A Bayesian destructive weighted Poisson cure rate model and an application to a cutaneous melanoma data

Josemar Rodrigues, Vicente G. Cancho, Mário de Castro, N. Balakrishnan

UFSCar/ICMC-USP/McMaster University-Canada

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Basic ideas

- The accumulated number of lesions or altered cells (initiated cells) follows a weighted Poisson distribution.
- Realistic interpretation of the biological mechanism of the occurrence of the event of interest with the cure fraction after a follow-up period.
- It includes a destructive process of tumor cells after an initial treatment or the capacity of an individual exposed to irradiation to repair altered cells that results in cancer induction.
- What is recorded is only the damaged portion of the original number of altered cells not eliminated by the treatment or repaired by the repair system of an individual (Rodrigues *et al.*, 2009b).
- Markov Chain Monte Carlo (MCMC) methods are used to develop Bayesian inference for the proposed model.

Weighted Poisson Distribution

- The weighted Poisson distributions (WPD) are modified Poisson distributions that provide a unified approach to handle both overdispersion and underdispersion (Kokonendji *et al.*, 2008)

$$p^{\mathrm{w}}(m;\eta,\phi) = P[M^{\mathrm{w}} = m;\eta,\phi] = \frac{\mathrm{w}(m;\phi)p^*(m;\eta)}{E_\eta[\mathrm{w}(M;\phi)]},\ m = 0,1,2,\ldots, \tag{1}$$

where $\mathrm{w}(\cdot;\phi)$ is a non-negative weight function with parameter $\phi \geq 0$ (selection or destructive mechanism of the Poisson distribution), $p^*(\cdot;\eta)$ is the pmf of a Poisson distribution with parameter $\eta > 0$.

Assumptions: Destructive WP cure rate model

- Iniated or altered cells: Let M^{w}: the number of irradiated or lesioned cells with a WPD.
- Repair processes (Klebanov *et al.*, 1993): Each initiated cells are endowed with the capacity to repair radiation injury. Let X_j, $j = 1, 2, \ldots, M^{w}$, be independent random variables, independently of M^{w}, following a Bernoulli distribution with success probability p indicating the presence of the j^{th} lesion .The variable D^{w}, representing the total number of altered cells (among the initial M^{w}) not eliminated by the treatment, is defined as

$$D^{w} = \begin{cases} X_1 + X_2 + \cdots + X_{M^{w}} & \text{if } M^{w} > 0, \\ 0 & \text{if } M^{w} = 0. \end{cases} \tag{2}$$

By damaged or unrepaired irradiation , we mean that $D^{w} \leq M^{w}$. The conditional distribution of D^{w}, given $M^{w} = m$, will therefore be referred to as damaged distribution.

Assumptions (continuation)

- Progression time: The number of unrepaired lesions D^w in (2) and the time V (progression time)to transform theses lesions into a detectable tumor associated are not observable (latent variables). So, the time from the start of the treatment to tumor detection (the event of interest) in a given individual is defined as the r.v.

$$Y = \min\{V_1, V_2, \ldots, V_{D^w}\} \tag{3}$$

for $D^w \geq 1$, and $Y = \infty$ if $D^w = 0$, which leads to a proportion p_0 of the population whose lesions are repaired, also called the "'weighted cured fraction"' . We assume that $V_1, V_2, \ldots$ are independent from D^w. We further assume that, conditional on D^w, the variables V_j are i.i.d..

Model formulation for a prolonged treatment

- According to Rodrigues *et al.* (2008), among others, the compound or damaged weighted cure surviving function of the random variable Y in (3) is given by

$$S_{\text{pop}}(y) = P[Y \geq y] = A_{D^{\text{w}}}\left(S(y)\right) = \sum_{m=0}^{\infty} P[D^{\text{w}} = m]\left\{S(y)\right\}^{m},$$

where $S(\cdot)$ denotes the common surviving function of the unobserved promotion time in (3) and $A_{D^{\text{w}}}(\cdot)$ is the probability generating function (pgf) of the compound variable D^{w}, which converges when $s = S(y) \in [0, 1]$

Model formulation for a prolonged treatment (continuation)

- The destructive weighted Poisson cure rate surviving function is given by

$$S_{\text{pop}}(y;\eta,\phi,p) = \exp\{-\eta p F(y)\}\frac{E_{\eta\{1-pF(y)\}}[\text{w}(M;\phi)]}{E_{\eta}[\text{w}(M;\phi)]}, \qquad (4)$$

where $F(y) = 1 - S(y)$. If we take $p = 1$, we get the weighted Poisson long-term surviving function in Rodrigues *et al.* (2009a).

Weighted cure rate (Rodrigues *et al.*, 2009b)

Theorem

Given a proper surviving function $S(\cdot)$ and $\mathrm{w}(0;\phi) > 0$, we have

$$\lim_{y\to\infty} S_{\mathrm{pop}}(y;\eta,\phi,p) = p_0 = \exp(-\eta p)\frac{E_{\eta(1-p)}[\mathrm{w}(M;\phi)]}{E_{\eta}[\mathrm{w}(M;\phi)]}, \qquad (5)$$

where p_0 denotes the proportion of "cured" or "immune" individuals present in the population from which the data were taken.

$$\eta = \underbrace{\eta p}_{\text{unrepair}} + \overbrace{\eta(1-p)}^{\text{repair}}$$

Model formulation for a prolonged treatment (continuation)

- We present the pmf of the variable D^{w} in (2). It follows from the fundamental formula for conditional probabilities that

$$P[D^{\mathrm{w}} = j; \eta, \phi, p] = \sum_{m=0}^{\infty} \underbrace{p^{\mathrm{w}}(m; \eta, \phi)}_{\text{weighted Poisson}} \overbrace{P[D^{\mathrm{w}} = j | M^{\mathrm{w}} = m; p]}^{\text{damaged distribution}}. \quad (6)$$

Destructive weighted Poisson distribution (Rodrigues *et al.*, 2009b)

In the next theorem, we present the pmf of the variable D^{w} in (2).

Theorem

Let the pmf of the discrete variable M^{w} be as before. Then, the compound variable D^{w} has a weighted Poisson distribution with parameter ηp and with weight function

$$\mathrm{w}_p(j;\eta,\phi,p) = E_{\eta(1-p)}[\mathrm{w}(j+U;\phi)], \tag{7}$$

where $U = M - j$ is a Poisson variable with parameter $\eta(1-p)$.

Some specific models (Rodrigues *et al.*, 2009b)

Table: Surviving function (S_{pop}), density function (f_{pop}) and cured fraction (p_0) for different destructive weighted Poisson cure rate models.

Destructive models	$S_{\text{pop}}(y)$	$f_{\text{pop}}(y)$	p_0
Length-biased Poisson $(\text{w}(m;\eta,\phi)=m)$	$e^{-\eta pF(y)}\{1-pF(y)\}$	$p\left\{\eta+\frac{1}{1-pF(y)}\right\}S_{\text{pop}}(y)f(y)$	$(1-p)e^{-\eta p}$
Exponentially weighted Poisson $(\text{w}(m;\phi)=e^{\phi m})$	$\exp\{-\eta pF(y)(2-e^{\phi})\}$	$\eta p(2-e^{\phi})S_{\text{pop}}(y)f(y)$	$\exp\{-\eta p(2-e^{\phi})\}$
Negative binomial $(\text{w}(m;\phi)=\Gamma(\phi^{-1}+m))$	$\{1+\phi\eta pF(y)\}^{-1/\phi}$	$\frac{\eta p}{1+\phi\eta pF(y)}S_{\text{pop}}(y)f(y)$	$(1+\phi\eta p)^{-1/\phi}$
COM–Poisson $(\text{w}(m;\phi)=(m!)^{1-\phi})$	$\frac{Z(\eta\{1-pF(y)\},\phi)}{Z(\eta,\phi)}$	$\frac{pf(y)}{Z(\eta,\phi)\{1-pF(y)\}}\sum_{j=1}^{\infty}\frac{j[\eta\{1-pF(y)\}]^j}{(j!)^{\phi}}$	$\frac{Z(\eta(1-p),\phi)}{Z(\eta,\phi)}$

Bayesian Inference (Rodrigues *et al.*, 2010)

- The likelihood function under non-informative censoring is given by

$$L(\boldsymbol{\vartheta}; \mathbf{t}, \boldsymbol{\delta}) \propto \prod_{i=1}^{n} \{f_{\text{pop}}(t_i; \boldsymbol{\vartheta})\}^{\delta_i} \{S_{\text{pop}}(t_i; \boldsymbol{\vartheta})\}^{1-\delta_i}, \tag{8}$$

- We shall assume a Weibull distribution for the unobserved lifetime in (3) with $F(v; \boldsymbol{\gamma}) = 1 - \exp(-v^{\gamma_1} e^{\gamma_2})$ and $f(v; \boldsymbol{\gamma}) = \gamma_1 v^{\gamma_1 - 1} \exp(\gamma_2 - v^{\gamma_1} e^{\gamma_2})$, for $v > 0$, $\gamma_1 > 0$ and $\gamma_2 \in \mathbb{R}$.
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$$\pi(\boldsymbol{\vartheta}) = \prod_{j=1}^{k_1} \pi(\beta_{1_j}) \prod_{j=1}^{k_2} \pi(\beta_{2_j}) \pi(\gamma_1) \pi(\gamma_2) \pi(\phi), \tag{9}$$

where $\beta_{1_j} \sim N(0, \sigma^2_{1_j})$, $j = 1, \ldots, k_1$, $\beta_{2_j} \sim N(0, \sigma^2_{2_j})$, $j = 1, \ldots, k_2$, $\gamma_1 \sim \text{Gamma}(a, b)$ and $\gamma_2 \sim N_1(0, \sigma^2_{\gamma_2})$, whereas $\phi \sim \text{U}(0, \log(2))$ for the exponentially weighted Poisson model and $\phi \sim \text{Gamma}(a, b)$ for the negative binomial and COM–Poisson models. Here, all the hyper-parameters are specified in order to ensure vague prior distributions.

Bayesian Inference (continuation)

- The link functions

$$\log\left(\frac{p_i}{1-p_i}\right) = \mathbf{x}_{1i}^{\top}\boldsymbol{\beta}_1 \quad \text{and} \quad \log(\eta_i) = \mathbf{x}_{2i}^{\top}\boldsymbol{\beta}_2, \tag{10}$$

  $i = 1, \ldots, n$, where $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$ denote vectors with k_1 and k_2 coefficients.

- The full conditional distributions of the parameters:

$$\pi(\boldsymbol{\beta}_1|\boldsymbol{\beta}_2, \gamma_1, \gamma_2, \phi, \mathbf{t}, \boldsymbol{\delta}) \propto L(\boldsymbol{\vartheta}; \mathbf{t}, \boldsymbol{\delta})\pi(\boldsymbol{\beta}_1),$$

$$\pi(\boldsymbol{\beta}_2|\boldsymbol{\beta}_1, \gamma_1, \gamma_2, \phi, \mathbf{t}, \boldsymbol{\delta}) \propto L(\boldsymbol{\vartheta}; \mathbf{t}, \boldsymbol{\delta})\pi(\boldsymbol{\beta}_2),$$

$$\pi(\gamma_1|\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \gamma_2, \phi, \mathbf{t}, \boldsymbol{\delta}) \propto L(\boldsymbol{\vartheta}; \mathbf{t}, \boldsymbol{\delta})\pi(\gamma_1),$$

$$\pi(\gamma_2|\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \gamma_1, \phi, \mathbf{t}, \boldsymbol{\delta}) \propto L(\boldsymbol{\vartheta}; \mathbf{t}, \boldsymbol{\delta})\pi(\gamma_2)$$

  and $\pi(\phi|\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \gamma_1, \gamma_2, \mathbf{t}, \boldsymbol{\delta}) \propto L(\boldsymbol{\vartheta}; \mathbf{t}, \boldsymbol{\delta})\pi(\phi)$. MCMC computations were implemented using the OpenBUGS 3.0.3 system Thomas *et al.* (2006).

Application:Cutaneous melanoma data

The data are part of an assay on cutaneous melanoma for the evaluation of postoperative treatment performance with a high dose of a certain drug (interferon alfa-2b) in order to prevent recurrence. The data were taken from Ibrahim *et al.* (2001) (E1690 data, available at http://merlot.stat.uconn.edu/~mhchen/survbook/; see also Kirkwood *et al.* (2000)). The sample comprises 417 patients without missing values. The observed time refers to the time in years until the patient's death or the censoring time (mean = 3.18 and standard deviation = 1.69). The percentage of censored observations was 56%. For illustrative purposes, we link the parameters p and η in (10) to nodule category (x_1) (1, n=82; 2, n=87; 3, n=137; 4, n=111) and age (x_2) (in years, mean = 48.0 and standard deviation = 13.1), respectively. Nodule category ranging from 1 to 4, respectively, is coded from the number of lymph nodes involved in the disease (0, 1, 2–3, and $\geq$4).

$$\log\left(\frac{p_i}{1-p_i}\right) = \beta_{1_0} + x_{1_i}\beta_{1_1} \quad \text{and} \quad \log(\eta_i) = x_{2_i}\beta_{2_1}, \quad i = 1, \ldots, 417. \tag{11}$$

Application (continuation)

Table: Model selection criteria on the adjusted models.

	Criterion			
Destructive model	*DIC*	*EAIC*	*EBIC*	*B*
Length-biased Poisson	1043.29	1049.25	1069.42	-521.76
Exponentially weighted Poisson	1036.78	1041.77	1065.97	-517.35
Negative binomial	1028.67	1035.19	1059.37	-514.42
COM–Poisson	1030.44	1037.34	1061.55	-515.07
Geometric	1028.97	1034.07	1054.24	-514.61

Application: (continuation)

Table: Posterior summaries for the probability of the presence of a competing cause (p) stratified by nodule category (1 to 4) under the destructive geometric model.

Probability of the presence of competing cause	Mean	Standard deviation	Percentile	
			2.5%	97.5%
p_1	0.200	0.066	0.098	0.356
p_2	0.388	0.122	0.192	0.677
p_3	0.599	0.152	0.323	0.904
p_4	0.767	0.136	0.478	0.977

Application (continuation)

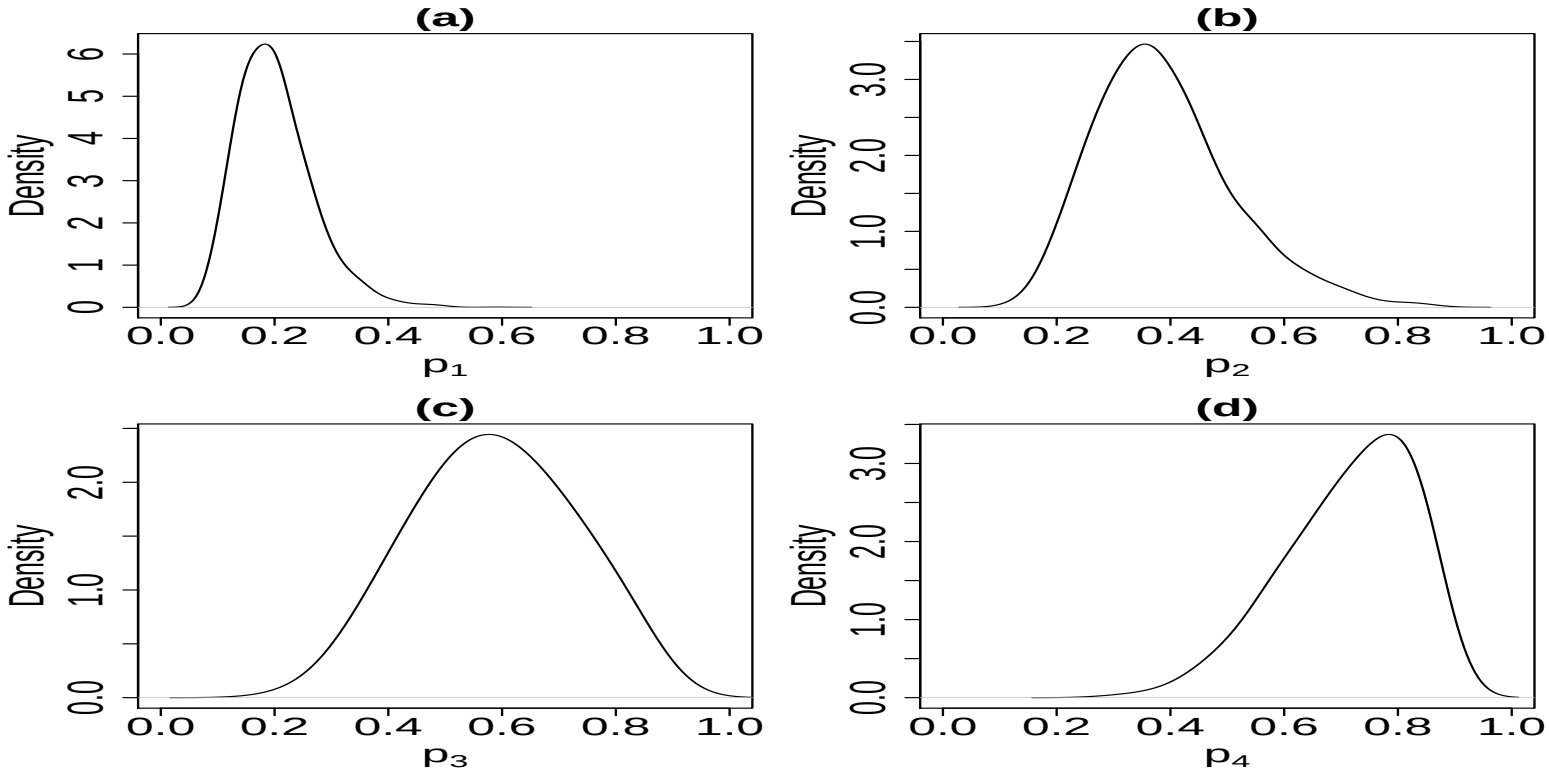

Figure: Approximate marginal posterior densities of the probability of presence of a competing cause (p) for the destructive geometric model according to nodule category from 1 (a) to 4 (d).

Application (continuation)

Table: Posterior summaries of the cured fraction (p_0) stratified by nodule category (1 to 4) for different ages under the destructive geometric model.

Age	Cured fraction	Mean	Standard deviation	Percentile	
				2.5%	97.5%
29	p_{0_1}	0.906	0.018	0.867	0.938
	p_{0_2}	0.834	0.023	0.783	0.876
	p_{0_3}	0.762	0.033	0.696	0.829
	p_{0_4}	0.710	0.042	0.635	0.805
47	p_{0_1}	0.857	0.026	0.801	0.903
	p_{0_2}	0.756	0.031	0.690	0.813
	p_{0_3}	0.664	0.041	0.586	0.749
	p_{0_4}	0.603	0.050	0.518	0.719
70	p_{0_1}	0.801	0.033	0.730	0.862
	p_{0_2}	0.676	0.036	0.600	0.745
	p_{0_3}	0.571	0.045	0.487	0.668
	p_{0_4}	0.506	0.053	0.419	0.632

Application (continuation)

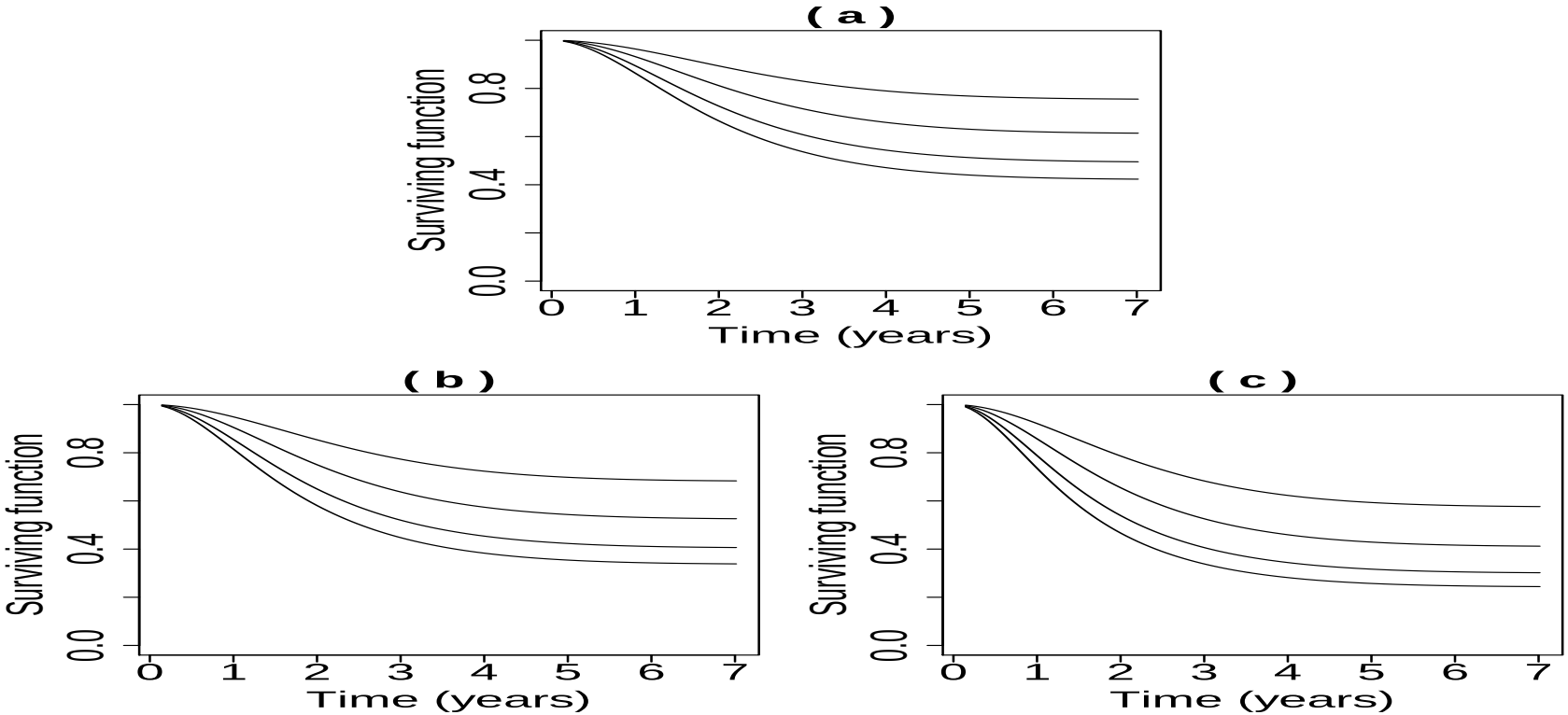

Figure: Surviving function under the destructive geometric model stratified by nodule category (1 to 4, from top to bottom) for (a) 29, (b) 47 and (c) 70 years old patients.

Conclusions

- The initial number of tumor cells in a competitive scenario is subject to a damage or repair system according to the binomial probability law.
- The cutaneous melanoma data was analyzed from a Bayesian viewpoint with vague prior distributions using MCMC procedures. The results are presented in many tables and plots, without considering the asymptotic results as is done usually in the frequentist theory.
- The Bayesian procedure and the destructive weighted Poisson cure rate model formulated here may be useful in assessing the probability of presence of the tumor cells after a prolonged treatment or the cured proportion of individuals in a population.
- The model may provide a Bayesian perspective to the stochastic model of radiation carcinogenesis and investigations involving the chemical induction of tumors in experimental animals in order to test the chemopreventative effects of various substances.

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