

Supplemental Material for Review of Statistical Software for Joint Longitudinal and Time-to-Event Models

Allison K.C. Furgal¹, Ananda Sen^{1,2}, and Jeremy M.G. Taylor¹

¹*Biostatistics Department, School of Public Health, University of Michigan, 1415 Washington
Heights, Ann Arbor, MI 48109*

²*Department of Family Medicine, Michigan Medicine, University of Michigan, 1018 Fuller St,
Ann Arbor, MI 48104*

S1 Generation of Survival Times in Joint Model Sim- ulations

The generalized hazard function for the survival submodel of Scenario 2 is

$$\lambda_i(t) = \lambda_0(t) \exp(\gamma_0 + \gamma_1 X_{1i} + \gamma_2 X_{2i} + \alpha m_i(t)) \quad (\text{S1})$$

where, in general terms,

$$Y_i(t) = m_i(t) + e_i(t) = \beta_0 + \beta_1 t + \beta_2 X_{1i} + \beta_3 X_{2i} + b_{0i} + b_{1i} t + e_i(t)$$

We set $\lambda_0(t) = 1$ and have a constant γ_0 absorbed into the exponential. After dropping the subscript i ,

$$\lambda(t) = \exp(\gamma_0 + \gamma_1 X_1 + \gamma_2 X_2 + \alpha(\beta_0 + \beta_1 t + \beta_2 X_1 + \beta_3 X_2 + b_0 + b_1 t))$$

Then the cumulative hazard function is

$$\begin{aligned}
\Lambda(t) &= \int_0^t \lambda(y) dy \\
&= \int_0^t \exp(\gamma_0 + \gamma_1 X_1 + \gamma_2 X_2 + \alpha(\beta_0 + \beta_1 y + \beta_2 X_1 + \beta_3 X_2 + b_0 + b_1 y)) dy \\
&= \frac{\exp(\gamma_0 + \alpha\beta_0 + \alpha b_0 + (\gamma_1 + \alpha\beta_2)X_1 + (\gamma_2 + \alpha\beta_3)X_2)}{\alpha\beta_1 + \alpha b_1} (\exp(\alpha\beta_1 t + \alpha b_1 t) - 1)
\end{aligned}$$

Let $U \sim \text{Unif}(0, 1)$ be a random survival probability and set $H(t) = -\log(U)$. Then

$$-\log(U) = \frac{\exp(\gamma_0 + \alpha\beta_0 + \alpha b_0 + (\gamma_1 + \alpha\beta_2)X_1 + (\gamma_2 + \alpha\beta_3)X_2)}{\alpha\beta_1 + \alpha b_1} (\exp(\alpha\beta_1 t + \alpha b_1 t) - 1)$$

$$\exp(\alpha\beta_1 t + \alpha b_1 t) = \frac{-\log(U)(\alpha\beta_1 + \alpha b_1)}{\exp(\gamma_0 + \alpha\beta_0 + \alpha b_0 + (\gamma_1 + \alpha\beta_2)X_1 + (\gamma_2 + \alpha\beta_3)X_2)} + 1$$

$$\alpha(\beta_1 + b_1)t = \log \left(\frac{-\log(U)(\alpha\beta_1 + \alpha b_1)}{\omega_0 \exp(\gamma_0 + \alpha\beta_0 + \alpha b_0 + (\gamma_1 + \alpha\beta_2)X_1 + (\gamma_2 + \alpha\beta_3)X_2)} + 1 \right)$$

and so

$$t = \frac{1}{\alpha(\beta_1 + b_1)} \log \left(\frac{-\log(U)(\alpha(\beta_1 + b_1))}{\exp(\gamma_0 + \alpha\beta_0 + \alpha b_0 + (\gamma_1 + \alpha\beta_2)X_1 + (\gamma_2 + \alpha\beta_3)X_2)} + 1 \right)$$

The calculation for a random intercept only model (Scenario 1) is the same but with $b_1 = 0$. Calculation for Scenario 3 (a shared parameter model) is simpler with $m_i(t)$ replaced by just b_i in (S1).

S2 Simulation Model Reparameterization

In Scenario 1, we fit a shared parameter model as in (8) with `joinerR` while the data was generated from the current-value model described in (5) and (6). So the data are generated from

$$Y = \beta_0 + \beta_1 t + \beta_2 X_1 + \beta_3 X_2 + b + e$$

and

$$\lambda(t) = \exp(\gamma_0) \exp(\gamma_1 X_1 + \gamma_2 X_2 + \alpha(\beta_0 + \beta_1 t + \beta_2 X_1 + \beta_3 X_2 + b)) \quad (\text{S2})$$

The longitudinal submodel is the same for `joiner` but the survival submodel is of the form

$$\lambda(t) = \lambda_0(t) \exp(\gamma_1^* X_1 + \gamma_2^* X_2 + \alpha^* b) \quad (\text{S3})$$

Rearranging terms in (S2),

$$\begin{aligned} \lambda(t) &= \exp(\gamma_0) \exp(\gamma_1 X_1 + \gamma_2 X_2 + \alpha(\beta_0 + \beta_1 t + \beta_2 X_1 + \beta_3 X_2 + b)) \\ &= \exp(\gamma_0 + \alpha\beta_0 + \alpha\beta_1 t) \exp((\gamma_1 + \alpha\beta_2)X_1 + (\gamma_2 + \alpha\beta_3)X_2 + \alpha b) \end{aligned}$$

Comparing this to (S3) we see that

$$\begin{aligned} \gamma_1^* &= \gamma_1 + \alpha\beta_2 \\ \gamma_2^* &= \gamma_2 + \alpha\beta_3 \end{aligned} \quad (\text{S4})$$

Since `joiner` assumes an unspecified baseline hazard, the form of the baseline hazard does not matter when estimating. When calculating the bias and MSE for the `joiner` model, we compare the estimates output to the combination of true parameters on the left hand side of the equations in (S4). In order to calculate the coverage probabilities for γ_1^* and γ_2^* , we estimate standard errors by bootstrapping. Specifically, we select, with replacement, data for 500 subjects and run a model on that bootstrap sample. We do this 100 times for each of the 100 simulated datasets and calculate $\gamma_1^* - \alpha\beta_2$ and $\gamma_2^* - \alpha\beta_3$. We then use the standard deviation of these values as an estimate of the standard error.

The coefficients for the covariates in the survival submodel of Scenario 2 work out to be exactly the same as above and standard errors were again found by bootstrapping.

In Scenario 3 the JM model is in a different form than the true model. The data are

generated from

$$Y = \beta_0 + \beta_1 t + \beta_2 X_1 + \beta_3 X_2 + b + e$$

$$\lambda(t) = \exp(\gamma_0) \exp(\gamma_1 X_1 + \gamma_2 X_2 + \alpha b)$$

Whereas JM fits a model of the form

$$\begin{aligned} \lambda(t) &= \lambda_0(t) \exp(\gamma_1^* X_1 + \gamma_2^* X_2 + \alpha(\beta_0 + \beta_1 t + \beta_2 X_1 + \beta_3 X_2 + b)) \\ &= \lambda_0(t) \exp(\alpha(\beta_0 + \beta_1 t)) \exp((\gamma_1^* + \alpha\beta_2) X_1 + (\gamma_2^* + \alpha\beta_3) X_2 + \alpha b) \end{aligned}$$

So we see that

$$\gamma_1^* + \alpha\beta_2 = \gamma_1$$

$$\gamma_2^* + \alpha\beta_3 = \gamma_2$$

Bias and MSE for γ_1^* and γ_2^* are calculated compared to the combinations $\gamma_1 - \alpha\beta_2$ and $\gamma_2 - \alpha\beta_3$, respectively. Standard errors are estimated with bootstrapping similar to the method described above for Scenario 1.

S3 Simulation Tables

Software	n models fit	Intercept		Time		X1		X2		Surv X1		Surv X2		Association	
		Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
Two-Stage	100	-0.24	2.68	-1.14	0.42	0.92	2.98	-0.44	0.84	2.31	21.69	4.11	6.96	-10.64	4.33
R JM Weib	93	-0.06	2.79	0.18	0.43	1.01	3.16	0.02	0.84	0.89	23.04	1.02	8.15	0.46	6.66
R JM Weib NA	92	-0.01	2.82	0.27	0.43	0.86	3.18	-0.15	0.82	0.55	23.17	2.08	7.23	-0.97	4.88
R JM PWC	100	-0.09	2.67	0.02	0.42	0.93	3.01	-0.04	0.83	2.72	22.81	0.22	7.49	0.88	5.76
R JM PWC NA	100	-0.08	2.67	0.02	0.42	0.91	3.01	-0.04	0.83	2.73	22.84	0.18	7.56	0.86	5.75
R JM Spl	93	-0.06	2.80	0.22	0.43	1.01	3.16	0.04	0.84	0.33	23.25	1.09	8.07	0.23	7.12
R JM Spl NA	93	-0.05	2.80	0.21	0.43	0.99	3.16	0.04	0.84	0.36	23.28	1.08	8.06	-0.05	6.48
R JM Unspec NA	100	-0.08	2.67	-0.01	0.42	0.92	3.01	-0.05	0.83	2.58	22.59	0.34	7.55	-0.01	5.65
SAS %JM Weib*	100	0.004	2.66	0.10	0.42	0.91	3.02	0.04	0.83	3.66	24.25	-1.61	11.47	6.73	11.76
SAS %JM PWC*	100	-1.80	2.69	-0.68	0.55	-0.40	2.98	-0.01	0.74	-8.02	23.98	-5.34	12.22	6.10	8.74
Stata Weib	33	-34.74	1.51	-10.99	0.42	5.67	0.89	-25.34	0.33	-3.01	3.07	-14.74	2.86	-32.59	1.89
R joineR**	100	0.59	1.09	-1.30	0.36	-0.15	0.81	-0.98	0.67	-17.46	7.23	-49.41	27.20	-12.00	7.38

Table S1: Bias*100 and MSE*100 (Mean Squared Error) of the estimates from Scenario 1.

* The SAS longitudinal model is misspecified, including a random slope not in the data generation model.

** The Surv X1 and Surv X2 estimates are compared to the value to which they converge and standard errors are estimated through bootstrapping. Details in Section S2.

Software	n models	Intercept	Time	X1	X2	Surv X1	Surv X2	Association
Two-Stage	100	0.16	0.06	0.17	0.09	0.47	0.26	0.18
R JM Weib	93	0.17	0.07	0.18	0.09	0.48	0.29	0.26
R JM Weib NA	92	0.17	0.07	0.18	0.09	0.48	0.27	0.22
R JM PWC	100	0.16	0.07	0.17	0.09	0.48	0.28	0.24
R JM PWC NA	100	0.16	0.07	0.17	0.09	0.48	0.28	0.24
R JM Spl	93	0.17	0.07	0.18	0.09	0.48	0.29	0.27
R JM Spl NA	93	0.17	0.07	0.18	0.09	0.49	0.29	0.26
R JM Unspec NA	100	0.16	0.07	0.17	0.09	0.48	0.28	0.24
SAS %JM Weib*	100	0.16	0.07	0.17	0.09	0.49	0.30	0.34
SAS %JM PWC*	100	0.16	0.07	0.17	0.09	0.49	0.25	0.29
Stata Weib	33	0.31	0.12	0.11	0.18	0.25	0.18	0.25
R joineR**	100	0.10	0.06	0.09	0.08	0.21	0.17	0.24

Table S2: Empirical Standard Deviations of the estimates from Scenario 1.

* The SAS longitudinal model is misspecified, including a random slope not in the data generation model.

** The Surv X1 and Surv X2 estimates are compared to the value to which they converge and standard errors are estimated through bootstrapping. Details in Section S2.

Software	n models	Intercept	Time	X1	X2	Surv X1	Surv X2	Association
Two-Stage	100	0.51	0.25	0.66	0.33	1.84	0.96	0.73
R JM Weib	93	0.51	0.25	0.67	0.33	1.87	0.99	0.87
R JM Weib NA	92	0.51	0.25	0.67	0.33	1.87	0.98	0.85
R JM PWC	100	0.51	0.25	0.66	0.33	1.87	0.99	0.86
R JM PWC NA	100	0.51	0.25	0.66	0.33	1.87	0.99	0.86
R JM Spl	93	0.51	0.25	0.67	0.33	1.87	0.98	0.87
R JM Spl NA	93	0.51	0.25	0.67	0.33	1.87	0.99	0.86
R JM Unspec NA	100	0.51	0.24	0.66	0.33	1.61	0.97	0.56
SAS %JM Weib*	100	0.51	0.25	0.67	0.33	1.90	1.01	0.99
SAS %JM PWC*	100	0.51	0.25	0.67	0.33	1.92	1.03	0.99
Stata Weib	33	0.13	0.11	0.19	0.10	0.61	0.33	0.29
R joineR**	100	0.51	0.24	0.65	0.33	2.01	0.94	0.75

Table S3: Average width of confidence intervals from Scenario 1.

* The SAS longitudinal model is misspecified, including a random slope not in the data generation model.

** The Surv X1 and Surv X2 estimates are compared to the value to which they converge and standard errors are estimated through bootstrapping. Details in Section S2.

Software	n models worked	Intercept		Time		X1		X2		Surv X1		Surv X2		Association	
		Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
Two-Stage	100	2.12	0.90	-5.80	0.87	-1.31	1.90	0.18	0.71	-1.17	13.55	-1.77	3.27	1.93	0.91
R JM Weib	88	1.35	0.94	-2.63	0.60	-0.32	1.87	0.34	0.69	1.66	15.11	-2.33	3.77	8.11	2.29
R JM Weib NA	95	0.92	0.88	-1.47	0.56	-0.84	1.83	-0.11	0.70	0.86	15.94	-2.33	3.65	7.56	1.89
R JM PWC	87	1.04	0.84	-1.98	0.53	-1.12	1.78	0.45	0.71	0.30	15.60	-2.86	3.78	9.18	2.10
R JM PWC NA	94	0.80	0.87	-1.15	0.57	-0.77	1.84	-0.31	0.68	1.08	16.40	-2.61	3.70	9.57	2.42
R JM Spl	83	0.52	0.88	-2.42	0.61	-0.72	1.93	0.61	0.76	-0.43	15.41	-1.91	3.88	7.30	1.94
R JM Spl NA	94	0.90	0.87	-1.32	0.57	-0.76	1.85	-0.29	0.67	0.38	15.93	-2.38	3.63	8.31	1.98
R JM Unspec NA	85	0.88	0.87	-1.62	0.59	-0.24	1.95	0.34	0.66	-0.38	15.18	-3.29	3.83	9.74	2.21
SAS %JM Weib	100	-4.88	0.85	-2.85	0.54	-0.67	1.77	-2.45	0.64	-1.28	15.47	-3.12	14.18	5.92	2.23
SAS %JM PWC	100	0.99	0.86	-1.44	0.57	-1.53	1.82	0.27	0.71	1.72	17.54	-3.72	15.14	15.92	6.35
Stata Weib	99	1.23	0.85	-1.78	0.57	-1.21	1.86	0.41	0.70	0.10	4.93	-2.46	3.42	8.06	1.93
R joineR	25	5.70	1.08	-2.39	0.78	-3.54	1.49	1.25	0.60	3.48	10.92	60.70	4.60	-4.67	1.12

Table S4: Bias*100 and MSE*100 of estimates from Scenario 2.

*The Surv X1 and Surv X2 estimates are compared to the value to which they converge, as described in Section S2.

Software	n models	Intercept	Time	X1	X2	Surv X1	Surv X2	Association
Two-Stage	100	0.09	0.07	0.14	0.08	0.37	0.18	0.09
R JM Weib	88	0.10	0.07	0.14	0.08	0.39	0.19	0.13
R JM Weib NA	95	0.09	0.07	0.14	0.08	0.40	0.19	0.12
R JM PWC	87	0.09	0.07	0.13	0.08	0.40	0.19	0.11
R JM PWC NA	94	0.09	0.08	0.14	0.08	0.41	0.19	0.12
R JM Spl	83	0.09	0.08	0.14	0.09	0.39	0.20	0.12
R JM Spl NA	94	0.09	0.07	0.14	0.08	0.40	0.19	0.11
R JM Unspec NA	85	0.09	0.08	0.14	0.08	0.39	0.19	0.11
SAS %JM Weib	100	0.11	0.07	0.13	0.08	0.40	0.18	0.12
SAS %JM PWC	100	0.09	0.07	0.13	0.08	0.42	0.19	0.20
Stata Weib	99	0.09	0.07	0.14	0.08	0.40	0.18	0.11
R joineR	25	0.09	0.09	0.12	0.08	0.34	0.22	0.10

Table S5: Empirical Standard Deviations of the estimates from Scenario 2.

*The Surv X1 and Surv X2 estimates are compared to the value to which they converge, as described in Section S2.

Software	n models	Intercept	Time	X1	X2	Surv X1	Surv X2	Association
Two-Stage	100	0.44	0.29	0.60	0.30	1.33	0.67	0.40
R JM Weib	88	0.43	0.29	0.59	0.29	1.35	0.68	0.42
R JM Weib NA	95	0.44	0.29	0.60	0.30	1.39	0.70	0.43
R JM PWC	87	0.90	0.28	0.59	0.29	1.39	0.70	0.46
R JM PWC	94	0.44	0.29	0.60	0.30	1.40	0.70	0.46
R JM Spl	83	0.42	0.28	0.56	0.28	1.38	0.70	0.46
R JM Spl NA	94	0.44	0.29	0.60	0.30	1.39	0.70	0.47
R JM Unspec NA	85	0.44	0.29	0.60	0.30	1.23	0.69	0.22
SAS %JM Weib	100	0.45	0.31	0.60	0.30	1.40	0.70	0.46
SAS %JM PWC	100	0.45	0.31	0.60	0.30	1.43	0.72	0.55
Stata Weib	99	0.44	0.29	0.60	0.30	1.39	0.70	0.44
R joineR*	25	0.44	0.29	0.62	0.31	1.66	0.74	0.43

Table S6: Average width of Confidence Intervals for Scenario 2.

*The Surv X1 and Surv X2 estimates are compared to the value to which they converge, as described in Section S2.

Software	n models worked	Intercept		Time		X1		X2		Surv X1		Surv X2		Association	
		Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
Two-Stage	100	0.62	1.09	-1.68	0.36	-0.34	0.82	-1.23	0.67	0.17	3.57	0.61	2.85	-6.47	5.18
R JM Weib**	82	0.60	0.91	-0.01	0.34	-0.47	0.73	0.28	0.56	-1.88	4.41	-1.41	3.28	-1.71	5.75
R JM Weib** NA	80	-1.20	1.09	0.95	0.41	0.45	0.72	0.75	0.68	-1.44	4.37	-2.54	3.62	1.59	5.97
R JM PWC**	88	0.43	1.00	-0.73	0.35	0.24	0.80	-0.40	0.64	-5.59	4.21	9.67	4.89	-26.48	13.16
R JM PWC NA**	89	0.68	0.99	-0.93	0.35	0.06	0.74	-0.50	0.66	-5.06	4.18	8.30	4.49	-24.36	12.36
R JM Spl**	97	0.24	1.08	-1.16	0.34	0.34	0.80	-0.40	0.65	-4.36	4.20	11.62	4.93	-28.04	12.67
R JM Spl NA**	100	0.24	1.07	-0.97	0.34	0.15	0.80	-0.66	0.67	-4.39	3.85	11.65	4.82	-28.53	11.96
R JM Unspec NA**	45	0.42	1.13	-1.62	0.41	0.81	0.66	0.29	0.70	-0.60	4.21	9.61	3.20	-21.76	8.00
SAS %JM Weib*	100	-1.43	1.24	-1.22	0.31	0.80	1.07	-2.22	0.82	0.86	3.24	1.85	167.99	3.40	47.32
SAS %JM PWC*	100	-0.61	1.17	-1.37	0.30	0.57	1.05	-2.25	0.83	2.08	3.65	4.48	168.58	5.65	23.61
Stata Weib	89	14.31	2.68	4.65	0.84	-0.18	0.87	-0.26	0.65	-0.74	11.99	-0.24	3.13	0.20	9.05
R joineR	100	0.59	1.09	-1.30	0.36	-0.15	0.81	-0.98	0.67	-22.46	9.22	-29.41	11.43	-12.00	7.38

Table S7: Bias*100 and Mean Squared Error (MSE)*100 of the estimates from Scenario 3.

* The SAS longitudinal model is misspecified, including a random slope not in the data generation model.

** The Surv X1 and Surv X2 estimates are compared to the value to which they converge and standard errors are estimated through bootstrapping. Details in Section S2.

Software	n models	Intercept	Time	X1	X2	Surv X1	Surv X2	Association
Two-Stage	100	0.10	0.06	0.09	0.08	0.19	0.17	0.22
R JM Weib**	82	0.10	0.06	0.09	0.08	0.21	0.18	0.24
R JM Weib NA**	80	0.10	0.06	0.09	0.08	0.21	0.19	0.25
R JM PWC**	88	0.10	0.06	0.09	0.08	0.20	0.20	0.25
R JM PWC NA**	89	0.10	0.06	0.09	0.08	0.20	0.20	0.25
R JM Spl**	97	0.10	0.06	0.09	0.08	0.20	0.19	0.22
R JM Spl NA**	100	0.10	0.06	0.09	0.08	0.19	0.19	0.20
R JM Unspec NA**	45	0.11	0.06	0.08	0.08	0.21	0.15	0.18
SAS %JM Weib*	100	0.11	0.05	0.10	0.09	0.18	0.18	0.69
SAS %JM PWC*	100	0.11	0.05	0.10	0.09	0.19	0.15	0.49
Stata Weib	89	0.08	0.08	0.09	0.08	0.19	0.18	0.30
R joineR	100	0.10	0.06	0.09	0.08	0.21	0.17	0.24

Table S8: Empirical Standard Deviations of the estimates from Scenario 3.

* The SAS longitudinal model is misspecified, including a random slope not in the data generation model.

** The Surv X1 and Surv X2 estimates are compared to the value to which they converge and standard errors are estimated through bootstrapping. Details in Section S2.

Software	n models	Intercept	Time	X1	X2	Surv X1	Surv X2	Association
Two-Stage	100	0.36	0.21	0.42	0.30	0.81	0.59	0.89
R JM Weib**	82	0.36	0.22	0.41	0.30	0.85	0.69	1.02
R JM Weib NA**	80	0.36	0.22	0.42	0.30	0.86	0.69	1.00
R JM PWC**	88	0.36	0.22	0.42	0.30	0.81	0.69	0.97
R JM PWC NA**	89	0.36	0.22	0.42	0.30	0.83	0.69	0.97
R JM Spl**	97	0.36	0.21	0.41	0.30	4.04	3.56	1.01
R JM Spl NA**	100	0.36	0.21	0.42	0.30	0.83	0.69	0.99
R JM Unspec NA**	45	0.36	0.21	0.41	0.30	0.80	0.60	0.11
SAS %JM Weib*	100	0.35	0.21	0.40	0.28	0.84	0.64	1.32
SAS %JM PWC*	100	0.35	0.21	0.40	0.28	0.82	0.62	1.33
Stata Weib	89	0.29	0.28	0.40	0.29	0.82	0.61	0.91
R joineR	100	0.36	0.20	0.41	0.29	0.84	0.59	1.06

Table S9: Average width of Confidence Intervals from Scenario 3.

* The SAS longitudinal model is misspecified, including a random slope not in the data generation model.

** The Surv X1 and Surv X2 estimates are compared to the value to which they converge and standard errors are estimated through bootstrapping. Details in Section S2.

S4 Other Software Implementations

S4.1 PROC NLMIXED in SAS

Both the %JM and %JMfit SAS macros call PROC NLMIXED to fit the joint model. PROC NLMIXED can also be used separately to fit a joint model in SAS that can not be fit with the macros described above. The NLMIXED procedure was designed for fitting nonlinear mixed models but has been used for fitting joint models (Gould et al., 2014; SAS Institute, 2015b,a; Schabenberger, 2004)(Littell et al., 2006, p.595). The user must specify the joint likelihood of the joint model but this procedure allows for much more flexibility. The association can take any form that the user writes into the joint likelihood. PROC NLMIXED fits the models by approximating the likelihood integrated over the random effects and then maximizing (SAS Institute, 2015b). Different options are available for integral approximation including adaptive Gaussian quadrature and first-order Taylor series expansion.

S4.2 %JMfit Macro in SAS

The %JMfit macro for the SAS software was created to fit joint models and while simultaneously assessing the fit of the models. A full description of the macro is given by Zhang et al. (2016). The %JMfit macro fits only shared parameter models as in (??). This macro can fit a joint model in one of four forms: SPM1L, SPM1Q, SPM2L, and SPM2Q described in (S5).

$$\begin{aligned} \text{SPM1L: } \lambda_i(t) &= \lambda_0(t) \exp\{X_{i2}\gamma + \alpha(b_{0i} + b_{1i}t)\} \\ \text{SPM1Q: } \lambda_i(t) &= \lambda_0(t) \exp\{X_{i2}\gamma + \alpha(b_{0i} + b_{1i}t + b_{2i}t^2)\} \\ \text{SPM2L: } \lambda_i(t) &= \lambda_0(t) \exp\{X_{i2}\gamma + \alpha(b_{0i} + b_{1i})\} \\ \text{SPM2Q: } \lambda_i(t) &= \lambda_0(t) \exp\{X_{i2}\gamma + \alpha(b_{0i} + b_{1i} + b_{2i})\} \end{aligned} \tag{S5}$$

One addition to %JMfit not readily available in other software is built-in decomposition of AIC, BIC, Δ AIC, and Δ BIC for examining goodness-of-fit, and comparing between the

joint model forms (SPM1L, SPM1Q, SPM2L, and SPM2Q)(Zhang et al., 2016). Estimation is done with the PROC NLMIXED procedure. This macro was not able to fit joint models to our simulated data or the adrenal cancer data. This macro generally had issues with the optimization convergence or quadrature accuracy.

S4.3 gsem Command in Stata

The `gsem` command in the `Stata` software was created to fit generalized structural equation models and multilevel data. It can be used for joint modeling with flexible latent processes but the survival outcome must be modeled parametrically (Marchenko, 2016)(Stata Corp LP, 2015, p.449-473). Common distributions for the survival submodel can be specified such as Exponential, Weibull, Gamma, or log-Normal (Stata Corp LP, 2015, p.95,467). The association is through shared parameters as in (??) but it is flexible since any random terms can be included.

S4.4 jmxtstset Command in Stata

The unofficial Stata command `jmxtstcox` fits joint models (Marchenko, 2016) and is currently available from the authors. The joint model in this command has a random-intercept Cox model and uses nonparametric maximum likelihood for estimation of model parameters. This command can also accommodate stratification and standard post-estimation commands in Stata such as `text`, `predict`, and `lincom` (Marchenko, 2016). The `jmxtstcox` command does not yet support random coefficients models; only a random intercept shared parameter model can be fit, but extensions are planned.

S4.5 MATLAB

MATLAB, a mathematical programming language, has been used for joint modeling. Estimation of parameters from the joint likelihood can be achieved with the `fmsearch` and `fmincon` functions, which are unconstrained and constrained nonlinear optimization function, respectively. The first is used when there is a closed form for the parameters, and the

constrained version is for when there is no closed form. This has been used by Thomason (2012) and Hwang (2013) who also provide sample code for MCMC estimation of these parameters in MATLAB.

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