Progress report on:

How to include time-varying exposures prone to measurement error in survival analyses?

TG4 subgroup:
Viviane Philipps, Veronika Deffner, Hendrieke Boshuizen, Laurence Freedman, Anne Thiébaut, Cécile Proust-Lima

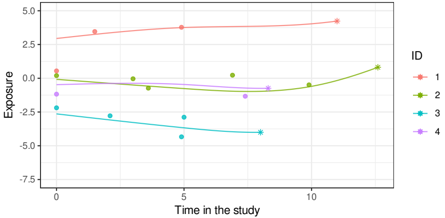
INSERM U1219, Bordeaux Population Health Research Center, Bordeaux, France
Univ. Bordeaux, ISPED, Bordeaux, France
`cecile.proust-lima@inserm.fr`

STRATOS meeting - March 27, 2023

Context

- Association between a time-varying exposure and a time to event:
  - BMI and incidence of breast cancer
  - Physical activity and incidence of Parkinson disease
  - Blood Pressure and cardiovascular event
  - ...

- Exposure data are **measures of an underlying continuous process**:
  - measured with error
  - measured at sparse and irregular times
  - influenced by the event occurence when endogenous / internal



Statistical model envisaged

- Cox model with time-varying covariate dedicated to
  - continuously observed time-varying covariate
    (value known at each observed survival time (event/censored))
  - observed without error
  - covariate not impacted by the event occurence: "external" exposure

Statistical model envisaged

- Cox model with time-varying covariate dedicated to
  - continuously observed time-varying covariate (value known at each observed survival time (event/censored)) ✗ sparse
  - observed without error ✗ error-prone
  - covariate not impacted by the event occurence: "external" exposure ✗ internal/endogenous

✗ these assumptions rarely apply in health studies (Prentice 1982; Andersen 2002)

Statistical model envisaged

- Cox model with time-varying covariate dedicated to
  - continuously observed time-varying covariate (value known at each observed survival time (event/censored)) ✗ sparse
  - observed without error ✗ error-prone
  - covariate not impacted by the event occurence: "external" exposure ✗ internal/endogenous

✗ these assumptions rarely apply in health studies (Prentice 1982; Andersen 2002)

- The target model is still a Cox model for time to event T_i:

$$\lambda_i(t) = \lambda_0(t)\exp(X_i(t)\gamma) \qquad t > 0$$

  - $X_i(t)$ is the "true" exposure process;
  - $\tilde{X}_{ij}$ are the observations at sparse times t_{ij} with $\max(t_{ij}) < T_i$ if internal covariate: $\tilde{X}_{ij} = X_i(t_{ij}) + \varepsilon_{ij}$ with $\epsilon_{ij} \underset{iid}{\sim} \mathscr{D}$

→ **How to leverage $\tilde{X}_{ij}$ observations to correctly estimate γ?**

Solutions identified in the literature

- How to satisfy the Cox model properties?
  - sparse: extrapolation/interpolation of values at all time points:
    - Last Value Carried Forward (LOCF)
    - predictions from a regression model
  - error-prone: regression model to separate observations from the underlying process
  - internal / truncation: account for the truncation induced by the event
    - inclusion of event information into the regression model (Multiple Imputation idea)
    - joint model of both processes

Solutions identified in the literature

- How to satisfy the Cox model properties?
  - sparse: extrapolation/interpolation of values at all time points:
    - ★ Last Value Carried Forward (LOCF)
    - ★ predictions from a regression model
  - error-prone: regression model to separate observations from the underlying process
  - internal / truncation: account for the truncation induced by the event
    - ★ inclusion of event information into the regression model (Multiple Imputation idea)
    - ★ joint model of both processes
- Properties of the methods identified in the literature

	LOCF	Regression Calibration (RC)	Multiple Imputation (MI)	Joint Model
Reference		Ye Biometrics 2008	Moreno-Bentancur Biostat 2018	Wulfsohn Biometrics 1997
sparse	✓	✓	✓	✓
error-prone	✗	✓	✓	✓
internal / truncation	✗	✗	✓	✓

Objective

Demonstrate (again) the problem of sparsely measured and prone-to-error time-varying covariates in Cox model

1. Extensive simulation study
2. Illustration with BMI and incidence of Breast cancer in E3N cohort

Generating "true" model for subject i (samples of 500 subjects)

- True exposure process:

$$X_i(t) = \boldsymbol{F}(t)(\boldsymbol{\beta} + \boldsymbol{u_i}) \quad \text{with} \quad \boldsymbol{u_i} \sim \mathcal{N}(0, \boldsymbol{B})$$

- Visit process j every y years (y=1,2) until administrative censoring at 10 years:

$$t_{ij} = j + \tau_{ij} \quad \text{with} \quad \tau_{ij} \sim \mathcal{U}(-1, 1)$$

- Repeated exposure observations at visit times:

$$\tilde{X}_{ij} = X(t_{ij}) + \varepsilon_{ij} \quad \text{with} \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma_\epsilon^2)$$

- Survival outcome (T_i, δ_i) with hazard

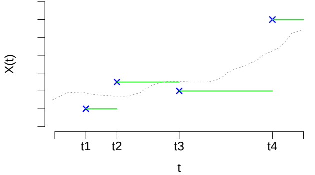
$$\lambda_i(t) = \lambda_0(t) \exp(X_i(t)\gamma) \quad \text{with a Weibull } \lambda_0(t)$$

\+ Eventually, truncation of $\tilde{X}$ at the event time
(are indicated in red the parameters that changed according to the scenarios)

Estimation models/techniques

- Naive LOCF Cox model: $\lambda_i(t) = \lambda_0(t)\exp(\tilde{X}_i(t)\gamma)$

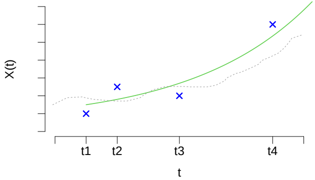
  with $\tilde{X}_i(t) = \tilde{X}_i(t_{ij})$ with $j = \max(k; t_{ik} \leq t)$



- Regression Calibration: $\lambda_i(t) = \lambda_0(t)\exp(\hat{X}_i(t)\gamma)$

  with $\hat{X}_i(t)$ predicted from LMM: $\tilde{X}_{ij} = \mathbf{F}(\mathbf{t})(\boldsymbol{\beta} + \boldsymbol{u_i}) + \varepsilon_{ij}$

  - classical RC: estimation of $\hat{\boldsymbol{\beta}}$ and $\hat{\boldsymbol{u}}_{\boldsymbol{i}}$ based on $\tilde{X}_{ij} < T_i$
  - external RC: estimation of $\hat{\boldsymbol{\beta}}$ and $\hat{\boldsymbol{u}}_{\boldsymbol{i}}$ based on $\tilde{X}_{ij}$ even after T_i



- Multiple Imputation: $\lambda_i(t) = \lambda_0(t)\exp(\hat{X}_i^m(t)\gamma)$

  with $\hat{X}_i^m(t)$ draws of predictions from LMM: $\tilde{X}_{ij} = \mathbf{F}(\mathbf{t})(\boldsymbol{\beta} + \boldsymbol{u_i}) + \beta_D D_{ij} + \beta_\Lambda \Lambda(T_i) + \varepsilon_{ij}$

- Joint model: $\lambda_i(t) = \lambda_0(t)\exp(X_i(t)\gamma)$; $X_i(t) = \mathbf{F}(\mathbf{t})(\boldsymbol{\beta} + \boldsymbol{u_i})$; $\tilde{X}_{ij} = X_i(t_{ij}) + \varepsilon_{ij}$

Variance estimation in the three two-stage approaches

- Multiple Imputation / Parametric bootstrap with the Rubin's rule
  - parameters in the LMM noted $\theta = (\beta, \text{vec}(B))$

- Internal, external regression calibration :
  - for b=1,...,500 draws: $\theta^b \sim \mathcal{N}(\hat{\theta}, \hat{V}(\hat{\theta}))$
  - BLUP $\hat{u}_i{}^b$ computed in θ^b
  - $\hat{X}^b(t)$ computed from θ^b and $\hat{u}_i{}^b$
  - Cox model estimated using $\hat{X}^b(t)$
  - Rubin's rule on $\hat{\gamma}^b$

- Multiple Imputation:
  - for b=1,..., 200 draws $\theta^b \sim \mathcal{N}(\hat{\theta}, \hat{V}(\hat{\theta}))$
  - draw of $\hat{u}_i{}^b \sim \mathcal{N}(\hat{u}_i(\theta^b), \hat{V}(\hat{u}_i(\theta^b)))$
  - $\hat{X}^b(t)$ computed from θ^b and $\hat{u}_i{}^b$
  - Cox model estimated using $\hat{X}^b(t)$
  - Rubin's rule on $\hat{\gamma}^b$

Variance estimation in the three two-stage approaches

- Multiple Imputation / Parametric bootstrap with the Rubin's rule
  - parameters in the LMM noted $\theta = (\beta, \text{vec}(B))$

- Internal, external regression calibration :
  - for b=1,...,500 draws: $\theta^b \sim \mathcal{N}(\hat{\theta}, \hat{V}(\hat{\theta}))$
  - BLUP $\hat{u}_i{}^b$ computed in θ^b
  - $\hat{X}^b(t)$ computed from θ^b and $\hat{u}_i{}^b$
  - Cox model estimated using $\hat{X}^b(t)$
  - Rubin's rule on $\hat{\gamma}^b$

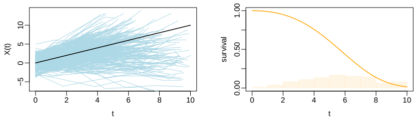
- Multiple Imputation:
  - for b=1,..., 200 draws $\theta^b \sim \mathcal{N}(\hat{\theta}, \hat{V}(\hat{\theta}))$
  - draw of $\hat{u}_i{}^b \sim \mathcal{N}(\hat{u}_i(\theta^b), \hat{V}(\hat{u}_i(\theta^b)))$
  - $\hat{X}^b(t)$ computed from θ^b and $\hat{u}_i{}^b$
  - Cox model estimated using $\hat{X}^b(t)$
  - Rubin's rule on $\hat{\gamma}^b$

(in the original work: only $\beta^b \sim \mathcal{N}(\hat{\beta}, \hat{V}(\hat{\beta}))$
$+ \hat{u}_i{}^b \sim \mathcal{N}(\hat{u}_i(\hat{\theta}), \hat{V}(\hat{u}_i(\hat{\theta})))$

Linear, weak asso, small measurement error (std$_\epsilon$=1)

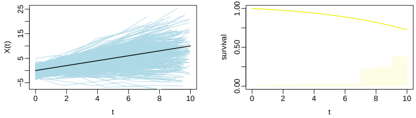
Medium Surival: 417 events, 3.4 measures /subject:

500	true	est	bias	ASE	ESE	95%CR
LOCF	0.2	0.0509	-74.53	0.0108	0.0115	0.00
RC	0.2	0.1900	-4.98	0.0159	0.0152	91.40
RC extern	0.2	0.1995	-0.25	0.0156	0.0159	95.00
MI	0.2	0.1975	-1.26	0.0191	0.0176	95.80
JM	0.2	0.2017	0.85	0.0169	0.0168	95.16



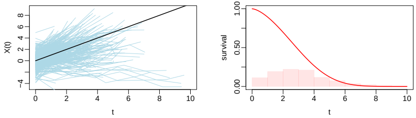
higher survival : 133 events, 4.9 measures /subject:

500	true	est	bias	ASE	ESE	95%CR
LOCF	0.2	0.1200	-40.01	0.0149	0.0175	0.40
RC	0.2	0.1910	-4.50	0.0219	0.0206	93.80
RC extern	0.2	0.1999	-0.03	0.0218	0.0216	95.60
MI	0.2	0.1954	-2.30	0.0245	0.0217	96.40
JM	0.2	0.2011	0.55	0.0226	0.0221	95.79



lower survival: 489 events, 2.1 measures /subject:

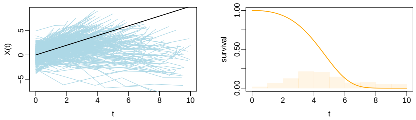
500	true	est	bias	ASE	ESE	95%CR
LOCF	0.2	0.0303	-84.84	0.0155	0.0162	0.00
RC	0.2	0.1829	-8.53	0.0231	0.0209	90.20
RC extern	0.2	0.1998	-0.08	0.0210	0.0208	96.60
MI	0.2	0.1974	-1.30	0.0302	0.0270	96.73
JM	0.2	0.2047	2.37	0.0251	0.0249	95.57



Linear, Strong asso, small measurement error (std$_\epsilon$=1)

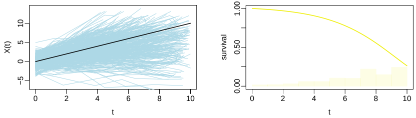
Medium Surival: 446 events, 2.9 measures /subject:

500	true	est	bias	ASE	ESE	95%CR
LOCF	0.4	0.0951	-76.22	0.0137	0.0141	0.00
RC	0.4	0.3523	-11.93	0.0225	0.0215	45.00
RC extern	0.4	0.3937	-1.58	0.0220	0.0226	92.60
MI	0.4	0.3934	-1.64	0.0336	0.0330	93.80
JM	0.4	0.4039	0.98	0.0290	0.0283	95.56



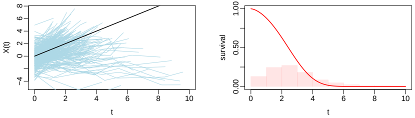
Higher survival: 277 events, 4.2 measures /subject:

500	true	est	bias	ASE	ESE	95%CR
LOCF	0.4	0.1562	-60.95	0.0127	0.0134	0.00
RC	0.4	0.3666	-8.36	0.0223	0.0214	68.00
RC extern	0.4	0.3944	-1.39	0.0224	0.0222	94.60
MI	0.4	0.3946	-1.34	0.0299	0.0272	97.00
JM	0.4	0.4027	0.69	0.0264	0.0257	96.80



lower survival: 487 events, 1.9 measures /subject:

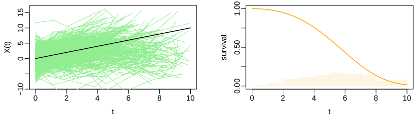
500/3/499	true	est	bias	ASE	ESE	95%CR
LOCF	0.4	0.0992	-75.19	0.0192	0.0188	0.00
RC	0.4	0.3308	-17.29	0.0332	0.0308	44.20
RC extern	0.4	0.3929	-1.77	0.0282	0.0283	94.00
(MI)	0.4	0.3862	-3.45	0.0483	0.0321	-
JM	0.4	0.4092	2.31	0.0442	0.0457	94.39



Linear, weak asso, large measurement error (std_ϵ=3)

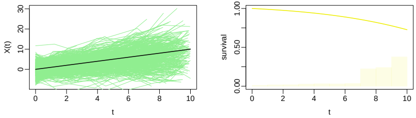
Medium Surival: 389 events, 3.5 measures /subject:

297	true	est	bias	ASE	ESE	95%CR
LOCF	0.2	0.0232	-88.40	0.0074	0.0069	0.00
RC	0.2	0.1647	-17.65	0.0186	0.0162	51.18
RC extern	0.2	0.1911	-4.43	0.0160	0.0161	90.57
MI	0.2	0.1995	-0.23	0.0297	0.0284	96.30
JM	0.2	0.2014	0.69	0.0244	0.0243	94.91



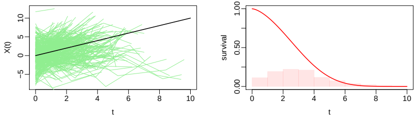
Higher Survival: 133 events, 4.9 measures/subject:

500	true	est	bias	ASE	ESE	95%CR
LOCF	0.2	0.0670	-66.50	0.0112	0.0117	0.00
RC	0.2	0.1639	-18.04	0.0232	0.0198	67.60
RC extern	0.2	0.1962	-1.91	0.0225	0.0223	94.40
MI	0.2	0.1902	-4.89	0.0337	0.0274	96.78
JM	0.2	0.2015	0.74	0.0273	0.0263	96.36



Lower Survival: 489 events, 2.1 measures /subject:

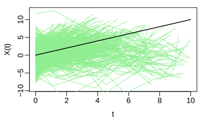
500/446/417	true	est	bias	ASE	ESE	95%CR
LOCF	0.2	0.0107	-94.65	0.0091	0.0084	0.00
RC	0.2	0.1508	-24.61	0.0336	0.0318	66.60
RC extern	0.2	0.1924	-3.81	0.0222	0.0224	93.80
MI	0.2	0.1915	-4.27	0.0506	0.0540	92.43
JM	0.2	0.2079	3.94	0.0456	0.0500	95.20

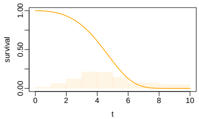


Linear, Strong asso, larger measurement error (std_ϵ=3)

Medium Surival:: 407 events, 3.1 measures /subject:

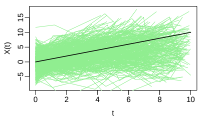
500	true	est	bias	ASE	ESE	95%CR
LOCF	0.4	0.0345	-91.37	0.0083	0.0077	0.00
RC	0.4	0.2607	-34.83	0.0307	0.0326	2.20
RC extern	0.4	0.3533	-11.69	0.0219	0.0237	43.00
MI	0.4	0.4184	4.61	0.0626	0.0828	88.73
JM	0.4	0.4036	0.89	0.0623	0.0703	93.38

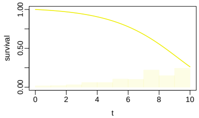




Higher Survival: 277 events, 4.2 measures / subject:

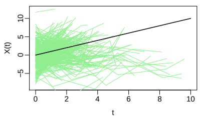
500	true	est	bias	ASE	ESE	95%CR
LOCF	0.4	0.0728	-81.80	0.0087	0.0084	0.00
RC	0.4	0.2825	-29.37	0.0239	0.0231	0.80
RC extern	0.4	0.3552	-11.21	0.0218	0.0235	46.00
MI	0.4	0.3894	-2.66	0.0494	0.0480	93.25
JM	0.4	0.4047	1.18	0.0451	0.0470	94.96

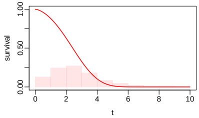




Lower Survival: 487 events, 1.9 measures /subject:

500/3/383	true	est	bias	ASE	ESE	95%CR
LOCF	0.4	0.0281	-92.97	0.0102	0.0093	0.00
RC	0.4	0.2350	-41.25	0.0580	0.0587	20.40
RC extern	0.4	0.3594	-10.16	0.0304	0.0319	69.80
(MI)	0.4	0.4388	9.71	0.1058	0.0770	-
JM	0.4	0.4074	1.85	0.1137	0.1452	86.16



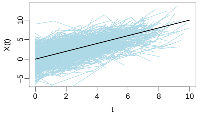


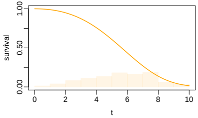
Linear, Medium Survival, Correlated random-effects

Negative correlation between random-effects so that the variability remains stable over time

Weak asso, std$_\epsilon$=2 (same as RE): 450 events, 3.3 measures /subject:

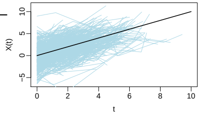
500/480	true	est	bias	ASE	ESE	95%CR
LOCF	0.2	-0.0511	-125.57	0.0106	0.0097	0.00
RC	0.2	0.1767	-11.65	0.0472	0.0426	93.40
RC extern	0.2	0.1984	-0.81	0.0389	0.0396	96.00
MI	0.2	0.2172	8.60	0.0793	0.0750	97.00
JM	0.2	0.2069	3.44	0.0510	0.0533	94.58

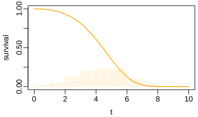




Strong asso, std$_\epsilon$=2 (same as RE): 494 events, 2.7 measures /subject:

500/484/461	true	est	bias	ASE	ESE	95%CR
LOCF	0.4	-0.0352	-108.79	0.0111	0.0091	0.00
RC	0.4	0.3273	-18.18	0.0625	0.0567	73.40
RC extern	0.4	0.3746	-6.35	0.0429	0.0452	88.20
MI	0.4	0.4434	10.86	0.1147	0.1473	90.00
JM	0.4	0.4081	2.03	0.0775	0.0816	95.66

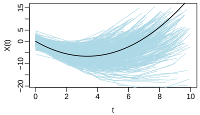


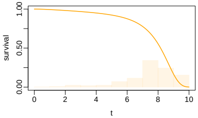


Quadratic trend, high survival

Weak asso, std$_\epsilon$=1 : 291 events, 4.3 measures /subject:

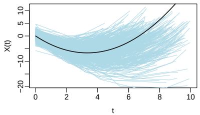
500/179/391	true	est	bias	ASE	ESE	95%CR
LOCF	0.2	0.1477	-26.13	0.0059	0.0057	0.00
RC	0.2	0.1891	-5.47	0.0092	0.0095	74.80
RC extern	0.2	0.1993	-0.34	0.0095	0.0097	94.60
MI	0.2	0.2225	11.24	0.0216	0.0220	83.80
JM	0.2	0.2010	0.49	0.0104	0.0105	95.14

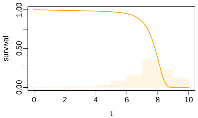




Strong asso, std$_\epsilon$=1 : 298 events, 4.3 measures /subject:

500/188/442	true	est	bias	ASE	ESE	95%CR
LOCF	0.4	0.2070	-48.24	0.0074	0.0068	0.00
RC	0.4	0.3305	-17.37	0.0145	0.0175	1.40
RC extern	0.4	0.3904	-2.40	0.0167	0.0182	87.60
MI	0.4	0.3811	-4.73	0.0425	0.0351	91.49
JM	0.4	0.3996	-0.11	0.0221	0.0236	93.44



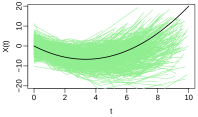


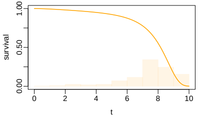
linear trend at the individual level / quadratic trend at the population level

Quadratic trend, high survival (cont'd)

Weak asso, std$_\epsilon$=3: 291 events, 4.3 measures / subject:

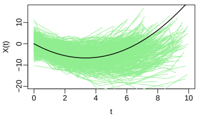
500/253/485	true	est	bias	ASE	ESE	95%CR
LOCF	0.2	0.1155	-42.25	0.0051	0.0048	0.00
RC	0.2	0.1592	-20.41	0.0089	0.0095	0.80
RC extern	0.2	0.1919	-4.07	0.0093	0.0096	84.20
MI	0.2	0.2021	1.07	0.0222	0.0186	97.63
JM	0.2	0.2000	0.01	0.0137	0.0146	93.40

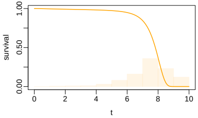




Strong asso, std$_\epsilon$=3 : 298 events, 4.3 measures / subject:

500/264/484	true	est	bias	ASE	ESE	95%CR
LOCF	0.4	0.1440	-64.01	0.0059	0.0056	0.00
RC	0.4	0.2272	-43.19	0.0129	0.0160	0.00
RC extern	0.4	0.3445	-13.87	0.0149	0.0166	7.20
MI	0.4	0.3096	-22.60	0.0380	0.0291	32.58
JM	0.4	0.3974	-0.66	0.0387	0.1593	82.44





linear trend at the individual level / quadratic trend at the population level

Conclusions

- Lessons learnt from the simulations:
  - LOCF strongly biased
  - Two stage methods valid only if they account for early truncation by the event :
    - ★ using data available after the event if external (Regression Calibration)
    - ★ incorporating information on the event if internal (Multiple Imputation)
  - JM works very well

  ⚠ these results valid under correct specification!

- Remarks:
  - Variance estimation with RC and MI using Rubin's rule
  - intermittent missing data (10% MCAR) : same results
  - Sequential two-stage approaches (Tsiatis 1995) / reset regression calibrations - no investigated

- Perspectives:
  - finalize the simulations (MI technique reimplemented with less constraints)
  - application to BMI and incidence of breast cancer
  - paper in preparation
  - follow-up project: regression calibration versus multiple imputation with multivariate data