Relaxed Poisson cure rate models

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ISI-Rio de Janeiro-2015

Outline

- Motivation
- Poisson cure rate model.
- Mittag-Leffler renewal process in $[0, 1]$
- Relaxed Poisson cure rate models.
- Simulation study
- Conclusions
- References.

Diagram: Latent model with renewal process in [0, 1]

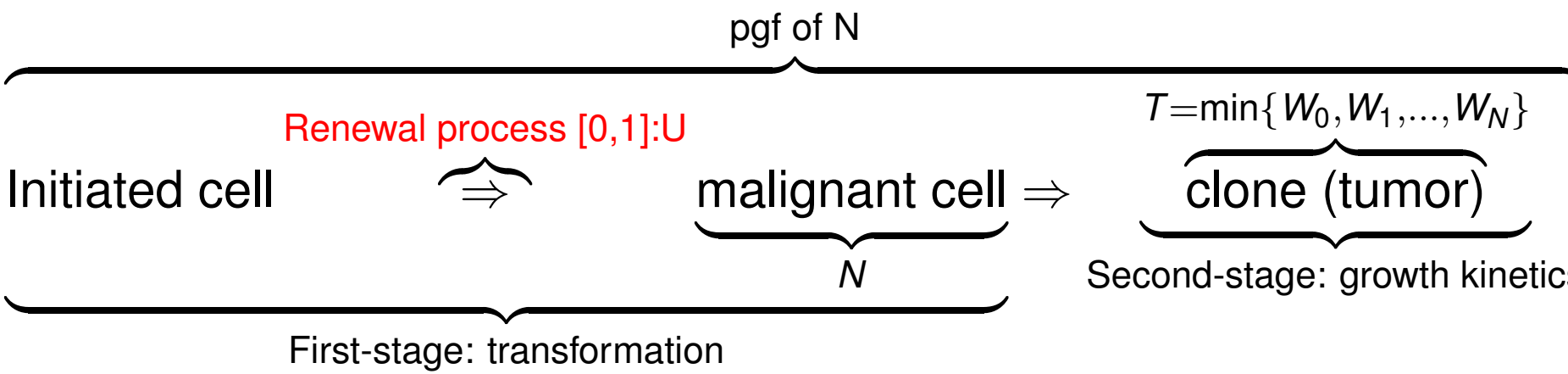

Figure: Two-stage carcinogenesis process (U: inter-renewal time between malignant cells and $P[W_0 = \infty] = 1$.)

Justifications:

- Dispersion (lack of independence between damaged cells, contagion, clustering, and heterogeneity): The number of damaged cell (N) could show a variability that differs from what they expect on the basis of the hypothesized model (Poisson). The variance=mean can be collapsed by the presence of dispersion.
- To interpret the dispersion of the malignant cells in terms of the risk function of the waiting time U.
- To make new generalizations of the Poisson cure model taking into account the dispersion scenario.
- The renewal process could be seen as a repair mechanism of initiated cells.

Poisson cure rate model(Yakovlev & Tsodikov, 1996)

- Renewal Poisson process on $[0, 1]$:

$$P[N = n] = \frac{\lambda^n e^{-\lambda}}{n!}$$

- Probability generating function: $A_N(s) = e^{-\lambda(1-s)}$.
- Survival function:$S_p(t) = P[T > t] = e^{-\lambda F(t)},\ t > 0$
- Cure rate :$p(0) = P[U_1 > 1] = P[N = 0] = e^{-\lambda}$
- Simulation study:

$$T = \begin{cases} Q_X(U), & \text{for } 0 < U \leq 1, \\ \infty, & \text{for } U \geq 1, \end{cases} \tag{1}$$

where $Q_W(.) = F^{-1}(.)$ is the quantil function and $U \sim \text{Exp}(\lambda)$.

The Mittag-Leffler function

- The Mittag-Leffler function $E_\alpha(z)$ is a fractional generalization of the exponential function $\exp(z)$ and it is defined by power series

$$E_\alpha(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k + 1)} = {}_1\Psi_1 \left[\begin{matrix} (1,1) \\ (1,\alpha) \end{matrix} ; z \right], \qquad (2)$$

  where $z > 0$, $\alpha > 0$ and ${}_1\Psi_1$ is the well-known Wright generalized hipergeometric function.
- This function was discovered by a Swedish Mathematician G.M. Mittag-Leffler (Mittag-Leffler, 1903) in 1902.
- Very popular in solving the problems of fractional order differential and integral equations, control systems and refined mathematical models of various physical, chemical, economical, management and bioengineering phenomena.

Risk function

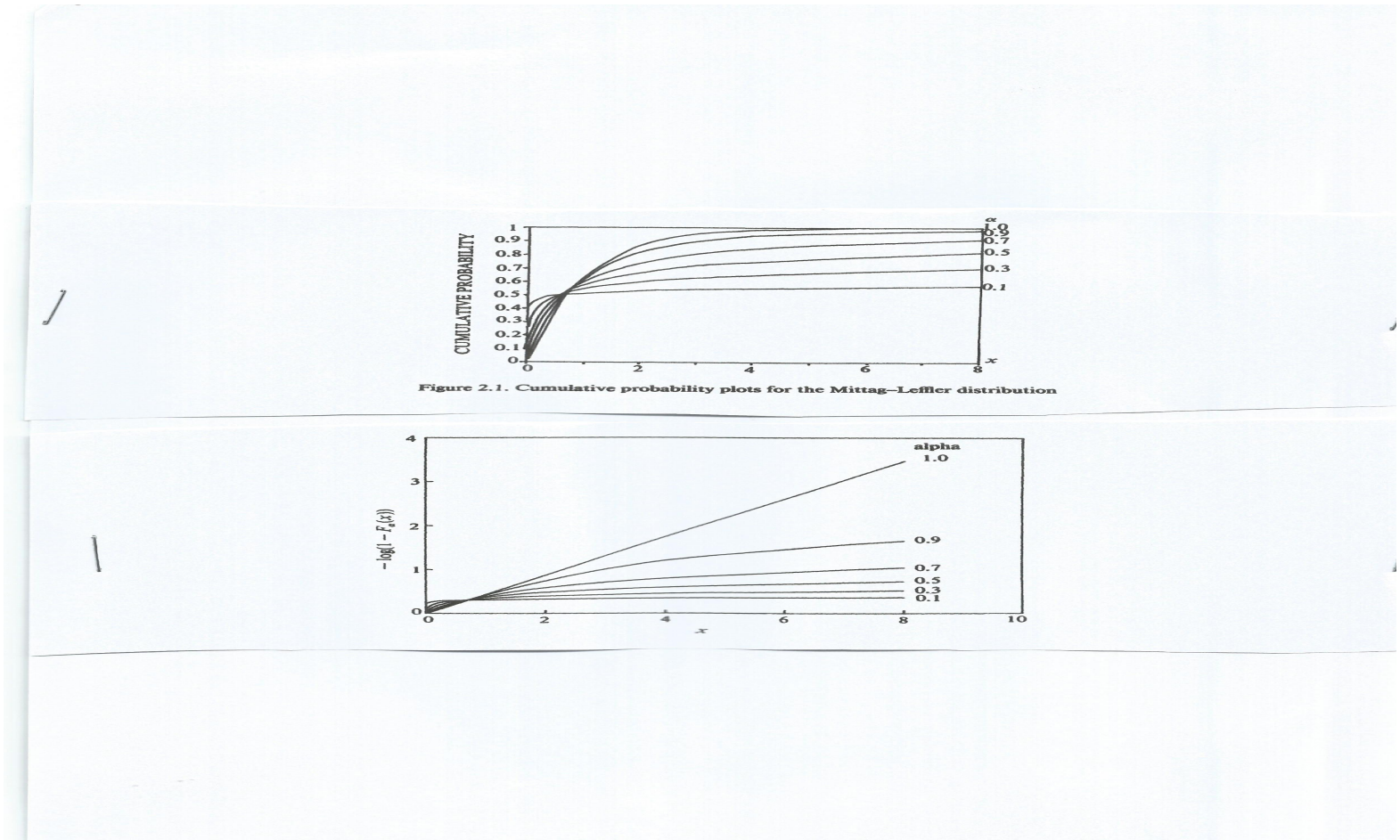

Figure: Cumulative distribution (Hazard) for ML distribution

Mittag-Leffler renewal process in $[0, 1]$

- Mittag-Leffler distribution of order α and scale parameter λ: It is an extension of the exponential distribution (Cahoy *et al.*, 2010) and given by

$$\Psi(t) = 1 - E_\alpha(-\lambda t^\alpha), \ t > 0, \tag{3}$$

  for $0 < \alpha \leq 1$ and $\lambda > 0$.
- Inter-arrival time: $U_i \sim ML(\alpha, \lambda)$.
- Relaxed P. process: Let $M = \max\{m : \ \sum_{i=1}^{m} U_i \leq 1\}$.

$$p(m; \lambda, \alpha) = P[M = m; \lambda, \alpha] = \frac{\lambda^m}{m!} \sum_{k=0}^{\infty} \frac{(m+k)!}{k!} \frac{(-\lambda)^k}{\Gamma(\alpha(k+m)+1)}, \tag{4}$$

  for $0 < \alpha \leq 1$.
- It makes the standard Poisson model more flexible by permitting non- exponential and heavy-tailed distributions which accommodates over-dispersion.

Relaxed Poisson survival function

- Probability generation function (Laskin, 2003):

$$A_M(s;\lambda,\alpha) = E_\alpha(\lambda(s-1)). \tag{5}$$

- Relaxed Poisson survival function(Rodrigues *et al.*, 2009):

$$S_\alpha(t) = P[T > t] = A_M(S(t);\lambda,\alpha) = E_\alpha(-\lambda F(t)). \tag{6}$$

Remark: From Berberan-Santos (2005) we obtain the promotion cure rate model and the geometric cure rate models as the limit cases as follows:

$$S_\alpha(t) = \begin{cases} \frac{1}{1+\lambda F(t)} & \text{for } \alpha = 0, \\ e^{-\lambda F(t)} & \text{for } \alpha = 1, \end{cases} \tag{7}$$

- Relaxed cure rate :

$$p_0 = P[M = 0] = E_\alpha(-\lambda) \tag{8}$$

Simulation study:

- Inter-arrival time: $U \sim ML(\alpha, \lambda)$.
- Simulation procedure: It flexibilizes the simulation procedure in (9).

$$T = \begin{cases} Q_X(U^\alpha), & \text{for } 0 < U^\alpha \leq 1, \\ \infty, & \text{for } U^\alpha \geq 1, \end{cases} \tag{9}$$

- Mittag-Leffler distribution: Let $V_i, i = 1, 2, 3$ independent uniform random variables in $[0, 1]$.

$$U = \frac{|\log(V_1)|^{\frac{1}{\alpha}}}{\lambda^{\frac{1}{\alpha}}} \frac{\sin(\alpha\pi V_2)[\sin(1-\alpha)\pi V_2]^{1/\alpha-1}}{[\sin(\pi V_2)]^{1/\alpha} |\log(V_3)|^{1/\alpha-1}}. \tag{10}$$

- Fractional Poisson process in $[0, 1]$.

$$M = \max\{m : \sum_{i=1}^{m} U_i \leq 1\}.$$

Example with simulated data

- We generate 200 observed times following the procedure in (9) with $\alpha = 0.5$ and $\lambda_i = \exp(\beta_0 + \beta_1 w_i)$, where the covariate w_i is generated from a Bernoulli with probability 0.5. We take $\beta_0 = -0.5$ and $\beta_1 = 0.7$.
- Weibull distribution : $W_i \sim$ Weibull(2,2)
- The censoring times are sampled from the uniform $(0, \rho)$, where ρ is set in order to control the proportion of censored observations on average to be approximately 55%.
- For Bayesian analysis we consider the following independent priors to perform the Metropolis–Hasting algorithm: $\beta_k \sim N(0, 10^2)$, $k = 0, 1$, $\gamma_l \sim$ G$(1, 0.01)$, $l = 1, 2$ and $\pi(\alpha) = 1/5$, for $\alpha \in \{0, 0.25, 0.5, 0.75, 1\}$.

Bayesian inference

Table: Posterior summaries of the parameters for the cure rate model in (6) for artificial data and $\alpha = 0.5$.

Parameter	Mean	Median	Standard deviation	HPD Interval (95	
				L	U
$\gamma_1 = 2$	1.963	1.984	0.093	1.751	2.15
$\gamma_2 = 2$	2.171	2.165	0.124	1.945	2.44
$\beta_0 = -0.5$	-0.551	-0.542	0.130	-0.8128	-0.31
$\beta_1 = 0.7$	0.693	0.6925	0.171	0.348	1.03

Posterior distribution for α

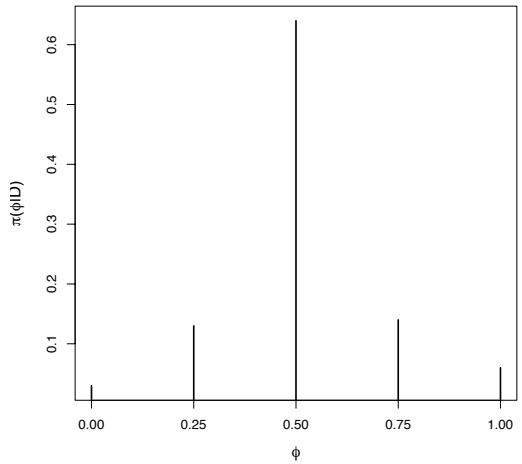

Figure: Posterior distribution of α.

Bayesian inference

Table: Posterior summaries of the parameters for the promotion cure rate model for artificial data.

Parameter	Mean	Median	Standard deviation	HPD Interval (9	
				L	U
$\gamma_1 = 2$	0.592	0.594	0.0848	0.4159	0.74
$\gamma_2 = 2$	0.6576	0.6548	0.0736	0.52031	0.81
$\beta_0 = -0.5$	-0.551	-0.5374	0.130	-0.8933	-0.2
$\beta_1 = 0.7$	0.5161	0.5104	0.2159	0.08087	0.93

Bayesian inference

Table: Bayesian criteria for the fitted models.

	DIC	EAIC	EBIC	LPML
Mittag-Lefller	107.7637	112.4998	128.9913	-52.74415
Promotion Time	444.4623	448.5852	461.7785	-222.1674

Conclusions:

To propose a new flexible cure rate model where the accumulated number of lesions or altered cells (M) follows a relaxed Poisson distribution such that:

- It is natural bridge between the popular promotion cure rate model and the geometric cure rate model.
- Take into account the over-dispersion of the damaged cells (clonogens).
- Survival function with a nice biological interpretation for the behavior of the neoplastic cells (clonogens) that give rise to malignant tumor regeneration.
- The renewal process could be seen as a repair mechanism of initiated cells.

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