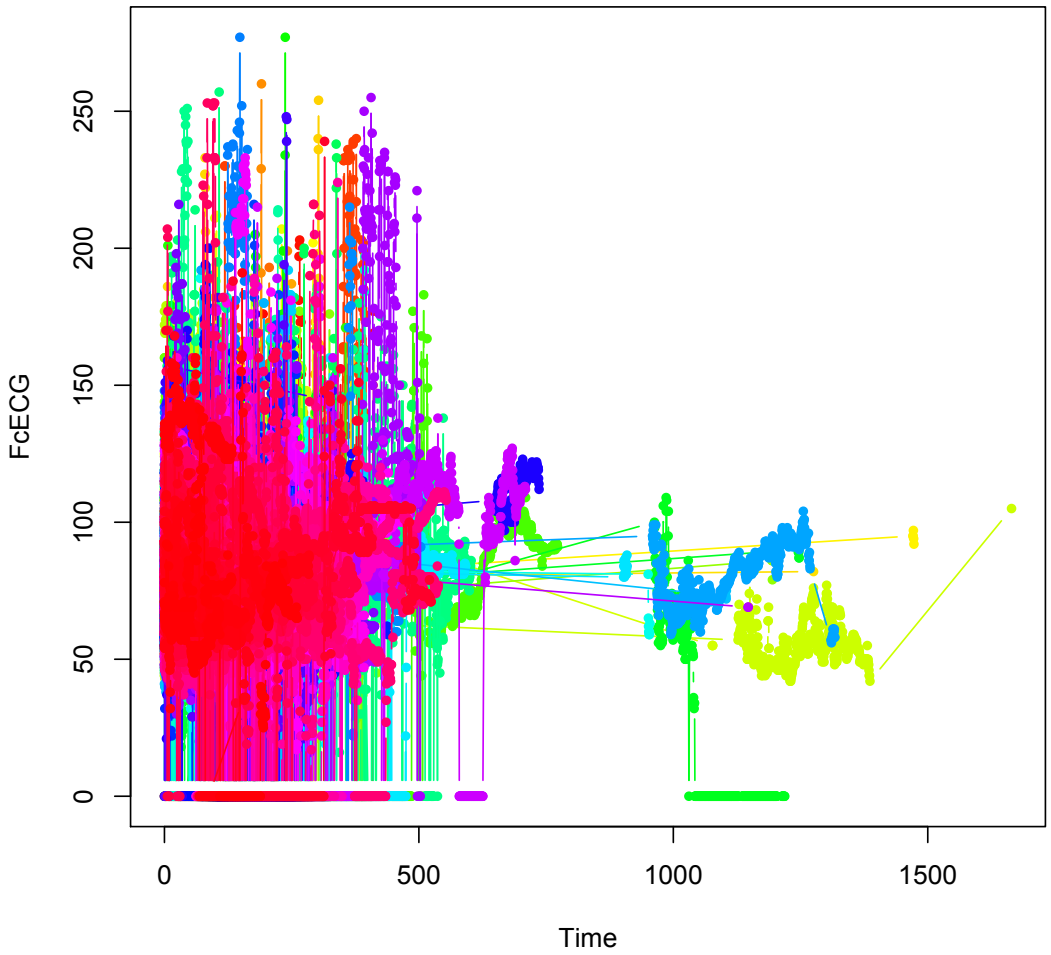


Complex, Multidimensional data: time, space



How to combine different types of the data for a physician decision making?

Simple example: Time evolution of FcECG during surgery



From original data to observation of patient path random variable?

A Patient path as observation of a random variable valued in a (complex) space of paths :

$$\mathbf{Y_t} = \left\{ \left(Y_{t_1}, ..., y_{t_d} \right)^\top \ : \ t_j \in \mathcal{T}_j, j = 1, ..., d \right\},$$

$$Y_{t_j} : \mathcal{P}_j \to \mathcal{S}_j$$

$\mathcal{T}_j \subseteq \mathbb{R}$, $\mathcal{S}_j = \mathbb{R}$ (curve)
$\mathcal{T}_j \subseteq \mathbb{R}$, $\mathcal{S}_j = \{e_1, e_2, \ldots, e_K\}$ (sequence)
$\mathcal{T}_j \subseteq \mathbb{R}^2$, $\mathcal{S}_j = \mathbb{R}$ (image/surface)
...

First goal : clustering

How to construct a generic model for irregularly stamped multivariate mixed functional data with missing values to perform clustering. Application: identify subgroups of patients?

Existing functional data clustering approaches

- The two-stage methods (dimension reduction+multivariate clustering): Kayano et al. (2010); Peng and Muller (2008); Rossi et al. (2004), Abraham et al. (2003),...
- Nonparametric methods (with distances or dissimilarities): Ieva et al (2012); Tokushige et al. (2007); Dabo-Niang et al. (2007); Ferraty and Vieu (2006); Tarpey and Kinateder (2003),...
- Nonparametric methods (heuristics or geometry criteria): Hébrail et al (2010), Yamamoto (2012),...
- Model-based approaches: Bouveyron and Jacques (2011); Chiou and Li (2007); Jacques and Preda (2013); James and Sugar (2003);...
- Raw data approach (discretized times): Bouveyron and Brunet (2012).

Model-based approach for irregularly stamped multivariate and mixed functional data

Recent works using Gaussians processes:

- clustering functional univariate categorical data : Preda et al. (2021)
- clustering functional univariate continuous data : **Leroy et al. (2020)**; Murphy and Murphy (2020)
- supervised learning for continuous multivariate functional data : Constantin et al. (2020)

State of the art

$\rightsquigarrow$

Introduction of Gaussian processes: Wiener, 1949.

$\rightsquigarrow$ Study of Gaussian processes: Thompson, 1956; Matheron, 1973; Cressie, 1993.

$\rightsquigarrow$ Application to the development of learning methods for regression problems O'Hagan, 1978; Williams and Rasmussen, 1996.

First approach for univariate continuous case: Leroy et al (2020)

Fix $n, K \geq 1$, $T > 0$ and $l_1, ..., l_n$.
Data is collected from n different patients. For $1 \leq i \leq n$, set:

- $t_i = (t_{i,1}, ..., t_{i,l_i}) \in [0, T]^{l_i}$: the observation times of patient i.
- $Y_i(t_{i,l_i}) \in \mathbb{R}$.
- Gaussian process mixture model:
  - we associate a latent binary random vector $Z_i = (Z_{i1}, ..., Z_{iK})$ to each individual, indicating in which cluster it belongs: if the $i-$th individual comes from the $k-$th cluster, then $Z_{ik} = 1$ and 0 otherwise.
  - Assume that these latent variables are coming from the same multinomial distribution: $Z_i \sim \mathcal{M}(1, \pi)$, $1 \leq i \leq n$, with $\pi = (\pi_1, \cdots, \pi_K)^t$ and $\sum_{k=1}^{K} \pi_k = 1$.

First approach for univariate continuous case: Leroy et al (2020)

Assume that the i–th individual belongs to the k–th group, let the data observed at time t be as observation of a sum of a cluster-specific mean process and an individual-specific centered process:

$$Y_i(t) = \mu_k(t) + f_i(t) + \varepsilon_i(t), \ \ t \in [0, T].$$

Hypotheses

For $1 \leq i \leq n$, and $1 \leq k \leq K$,

$\rightsquigarrow$ $\mu_k(\cdot) \sim \mathcal{GP}(m_k(\cdot), c_{\gamma_k}(\cdot,\cdot))$: common mean process of the $k-$ cluster,

$\rightsquigarrow$ $f_i(\cdot) \sim \mathcal{GP}(0, A_{\theta_i(\cdot,\cdot)})$: specific process of the $i-$ individual,

$\rightsquigarrow$ $\varepsilon_i(\cdot) \sim \mathcal{GP}(0, \sigma_i^2 I)$: specific noise the $i-$individual,

$\rightsquigarrow$ $\Theta = \{(\gamma_k)_{1\leq k\leq K}, (\theta_i)_{1\leq i\leq n}, (\sigma_i^2)_{1\leq i\leq n}, \pi\}$: the set of all parameters of the model.

Hypotheses

- $\{\mu_k\}_{1\leq k\leq K}$ are independent,
- $\{f_i\}_{1\leq i\leq n}$ are independent,
- $\{Z_i\}_{1\leq i\leq n}$ are independent,
- $\{\varepsilon_i\}_{1\leq i\leq n}$ are independent,
- For all $1 \leq i \leq n$, $1 \leq k \leq K$, $\mu_k, f_i,\ Z_i$ are independent.

Inference: a variational version of the EM algorithm is used (MagmaClustR, Leroy et al (2020)).

Extensions

- The multivariate continuous case: $Y_i(t) \in \mathbb{R}^d,\ 1 \leq i \leq n,\ t \in [0, T]$, with $d \geq 1$.

- The categorical case: $Y_i(t) \in C,\ 1 \leq i \leq n,\ t \in [0, T]$, where C is a finite set.

A more general extension: the multivariate mixed case

Fix $n, d, p, q, K \geq 1$, $T > 0$, with $p + q = d$, $(l_{i,j})_{1 \leq i \leq n, 1 \leq j \leq d}$ positive integers. Set p positive integer $c_1, ..., c_p$.
Consider p finite sets $C_j = \{1, ..., c_j\}$ for $1 \leq j \leq p$, n different patients.
For $1 \leq i \leq n$, set

$\rightsquigarrow$ $t_{i,l}^{(j)} \in [0, T]$ $1 \leq j \leq d, 1 \leq l \leq l_{i,j}$: the observation times.

$\rightsquigarrow$ $(Y_i^{(j)}(t_{i,l}^{(j)}))_{1 \leq j \leq d, 1 \leq l \leq l_{i,j}} \in C_1 \times ... \times C_p \times \mathbb{R}^q$.

$\rightsquigarrow$ $p_{c,l}^{(j)}(t_{i,l}^{(j)}) = \mathbb{P}(Y_i^{(j)}(t_{i,l}^{(j)}) = c_j)$, for $c \in C_j$, $1 \leq j \leq p$ and $1 \leq l \leq l_{i,j}$.

Gaussian process mixture model

- We associate a latent binary random vector $Z_i = (Z_{i1}, ..., Z_{iK})$ to each i–individual, indicating in which cluster it belongs: if the i–th individual comes from the k–th cluster, then $Z_{ik} = 1$ and 0 otherwise.
- Assume that these latent variables are coming from the same multinomial distribution: $Z_i \sim \mathcal{M}(1, \pi)$, $1 \leq i \leq n$, with $\pi = (\pi_1, \cdots, \pi_K)^t$ and $\sum_{k=1}^{K} \pi_k = 1$.

The model

Assuming that the i–th individual belongs to the k–th group, we can define its functional expression as the sum of a cluster-specific mean process and an individual-specific centred process:

$$\begin{cases} p_{c,i}^{(j)}(t^{(j)}) = & \dfrac{\exp(m_{k,c}^{(j)}(t^{(j)}))}{1+\sum_{c=2}^{c_j}\exp(m_{k,c}^{(j)}(t^{(j)}))}, \ 2 \le c \le c_j, \ 1 \le j \le p, \\ Y_i^{(j)}(t^{(j)}) = & \mu_k^{(j)}(t^{(j)}) + f_i^{(j)}(t^{(j)}) + \varepsilon_i^{(j)}(t^{(j)}), \ p+1 \le j \le d, \end{cases}$$

$t^{(j)} \in [0, T], \ 1 \le j \le d.$

Hypotheses

For $1 \leq j \leq d$, $1 \leq i \leq n$, and $1 \leq k \leq K$,

$\rightsquigarrow$ $\mu_k^{(j)}(\cdot) \sim \mathcal{GP}(m_k^{(j)}(\cdot), c^{(j)}_{\gamma_k^{(j)}}(\cdot,\cdot))$: common $j-$mean process of the $k-$cluster,

$\rightsquigarrow$ $f_i^{(j)}(\cdot) \sim \mathcal{GP}(0, A^{(j)}_{\theta_i^{(j)}}(\cdot,\cdot))$: specific $j-$process of the $i-$individual,

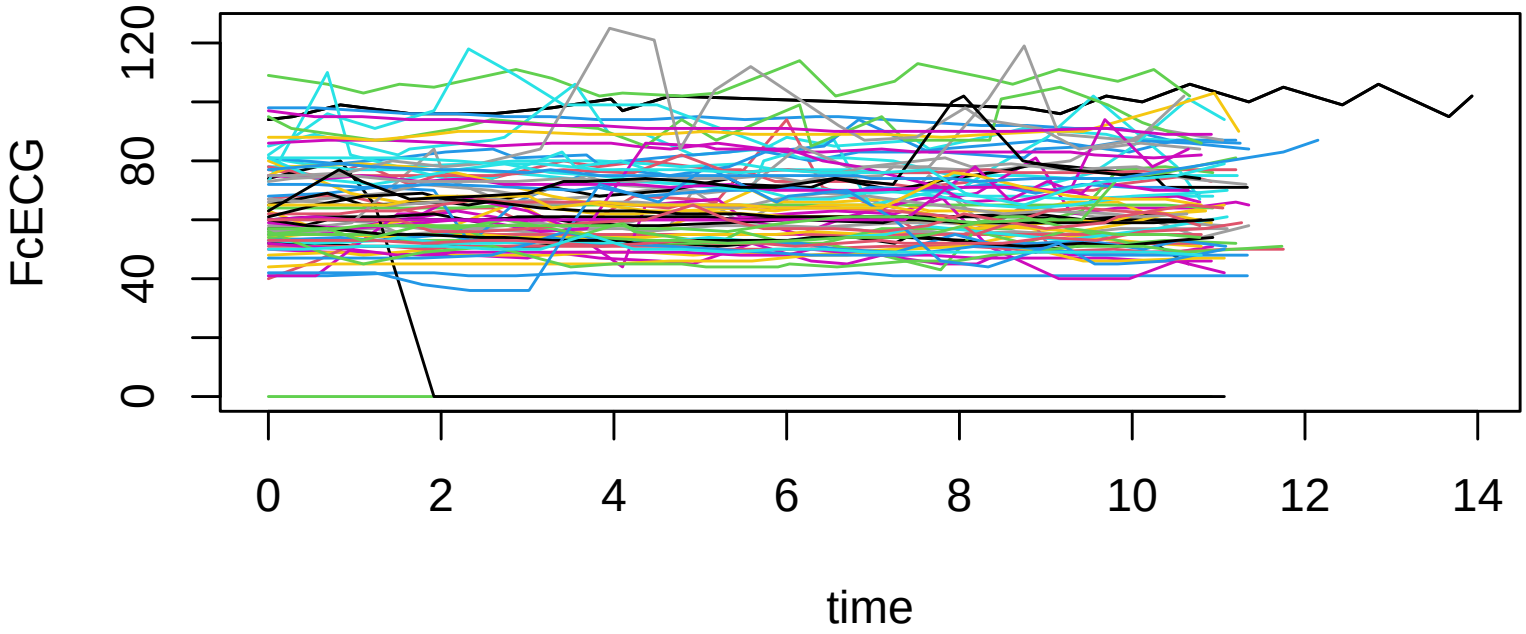
$\rightsquigarrow$ $\varepsilon_i^{(j)}(\cdot) \sim \mathcal{GP}(0, \sigma_i^{2(j)} I)$: specific $j-$noise of the $i-$individual,

$\rightsquigarrow$ $\Theta = \{(\gamma_k^{(j)})_{1\leq j\leq d, 1\leq k\leq K}, (\theta_i^{(j)})_{1\leq j\leq d, 1\leq i\leq n}, (\sigma_i^2)^{(j)}_{1\leq j\leq d, 1\leq i\leq n}, \pi\}$: the set of all parameters of the model.

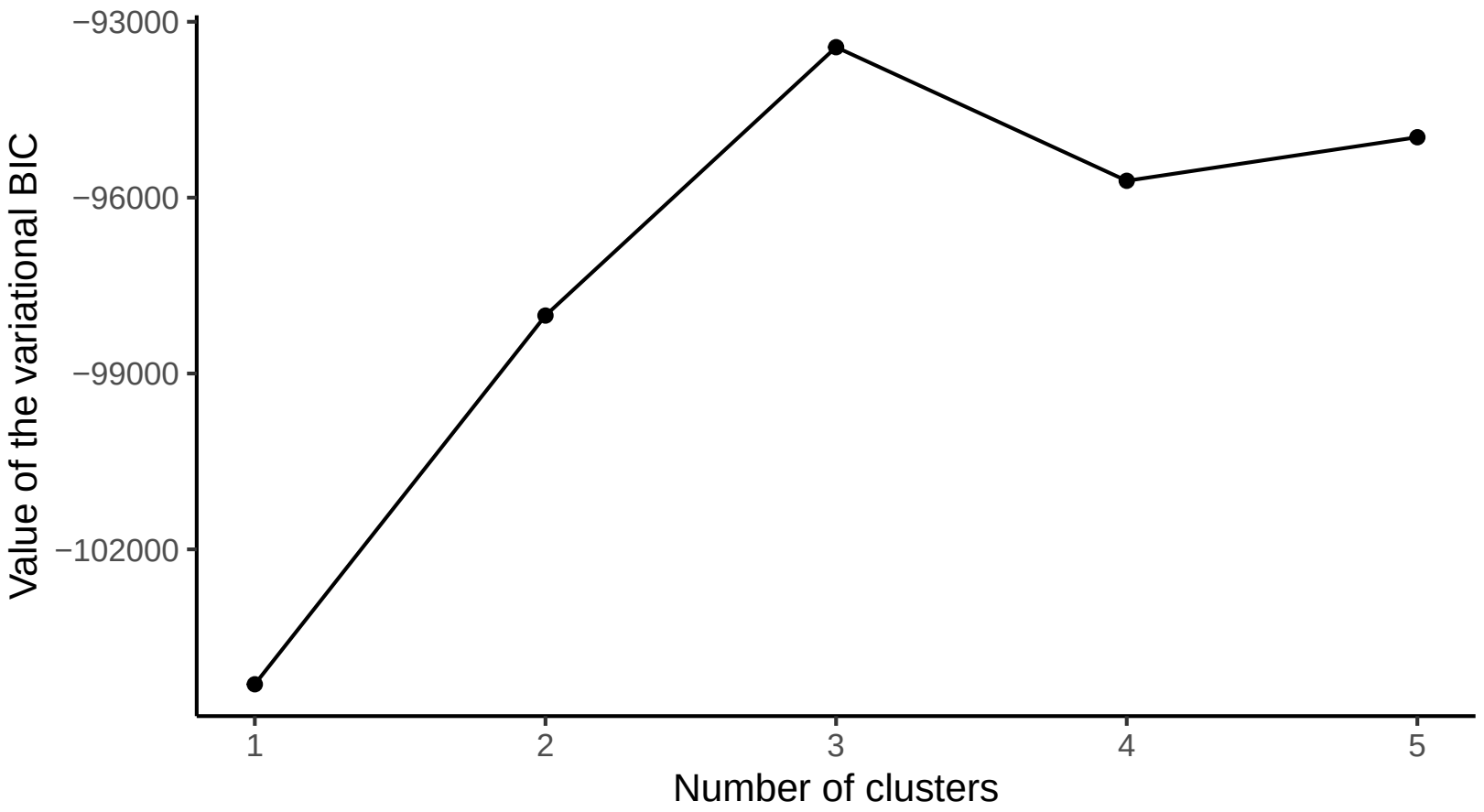
Hypotheses

- $\{\mu_k\}_{1\leq k\leq K}$ are independent,
- $\{f_i\}_{1\leq i\leq n}$ are independent,
- $\{Z_i\}_{1\leq i\leq n}$ are independent,
- $\{\varepsilon_i\}_{1\leq i\leq n}$ are independent,
- For all $1 \leq i \leq n$, $1 \leq k \leq K$, $\mu_k, f_i,\ Z_i$ are independent,
- For all $1 \leq i \leq n$, $\{Y_i^{(j)}|Z_i\},\ 1 \leq j \leq d$ are independent.

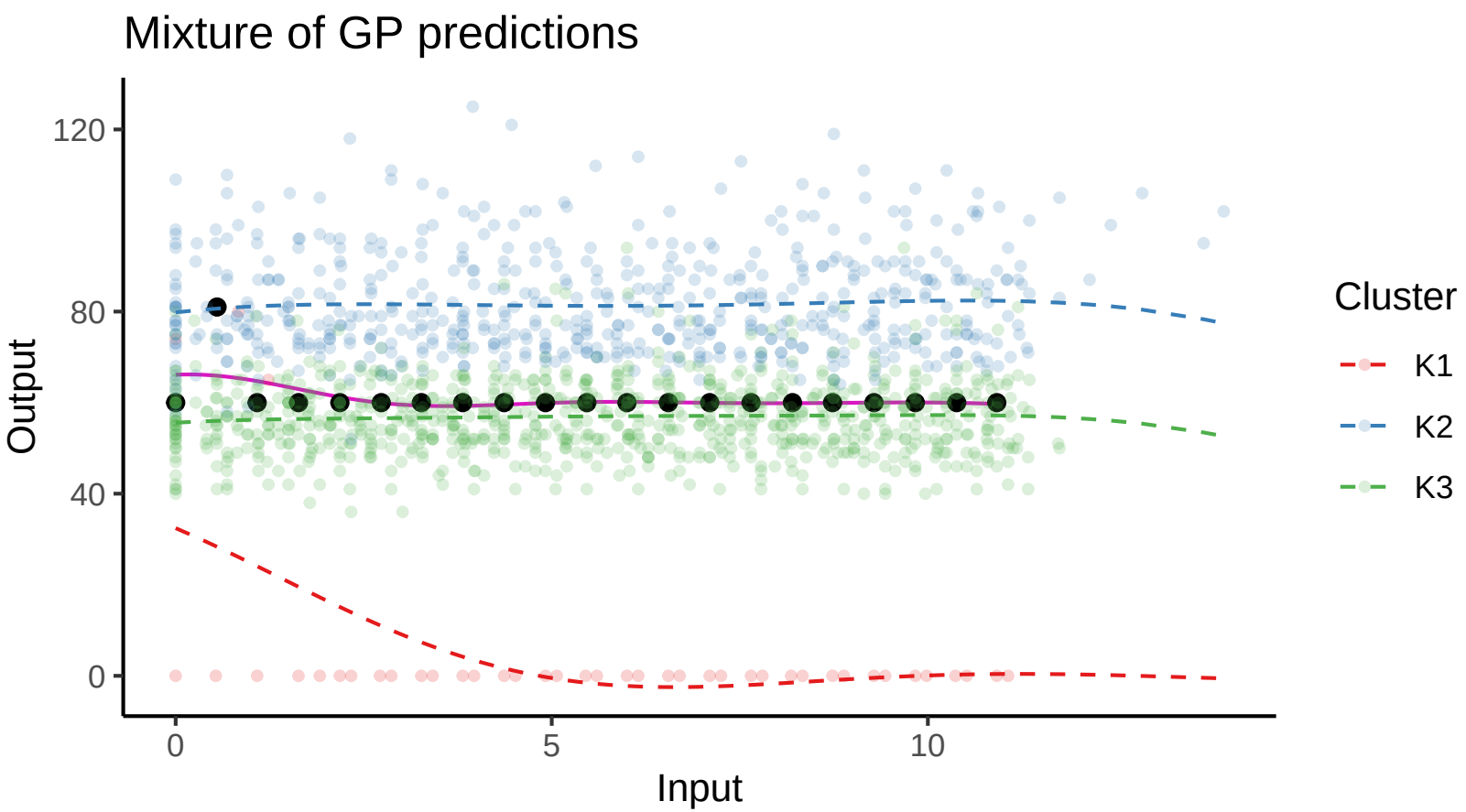
Evolution of FcECG as a function of time



Selection of the clusters number



Clustering


Mixture of GP predictions
120
80
40
0
Output
0
5
10
Input
Cluster
K1
K2
K3

- Perform clustering using the Gaussian processes mixture model described above in the multivariate continuous case.
- Perform clustering using the Gaussian processes mixture described above in the categorical case.
- Perform clustering using the Gaussian processes mixture described above in the multivariate mixed case.
- Take into account the possibility of having missing data.
- Predict the future of a patient path in term of covariates.
- Answer clinicians' questions based on our generic model.
- Develop a package aimed at clinicians.

Thank you for your attention!

Sidi Bou said, Tunisia