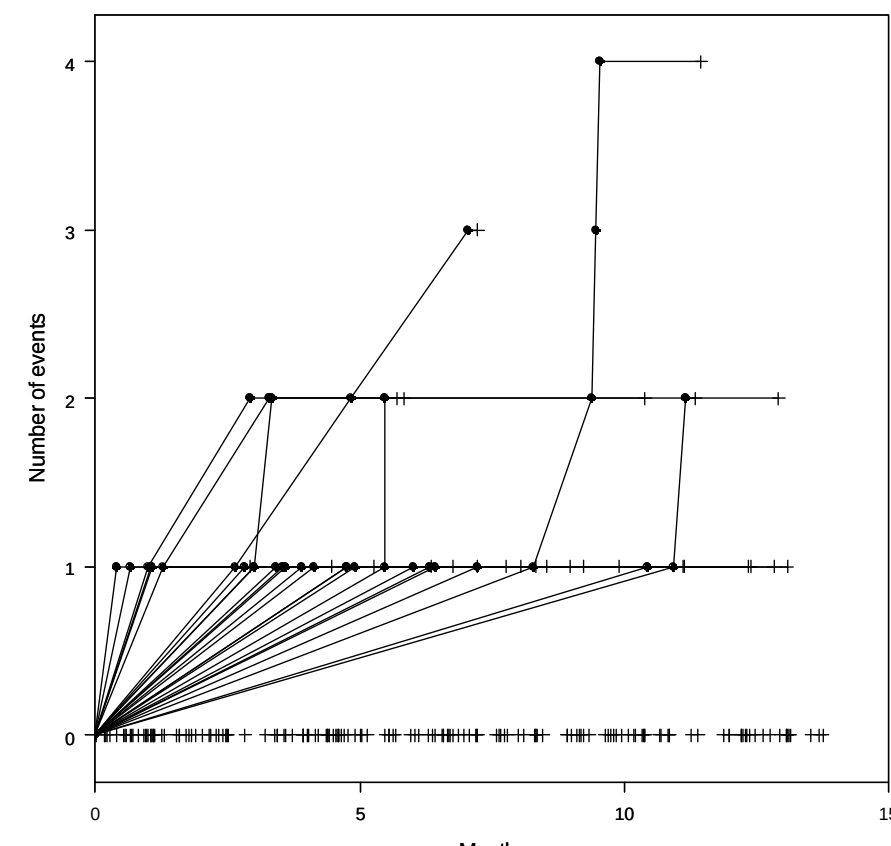


Introduction	Objectives
- Analysis of repeated time to event data requires - frailty model [1] - specific estimation methods - Karlsson <i>et al.</i> [2] compared SAEM and Laplace estimation in NONMEM - MONOLIX evaluated by simulation for discrete data [3]and count data [4] but not for time to event data	(1) To assess the performance of the SAEM algorithm in MONOLIX [6] and the Adaptative Gaussian Quadrature in PROC NL MIXED of SAS (2) To evaluate the power of test of dichotomous covariate on the occurrence of events

Real dataset																	
185 treated patients of the French GD registry 26 bone events (BE), total BE number 36  Spaghetti plot of the number of events as a fonction of time since the initiation of treatment	- Exponential model - parameter λ - additive random effect on $\log(\lambda)$ - N patients $i=1,\dots N$ $\lambda_i = \lambda \exp(b_i)$ with $b_i \sim N(0, \omega^2)$ - Estimate <table><tr><th></th><th>MONOLIX</th><th>NLMIXED</th></tr><tr><td>$\lambda \text{ month}^{-1} \text{ (se)}$</td><td>$1.4 \cdot 10^{-3} \text{ (}0.5 \cdot 10^{-3}\text{)}$</td><td>$1.2^{-3} \text{ (}0.5 \cdot 10^{-3}\text{)}$</td></tr><tr><td>$\omega(\text{se})$</td><td>1.1 (0.4)</td><td>1.2 (0.3)</td></tr></table>		MONOLIX	NLMIXED	$\lambda \text{ month}^{-1} \text{ (se)}$	$1.4 \cdot 10^{-3} \text{ (}0.5 \cdot 10^{-3}\text{)}$	$1.2^{-3} \text{ (}0.5 \cdot 10^{-3}\text{)}$	$\omega(\text{se})$	1.1 (0.4)	1.2 (0.3)	- Exponential model for censure <table><tr><th></th><th>MONOLIX</th><th>NLMIXED</th></tr><tr><td>$\lambda \text{ month}^{-1} \text{ (se)}$</td><td>$0.13 \cdot 10^{-3} \text{ (}0.1 \cdot 10^{-3}\text{)}$</td><td>$0.14^{-3} \text{ (}0.1 \cdot 10^{-3}\text{)}$</td></tr></table> - Covariate (with MONOLIX) $\lambda_i = \lambda \exp(b_i + \beta \text{cov}_i)$ 2 covariates are significant with Likelihood Ratio Test (LRT) - BE before treatment $\exp(\beta)=4.1 \text{ (1.7)}$, $p=0.01$ - Splenectomy $\exp(\beta)=2.7 \text{ (1.1)}$, $p=0.02$		MONOLIX	NLMIXED	$\lambda \text{ month}^{-1} \text{ (se)}$	$0.13 \cdot 10^{-3} \text{ (}0.1 \cdot 10^{-3}\text{)}$	$0.14^{-3} \text{ (}0.1 \cdot 10^{-3}\text{)}$
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Simulation study	
Simulation protocol - Standard scenario - number of patients: 200 $\lambda=2 \cdot 10^{-3}$ $\omega=1$ 3 levels of censoring - max follow-up=144 months (No) - low censure: $\lambda=5 \cdot 10^{-3}$ (Low) - high censure: $\lambda=0.1 \cdot 10^{-3}$ (High) - Estimations were performed with MONOLIX v.4.0 (3 markov chains) and SAS v.9.3 (5 quadrature points)	(1) Estimation performance 100 datasets were simulated (R software) - Influence of: - N=100, 200, 400 $\lambda=2 \cdot 10^{-3}, 4 \cdot 10^{-3}$ $\omega=0.5, 1, 2$ Comparison - Estimated relative error (%) - Relative bias and root mean square error (RMSE) (%)
	(2) Test performance 500 datasets were simulated (R software) - Influence of $\exp(\beta)=1, 1.5, 2$ or 3 Comparison - Wald Test and LRT - Type 1 error = % of datasets where p-value <0.05 under H_0 ($\exp(\beta)=1$) - Predictive interval 95% of 5% [3.1;6.9] - Power = % of datasets where p-value <0.05 under H_1 - Loglikelihood was estimated by Importance Sampling in MONOLIX

Results

Example of simulation standard scenario

% of patients	0 event	1 event	more than 1 event
No censure	74	19	7
Low censure	86	11	3
High censure	87	10	3

Relative bias and RMSE for standard scenario (in %)

λ		MONOLIX	NLMIXED
No censure	Bias	1.8	1.6
	RMSE	20.1	19.9
Low censure	Bias	-0.0008	1.9
	RMSE	23.1	23.3
High censure	Bias	-1.3	1.5
	RMSE	27.5	27.1

ω		MONOLIX	NLMIXED
No censure	Bias	-5.2	-3.6
	RMSE	22.1	18.6
Low censure	Bias	-3.4	-2.5
	RMSE	27.0	21.3
High censure	Bias	-9.1	-5.9
	RMSE	37.3	30.0

Variation of the number of patients

Variation of λ and ω

Type 1 error and Power of the Wald Test and LRT for standard scenario

Conclusion	
- Both algorithms provide good estimate of the parameters - Bias are low (<5%) - RMSE are reasonable (<40%) - Problems in extreme cases: few patients or small variability	- Tests have adequate properties - Type 1 errors close to 5% - Powers vary as expected, increasing when β increased - Perspective: evolution for time dependant covariate

References
[1] Hougaard, P. (1995), <i>Lifetime Data Analysis</i>, 1(3):255-273. [2] Karlsson, K.E. <i>et al.</i> (2011), <i>The AAPS Journal</i>, 13(1):83-91. [3] Savic, R., Lavielle, M. (2009), <i>Journal of Pharmacokinetics and Pharmacodynamics</i>, 36(4):367-379. [4] Savic, R.M. <i>et al.</i> (2011), <i>The AAPS Journal</i>, 13(1):44-53. [5] Stirnemann, J. <i>et al.</i>(2010), <i>Arthritis Research and Therapy</i>, 12(4):R156. [6] http://software.monolix.org