

# Web-based Supplementary Materials for Using the SAEM algorithm for mechanistic joint models characterizing the relationship between nonlinear PSA kinetics and survival in prostate cancer patients

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## Web Appendix A: Preliminary sensitivity analysis

We present below the results of the sensitivity analysis for  $p$  and  $g$  using the longitudinal PSA data and the model which assumed a treatment effect on cell angiogenesis. Four orders of magnitude for  $p$  and  $g$  were explored and selection was made according to the BIC (Web Table 1).

The parameters values were largely insensitive to the change of  $p$  and  $g$  values, except  $N_{max}$ , the maximum number of PSA-producing cells, which, as expected, decreased when  $p$ , the rate of PSA production, increases (Web Tables 2 and 3).

Web Table 1: Estimated BIC (s.e.) according to the values of  $p$  and  $g$  using only the PSA measurements in the 400 patients of the training dataset

	$p$				
	0.2	2	20	200	
$g$	$10^{-5}$	10488 (6)	10586 (5)	10492 (7)	10491 (7)
	$10^{-6}$	10184 (8)	10208 (7)	10238 (7)	10207 (8)
	$10^{-7}$	10166 (8)	10186 (8)	10155 (7)	10194 (7)
	$10^{-8}$	10188 (8)	10165 (7)	10181 (8)	10182 (7)

Web Table 2: Parameters estimates (relative standard error (%)) of PSA kinetics in the 400 patients of the training dataset for the 16 combinations of  $p$  and  $g$  values used in the sensitivity analysis (first part).

	$p = 0.2$ $g = 10^{-5}$	$p = 0.2$ $g = 10^{-6}$	$p = 0.2$ $g = 10^{-7}$	$p = 0.2$ $g = 10^{-8}$	$p = 2$ $g = 10^{-5}$	$p = 2$ $g = 10^{-6}$	$p = 2$ $g = 10^{-7}$	$p = 2$ $g = 10^{-8}$
$\alpha_S$ (day $^{-1}$ )	0.055 (3)	0.064 (3)	0.059 (3)	0.059 (3)	0.055 (3)	0.061 (3)	0.055 (3)	0.067 (3)
$RF$	0.9813 (0)	0.9976 (0)	0.9997 (0)	0.9999 (0)	0.9806 (0)	0.9977 (0)	0.9996 (0)	0.9999 (0)
$RE$	0.80 (1)	0.81 (1)	0.78 (1)	0.78 (1)	0.81 (1)	0.81 (1)	0.77 (1)	0.81 (1)
$\varepsilon$	0.56 (4)	0.44 (4)	0.49 (4)	0.47 (4)	0.55 (4)	0.47 (4)	0.53 (4)	0.41 (4)
$PSA_b$ (ng.mL $^{-1}$ )	21.6 (8)	22.0 (8)	22.1 (8)	22.2 (8)	21.4 (8)	22.1 (8)	22.2 (8)	22.3 (8)
$N_{max}$ (mL $^{-1}$ )	4403 (2)	6248 (2)	4817 (2)	4492 (2)	518 (3)	639 (3)	508 (3)	518 (3)
$\omega_{\alpha_S}$	0.51 (5)	0.53 (4)	0.49 (4)	0.52 (5)	0.54 (5)	0.50 (5)	0.51 (4)	0.47 (5)
$\omega_{RF}$	1.89 (4)	2.28 (4)	2.57 (4)	2.84 (4)	1.92 (4)	2.36 (4)	2.58 (4)	2.73 (4)
$\omega_{RE}$	0.72 (5)	0.69 (4)	0.72 (4)	0.67 (5)	0.75 (4)	0.66 (5)	0.69 (4)	0.64 (4)
$\omega_{\varepsilon}$	1.30 (6)	1.19 (6)	1.26 (6)	1.28 (6)	1.38 (7)	1.22 (5)	1.32 (6)	1.03 (5)
$\omega_{PSA_b}$	1.63 (4)	1.63 (4)	1.63 (4)	1.64 (4)	1.62 (4)	1.63 (4)	1.63 (4)	1.64 (4)
$\omega_{N_{max}}$	2.09 (5)	2.19 (6)	2.14 (5)	2.23 (6)	2.07 (6)	2.25 (6)	2.32 (6)	2.31 (6)
$\sigma$	0.33 (1)	0.32 (1)	0.32 (1)	0.32 (1)	0.33 (1)	0.32 (1)	0.32 (1)	0.32 (1)

Web Table 3: Parameters estimates (relative standard error (%)) of PSA kinetics in the 400 patients of the training dataset for the 16 combinations of  $p$  and  $g$  values used in the sensitivity analysis (second part).

	$p = 20$ $g = 10^{-5}$	$p = 20$ $g = 10^{-6}$	$p = 20$ $g = 10^{-7}$	$p = 20$ $g = 10^{-8}$	$p = 200$ $g = 10^{-5}$	$p = 200$ $g = 10^{-6}$	$p = 200$ $g = 10^{-7}$	$p = 200$ $g = 10^{-8}$
$\alpha_S$ (day $^{-1}$ )	0.065 (3)	0.059 (3)	0.070 (3)	0.063 (3)	0.078 (3)	0.063 (3)	0.068 (3)	0.063 (3)
$RF$	0.9842 (0)	0.9968 (0)	0.9998 (0)	0.9999 (0)	0.9869 (0)	0.9974 (0)	0.9997 (0)	0.9999 (0)
$RE$	0.83 (1)	0.79 (1)	0.83 (1)	0.80 (1)	0.87 (1)	0.81 (1)	0.82 (1)	0.80 (1)
$\varepsilon$	0.45 (4)	0.48 (4)	0.39 (4)	0.44 (4)	0.37 (4)	0.45 (4)	0.41 (4)	0.43 (4)
$PSA_b$ (ng.mL $^{-1}$ )	21.6 (8)	22.1 (8)	22.2 (8)	22.2 (8)	21.5 (8)	21.8 (8)	22.2 (8)	22.5 (8)
$N_{max}$ (mL $^{-1}$ )	72 (4)	48 (4)	62 (4)	50 (4)	8 (8)	6 (9)	6 (9)	6 (9)
$\omega_{\alpha_S}$	0.52 (5)	0.49 (5)	0.45 (4)	0.51 (5)	0.49 (5)	0.51 (4)	0.50 (5)	0.48 (5)
$\omega_{RF}$	1.84 (4)	2.35 (4)	2.62 (4)	2.79 (4)	1.93 (4)	2.38 (4)	2.71 (4)	2.66 (4)
$\omega_{RE}$	0.68 (5)	0.61 (4)	0.64 (4)	0.60 (4)	0.59 (4)	0.66 (5)	0.57 (4)	0.61 (4)
$\omega_{\varepsilon}$	1.14 (6)	1.38 (6)	1.07 (6)	1.25 (6)	1.06 (5)	1.20 (6)	1.16 (6)	1.22 (6)
$\omega_{PSA_b}$	1.63 (4)	1.63 (4)	1.64 (4)	1.65 (4)	1.63 (4)	1.63 (4)	1.63 (4)	1.64 (4)
$\omega_{N_{max}}$	2.26 (6)	2.17 (6)	2.10 (6)	2.08 (5)	2.15 (5)	2.29 (6)	2.12 (5)	2.27 (6)
$\sigma$	0.33 (1)	0.32 (1)	0.32 (1)	0.32 (1)	0.33 (1)	0.32 (1)	0.32 (1)	0.32 (1)

## Web Appendix B: Sensitivity analysis for the baseline hazard function

The assumption of parametric baseline hazard function was relaxed and we evaluated the effect of using piecewise constant, linear and restricted cubic splines, for the final joint model where the baseline hazard function was simply exponential. In each case, spline functions were tested using 3 knots corresponding to the 10<sup>e</sup>, 50<sup>e</sup> and 90<sup>e</sup> percentiles of the observed times-to-death, i.e.,  $t_1 = 192$ ,  $t_2 = 520$  and  $t_3 = 947$  days, respectively (Harrell, 2001).

- The piecewise constant function was defined as followed:

$$h_0(t) = a_1 + a_2\mathbb{1}_{[t_1, t_2[} + a_3\mathbb{1}_{[t_2, t_3[} + a_4\mathbb{1}_{[t_3, \infty[}.$$

- The linear spline function was defined as followed:

$$\log(h_0(t)) = a_1 + a_2t + b_1(t - t_1)_+ + b_2(t - t_2)_+ + b_3(t - t_3)_+$$

$$\text{where } (t - t_1)_+ = \begin{cases} 0 & \text{if } t < t_1 \\ t - t_1 & \text{if } t > t_1 \end{cases}$$

- The restricted cubic spline function was defined as followed:

$$\log(h_0(t)) = a_1 + a_2t + a_3\left[(t - t_1)_+^3 - (t - t_2)_+^3 \frac{t_3 - t_1}{t_3 - t_2} + (t - t_3)_+^3 \frac{t_2 - t_1}{t_3 - t_2}\right]$$

As can be seen in the Web Table 4, none of these models reduced the BIC over the exponential model.

Web Table 4: Parameters estimates (relative standard error (%)) of PSA kinetics and survival in the 400 patients of the training dataset for the 3 spline functions considered for  $h_0$  compared to the final joint model (exponential  $h_0$ )

$h_0$	<b>Exponential</b>		<b>Piecewise constant</b>		<b>Linear spline</b>		<b>Restricted cubic spline</b>	
-2LL	14326 (8)		14317 (7)		14325 (7)		14333 (7)	
BIC	14421 (8)		14431 (7)		14445 (7)		14441 (7)	
$\alpha_S$	0.067	(3)	0.067	(3)	0.081	(3)	0.060	(3)
$RF$	0.9998	(0)	0.9998	(0)	0.9999	(0)	0.9998	(0)
$RE$	0.82	(1)	0.79	(1)	0.84	(0)	0.77	(1)
$\varepsilon$	0.43	(3)	0.43	(4)	0.33	(4)	0.48	(4)
$PSA_b$	21.9	(8)	21.8	(8)	22.0	(8)	22.0	(8)
$N_{max}$	120	(4)	80	(4)	166	(5)	64	(4)
$\lambda$	906	(7)	-	-	-	-	-	-
$a_1$	-	-	0.000913	(3)	-6.79	(1)	-7.09	(1)
$a_2$	-	-	0.00041	(4)	$7.6 \times 10^{-6}$	(15)	0.0014	(13)
$a_3$	-	-	0.00029	(8)	-	-	$-3.7 \times 10^{-9}$	(18)
$a_4$	-	-	$5.0 \times 10^{-6}$	(136)	-	-	-	-
$b_1$	-	-	-	-	$7.7 \times 10^{-6}$	(86)	-	-
$b_2$	-	-	-	-	$7.1 \times 10^{-6}$	(129)	-	-
$b_3$	-	-	-	-	$2.1 \times 10^{-5}$	(472)	-	-
$\beta$	0.00032	(21)	0.0031	(5)	0.0029	(52)	0.011	(10)
$\beta'$	0.39	(7)	0.38	(5)	0.39	(5)	0.36	(11)
$\omega_{\alpha_S}$	0.48	(5)	0.51	(5)	0.51	(5)	0.49	(5)
$\omega_{RF}$	2.55	(4)	2.61	(4)	2.38	(4)	2.47	(4)
$\omega_{RE}$	0.59	(5)	0.10	(5)	0.07	(5)	0.11	(5)
$\omega_\varepsilon$	0.95	(6)	0.97	(6)	0.91	(6)	1.12	(6)
$\omega_{PSA_b}$	1.64	(4)	1.64	(4)	1.64	(4)	1.64	(4)
$\omega_{N_{max}}$	2.57	(7)	2.35	(6)	2.51	(7)	2.37	(6)
$\sigma$	0.32	(1)	0.32	(1)	0.32	(1)	0.32	(1)