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# A latent mixed-effects model for longitudinal categorical data in Parkinson disease

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<https://gitlab.com/icm-institute/aramislab/leaspy>

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## ➤ Introduction

We propose an extension of Leaspy [1,2,3] as a **generic method to analyze longitudinal categorical data** :

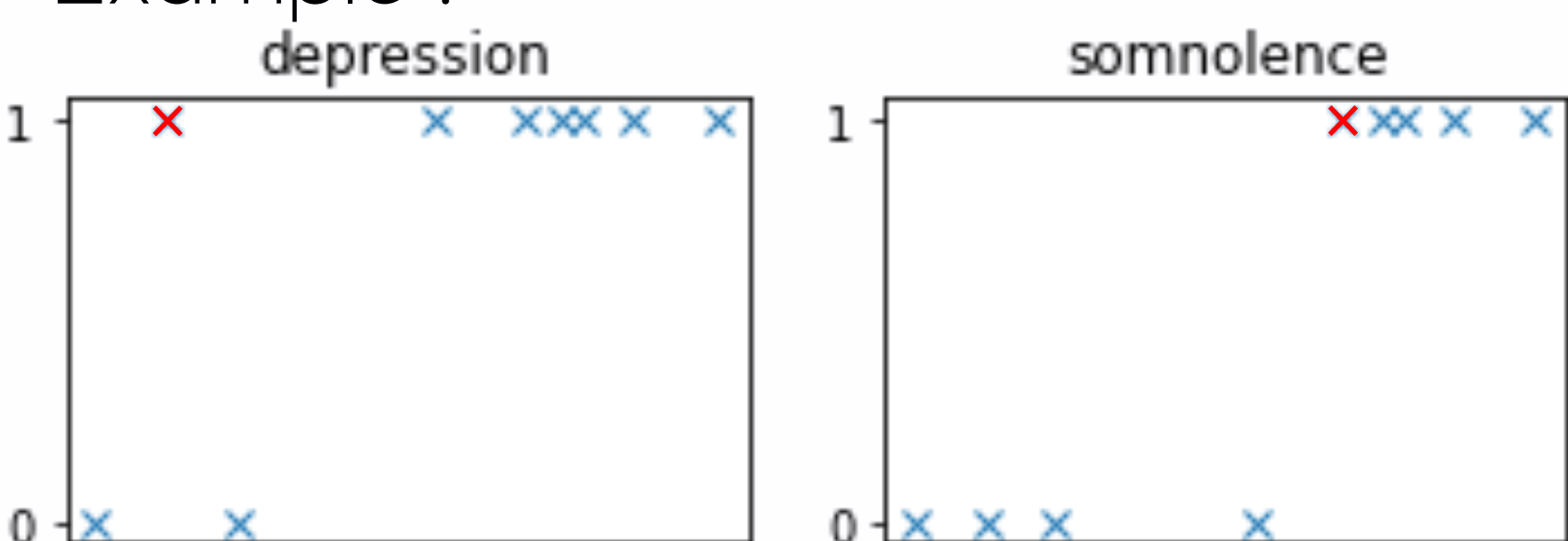
- a **non-linear mixed effect model** describes the **latent evolution** of the disease
- **personalization of individual parameters** allows to **partially predict future data**
- the **multivariate model** jointly estimates observations

We applied the model to the NSPARK database, focusing on the onset of disease-related symptoms for Parkinson disease patients. We show the potential of this method on data as noisy and coarse as presence/absence of symptoms at each visit.

## ➤ Database

N	Initial age	Diagnosis
2821	66.6 ± 10.7	PD
# reported symptoms	# visits	Follow-up duration
23*	5.0 ± 1.5	2.6 ± 1.3

Example :



Due to the noise in the data and the treatment impact, we decided to look at the **first occurrence** of each symptom (onset).

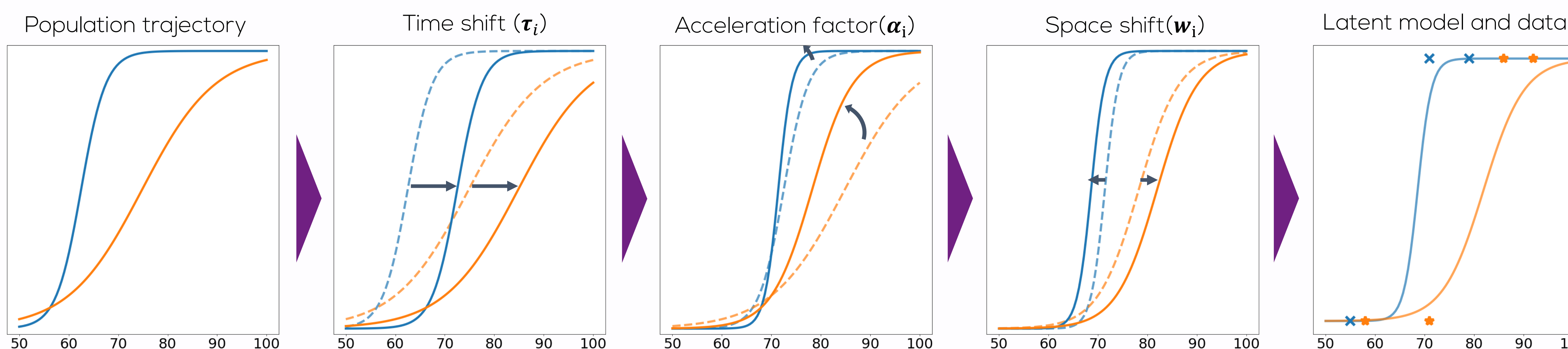
## ➤ Method

- Observations :  $\mathbf{y}_{ij} \in \{0,1\}^n$  of patient  $i$  at time  $\mathbf{t}_{ij}$  (array of 0/1 for each of the  $n$  symptoms)
- Latent model : we model  $\mathbf{y}_{ij}$  as a Bernoulli realization with parameter  $\boldsymbol{\eta}_{ij} \in \mathcal{M}$  a Riemannian manifold;  $\boldsymbol{\eta}_{ij} = \mathbb{P}(\mathbf{y}_{ij} = 1)$  is a function of the time describing the evolution of the Bernoulli parameter
- Population average trajectory :  $\boldsymbol{\gamma}_0(t)$  is a geodesic in  $\mathcal{M}$
- Individual effect :
  - Space-shift parameter  $\mathbf{w}_i$  describes the shift of the individual trajectory in  $\mathcal{M}$  :  $\boldsymbol{\gamma}_i(t) = \text{Exp}_{\mathbf{w}_i}(\boldsymbol{\gamma}_0(t))$  [exp-parallelization]
  - Time reparameterization : time-shift  $\boldsymbol{\tau}_i$  and acceleration factor  $\boldsymbol{\alpha}_i$  for individual disease timeline  $\hat{\mathbf{t}}_{ij} = \boldsymbol{\alpha}_i(\mathbf{t}_{ij} - \boldsymbol{\tau}_i)$
- Non-linear mixed effect model :  $\boldsymbol{\eta}_{ij} = \boldsymbol{\gamma}_i(\hat{\mathbf{t}}_{ij})$
- Estimation of parameters with a Monte Carlo Markov Chain Stochastic Approximation of Expectation-Maximization algorithm (MCMC SAEM)

Comparing to previous Leaspy model [1,2,3], this model seeks to minimize the crossentropy between  $\boldsymbol{\eta}_{ij}$  and  $\mathbf{y}_{ij}$  and not the mean squared error.

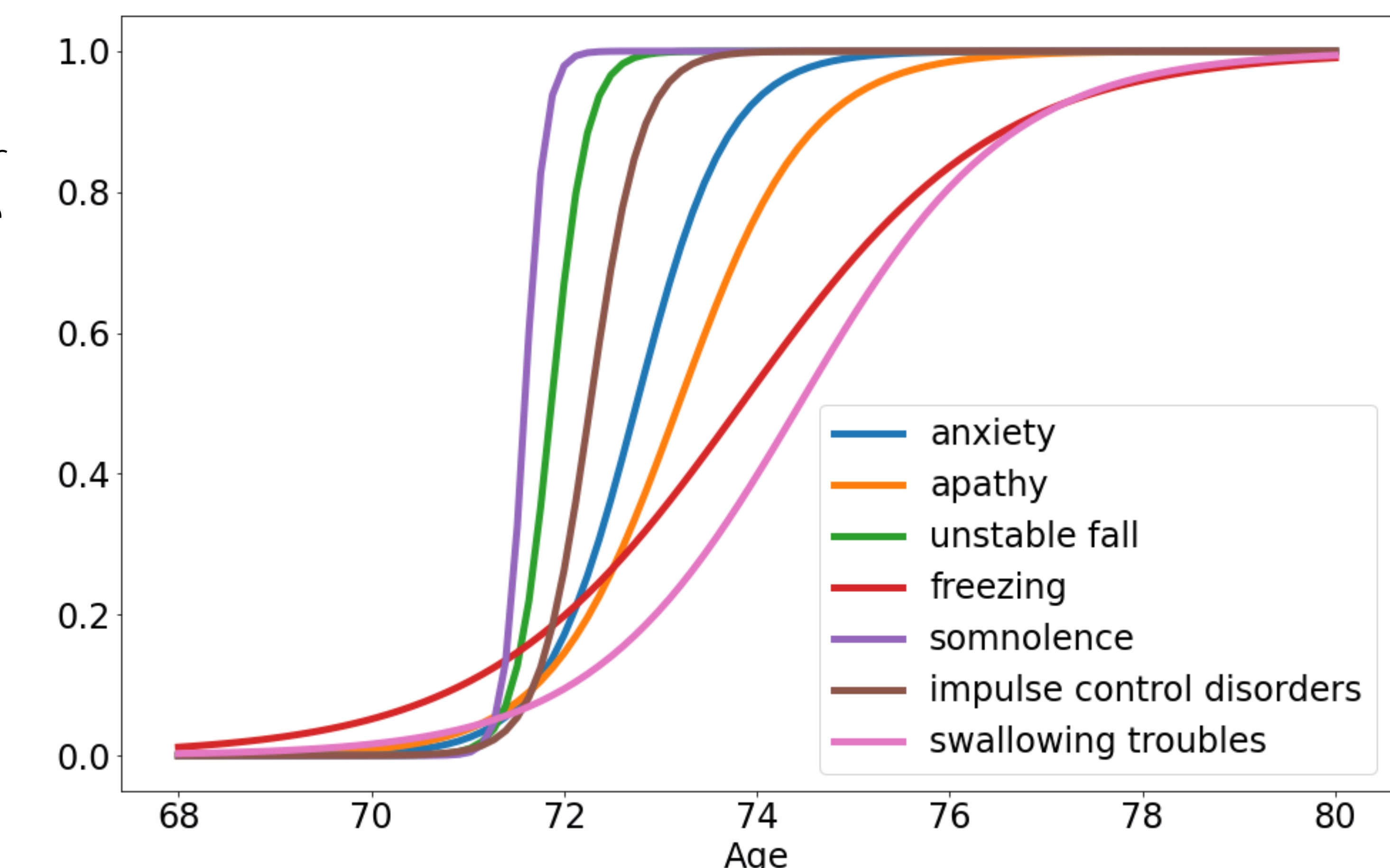
The code will be available in a future release in Leaspy library (see git link).

From population average trajectory to individual latent disease progression with two symptoms (blue and orange)



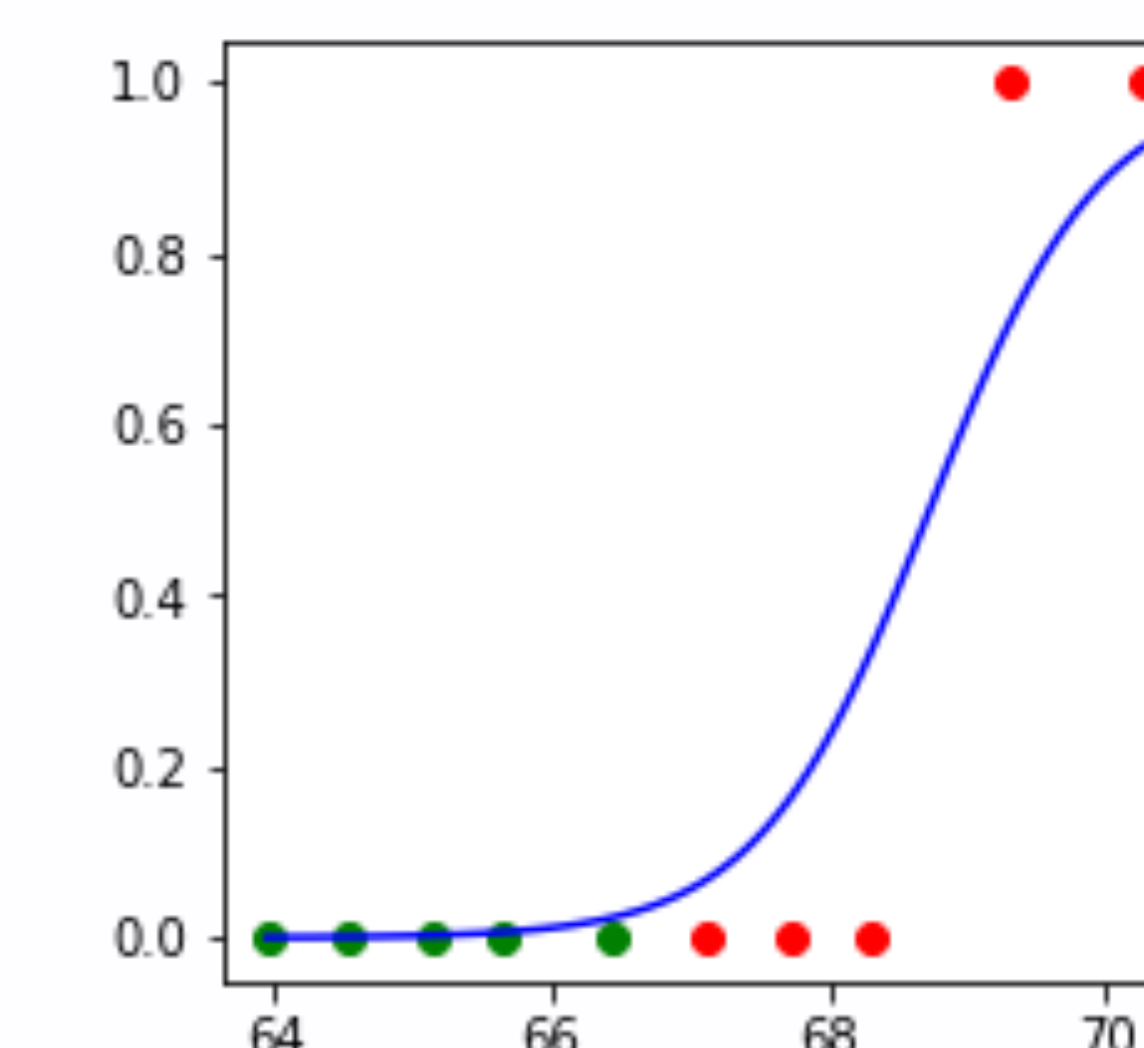
## ➤ Results

- Population trajectory (figure on the right) shows the order in which symptoms usually appear
- The sharper the slope the more precise the onset of the symptom
- A slower progressing curve means the symptom is less predictable
- Performance is evaluated with ROC AUC for all symptoms : mean AUC is 0.83 on the fitted data
- Personalized trajectory with individual parameters allows to partially predict the onset of symptoms in future visits (not used in model fitting)
- Two groups appear :
  - 11 symptoms with AUC under 0.6, hard to predict
  - 12 symptoms with AUC around 0.65-0.7, showing prediction potential
- The inherent variance linked to disease's symptoms as well as treatment's effect explains the difficulties of the described prediction task

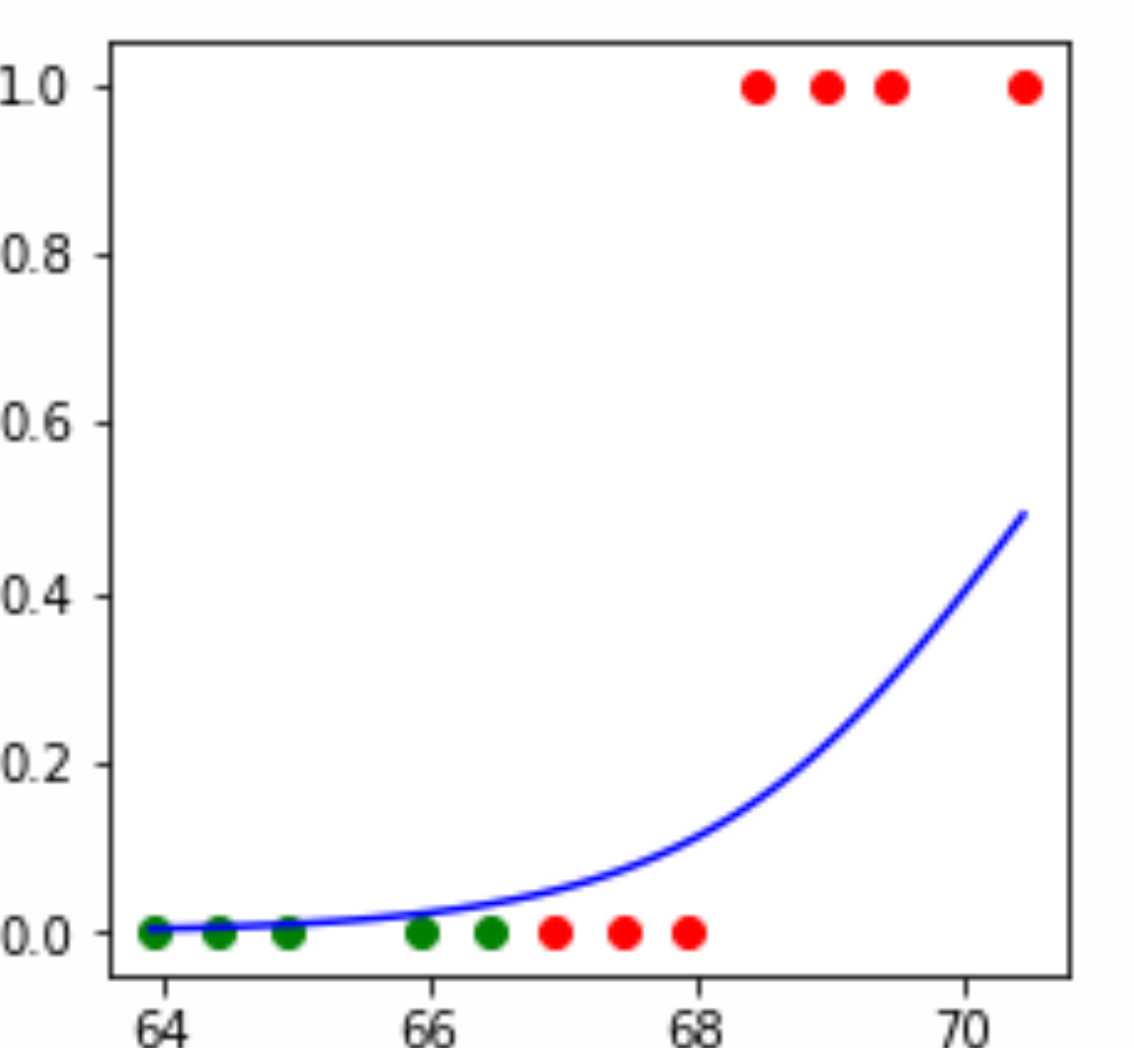


Prediction : past visits (green) are used to fit the individual trajectory (blue) which is then used to predict future visits (red)

Apathy (good predictability)



Freezing (harder to predict)



## ➤ Conclusions

Our model is an attempt to link fine-grained continuous disease progression models and raw binary data, which is more noisy and provides less information. However we show that it is possible to exploit such data. The mixed-effect model allows to describe an average population trajectory while the individualization of the disease progression can be used to obtain partial prediction power. This can be a powerful tool to leverage categorical markers for disease understanding and eventually prognostic system.

## ➤ References

- [1] Schiratti J-B, Allasonnière S, Colliot O, Durrleman S. Learning spatiotemporal trajectories from manifold-valued longitudinal data. In Advances in Neural Information Processing Systems, pp. 2395–2403, 2015.
- [2] Schiratti J-B, Allasonnière S, Colliot O, Durrleman S. A Bayesian mixed-effects model to learn trajectories of changes from repeated manifold-valued observations. In Journal of Machine Learning Research (JMLR) 18(1), pp. 4840-4872, 2017.
- [3] Louis M., Couronné R., Koval I., Charlier B., Durrleman S. Riemannian geometry learning for disease progression modelling. In International Conference on Information Processing in Medical Imaging, pp. 542-553, 2019.