Modeling and Identifiability of Non-homogeneous Poisson Process Cure rate Model

Technical Report No. ASU/2022/2
Dated 12 May, 2022

C S Soorya, Department of Statistics, Cochin University of Science and Technology
G Asha, Department of Statistics, Cochin University of Science and Technology
and
Anup Dewanji, Applied Statistics Unit, Indian Statistical Institute, Kolkata

Applied Statistics Unit
Indian Statistical Institute
Kolkata 700 108

Modeling and Identifiability of Non-homogeneous Poisson Process Cure rate Model

Soorya C S [1], G Asha[2] and Anup Dewanji[3]
1, 2. *Department of Statistics Cochin University of Science and Technology, Cochin-22 India.*
3. *Applied Statistics Unit, Indian Statistical Institute, Kolkata, India.*

Abstract

The promotion time cure models or bounded cumulative hazards model(BCH) was proposed as an alternative to the mixture cure models. In the present paper, this model is modified to provide a class of cure rate models based on a non-homogeneous poisson process. The properties of this class are studied. Also, when censored observations are present, distinguishing censored individuals from the cured group lead to identifiability issues in the members of this class. These identifiability issues are investigated and finally few members of this class are provided.

Keywords: Cure rate, Identifiability, Non-homogenous Poisson process.

1. Introduction

In classical survival analysis, one of the main assumptions is to consider that all subjects will eventually experience the event of interest. But it often happens that a fraction of subjects will never experience it. These subjects are usually considered as having infinite survival times and are said to be cured. In order to take this feature into account, classical survival models have been extended to what are commonly referred to as cure models. A prominent example comes from medical studies where one is interested in the time until the recurrence of a certain disease. Some patients will never suffer a relapse of a given disease and are hence cured of their disease. In the literature, two main families of cure regression models have been proposed, called mixture cure models and promotion time cure models. The latter models are also called bounded cumulative hazard(BCH) models or proportional hazards (PH) cure models.

The mixture cure model was proposed by Boag [2] and Berkson and Gage [1] and belongs to the class of two-part models that considers jointly the modeling of a response variable for two different groups identified by a binary variable. The BCH model was proposed by Yakovlev et al. [12] as an adaptation of the Cox [4] PH model to allow for a cure fraction, and that has a strong appeal for its natural biological interpretation. The model is often phrased in terms of times to relapse of cancer, since it has a clear biological interpretation in that context. The probability of tumor cure for the model proposed by Yakovlev et al. [12] is defined as the probability of no carcinogenic tumor cells surviving by the end of treatment. A cell is carcinogenic if it is capable of producing a cell clone, that is a group of cells that have this cell as their common parent. There is biological evidence that the majority of recurrent tumors are clonal in origin (You et al. [14], Tang et al. [11]).

[1]Corresponding author email: asha@cuast.ac.in

Chen et al. [3] provided a natural motivation and interpretation of Yakovlev et al. [12] model and derived several novel properties of it. The model proposed is a simple mechanistically motivated model of tumor recurrence yielding an improper survival distribution.
Suppose an individual is assumed to have N carcinogenic cells left active after the initial treatment, where $N \geq 0$ has a Poisson distribution with mean λ. Let Z_j be the time that the j^{th} carcinogenic cell to produce an observable cancer mass. The Z_j are assumed to be independent and identically distributed with some distribution function $F(t) = 1 - S(t)$. The time to relapse of cancer can be defined by $T = min\{Z_j; 1 \leq j \leq N\}$, where $N \sim Poisson(\lambda)$. The survival function for the population, denoted by S_{BCH}, is given by

$$\begin{aligned} S_{BCH}(t) &= \text{P(no observable cancer cell by time t)} \\ &= P[N = 0] + P[N > 1, Z_1 > t, ..., Z_N > t] \\ &= e^{-\lambda} + \sum_{k=1}^{\infty} S(t)^k \frac{\lambda^k}{k!} e^{-\lambda} \\ &= e^{-\lambda F(t)} \end{aligned} \tag{1.1}$$

The parameter λ represents the mean number of carcinogenic cells. In presence of covariates, which are mainly introduced through λ, this parameter has a double interpretation. First, when λ is large, the number of carcinogenic cells is large and the probability of being cured is small. Second, a larger value for λ is also representative of a lower survival probability because a larger number of carcinogenic cells induces a smaller survival time. As can be seen, λ contains two types of effects, on the cure probability and on the survival, which cannot be separated. For cured observations, the associated probability is given by $\lim_{t\to\infty} S_{pop}(t) = \exp(-\lambda)$.
Since N is the number of active cancer cells after the initial treatment, it need not be time dependent. But cancer cells are also born due to instantaneous mutation from the pool of normal stem cells. So, in addition to the N cancer cells left after the initial treatment, there is a continuous though the rare flow of mutated cancer cells from the pool of normal stem cells. Also, the initial N cells go through the natural process of cell division and death. Even though in the model (1.1), parameters have some clear biological meaning, it has a drawback in the sense that it fails to include this additional flow of cancer cells due to mutation, cell division and also cell death. Therefore, the total number of carcinogenic cells is a stochastic function of time. In this paper, we propose a model to overcome this. Let $N(t)$ be the number of active cancer cells at time t. For simplicity, we make the simplistic assumption that these $N(t)$ carcinogenic cells arise according to a non-homogeneous Poisson process (NHPP) with rate $\lambda(t)$ and $N(0) = 0$.

The remainder of the paper is organised as follows. Section 2 introduces and details the non-homogeneous Poisson process cure model (NHPP Cure Model). The model is generally not identifiable. We examine these identifiability issues of the proposed model and provide conditions for the same in Section 3. Examples of identifiable models with different baseline distributions and intensity functions are presented in Section 4. In Section 5, we present a simulation algorithm for simulating right censored data from the models discussed in Section 3. We conclude this paper with a discussion and summary on our findings in Section 6.

2. Non-homogeneous poisson process(NHPP) cure rate model

Let $N(t)$ be the number of carcinogenic cells present at time t. Assume that $N(t)$ has Non Homogeneous Poisson Process (NHPP) with intensity $\lambda(t)$. The mean value function $\Lambda(t) = \int_0^t \lambda(u)du$. Let s_j denote the time to inception of the j^{th} carcinogenic cell. Let w_j denote the time, since inception at time s_j, required by the j^{th} carcinogenic cell to develop to a detectable cancer mass or clone. Define a response function $Y(t-s_j, w_j)$ as

$$Y(t-s_j, w_j) = \begin{cases} 0, & \text{if } w_j > t-s_j \\ 1, & \text{Otherwise} \end{cases} \tag{2.1}$$

Note that $P[Y(t-s_j, w_j) = 0] = S(t-s_j)$ where $S(t) = P[w_j > t]$ such that $\lim_{t\to\infty} S(t) = \theta$, $0 \leq \theta < 1$. This means that there may be a positive probability θ that a carcinogenic cell does not at all grow to a be detectable clone.This is a clear possibility if the clonal growth is explained by a linear birth and death process (Moolgavkar and Luebeck [9]).

If $Z(t)$ is the total number of diagnosed carcinogenic clone at time t, then

$$Z(t) = \sum_{j=1}^{N(t)} Y(t-s_j, w_j). \tag{2.2}$$

Then $Z(t)$ has a Filtered Non Homogeneous Poisson Process (FNHPP) Parzen [10] (page no:145). For the $FNHPP$ defined by (2.2), for any $t > 0$ and real number u, the characteristic function of $Z(t)$ is

$$\phi_{Z(t)}(u) = \exp \int_0^t \lambda(s) \exp[iu-1] F(t-s) ds, \tag{2.3}$$

where $F(t) = 1 - S(t)$. This implies that $Z(t)$ follows a Poisson distribution with

$$E[Z(t)] = \int_0^t \lambda(s) F(t-s) ds. \tag{2.4}$$

Therefore, if T denotes the disease free time of an individual, then the survival function of T, denoted by $S_{pop}(t)$, is given by

$$\begin{aligned} S_{pop}(t) =& P[T > t] = P[Z(t) = 0] \\ =& e^{-\int_0^t \lambda(s) F(t-s) ds}. \end{aligned} \tag{2.5}$$

It is interesting to look into conditions under which $S_{pop}(t)$ in (2.5) qualifies as a cure rate model. The next few results discussed are focused in this direction.

Theorem 2.1. *For a given baseline distribution $F(t)$ or equivalently baseline survival distribution $S(t)$ with $\lim_{t\to\infty} S(t) = \theta$, $0 \leq \theta < 1$,*

$$\lim_{t\to\infty} S_{pop}(t) = 0 \iff \lim_{t\to\infty} \Lambda(t) = \lim_{t\to\infty} \int_0^t \lambda(u)du = \infty. \tag{2.6}$$

Proof. Write

$$D(t) = \int_0^t \lambda(s)\big(1 - S(t-s)\big)ds$$

so that,

$$S_{pop}(t) = \exp\left[-D(t)\right] \tag{2.7}$$

It is equivalent to show that

$$\lim_{t\to\infty} D(t) = \infty \iff \lim_{t\to\infty} \Lambda(t) = \infty$$

Since $S(t) \to \theta$, for every $\varepsilon > 0$, there exists a t_0 such that $\forall t \geq t_0$,

$$S(t) - \theta \leq \varepsilon$$

implying,

$$1 - S(t) \geq 1 - (\theta + \varepsilon).$$

Note that

$$D(t) = \int_0^t \lambda(s)\big(1 - S(t-s)\big)ds = \int_0^t \lambda(t-u)\big(1 - S(u)\big)du$$

For $t \geq t_0$, we have

$$\begin{aligned} D(t) &\geq \int_0^{t_0} \lambda(t-u)\big(1 - S(u)\big)du + \big(1 - (\theta+\varepsilon)\big)\int_{t_0}^t \lambda(t-u)du \\ &= \int_0^{t_0} \lambda(t-u)\big(1 - S(u)\big)du + \big(1 - (\theta+\varepsilon)\big)\int_0^{t-t_0} \lambda(u)du \end{aligned}$$

For $\Lambda(t) \to \infty$, we have $\int_0^{t-t_0} \lambda(u)du \to \infty$ as $t \to \infty$. Hence, choosing $\varepsilon > 0$, such that $\big(1 - (\theta + \varepsilon)\big) > 0$, $D(t) \to \infty$ as $t \to \infty$. Conversely, since $D(t) \leq \int_0^t \lambda(s)\,ds$ (since $1 - S(t-s) \leq 1$), as $D(t) \to \infty$, we have $\Lambda(t) \to \infty$ as $t \to \infty$. □

Hence from Theorem 2.1, it follows that if the mean intensity function $\Lambda(t) \to \infty$ then $S_{pop}(t) \to 0$ as $t \to \infty$. This means that a bounded cumulative intensity should reflect a cure rate model with $\lim_{t\to\infty} S_{pop}(t) > 0$, as stated in the corollary below.

Corollary 2.1. *For a given baseline $S(t)$ with $\lim_{t\to\infty} S(t) = \theta$, for $0 \leq \theta < 1$,*

$$\lim_{t\to\infty} S_{pop}(t) > 0 \iff \lim_{t\to\infty} \Lambda(t) < \infty$$

Theorem 2.2. *For a given baseline $S(t)$ with $\lim_{t\to\infty} S(t) = \theta$, and $\lim_{t\to\infty} \Lambda(t) = \alpha < \infty$, for any positive real α, the survival function of T, as in (2.5) has a cure fraction*

$$c = \lim_{t\to\infty} S_{pop}(t) = e^{-(1-\theta)\alpha}. \tag{2.8}$$

Proof. Note that, for arbitrary $\varepsilon > 0$, $\exists\, t_0$ such that $\forall\, t \geq t_0$, as in the proof of Theorem 2.1,

$$\begin{aligned} D(t) &\geq \int_0^{t_0} \lambda(t-u)\big(1-S(u)\big)du + (1-\theta-\varepsilon)\int_0^{t-t_0} \lambda(k)dk \\ &\geq (1-\theta-\varepsilon)\int_0^{t-t_0} \lambda(k)dk \end{aligned}$$

Hence,

$$\lim_{t\to\infty} D(t) \geq (1-\theta-\varepsilon)\lim_{t\to\infty}\int_0^{t-t_0} \lambda(k)dk \tag{2.9}$$

Again,

$$D(t) \leq \big(1-S(t)\big)\int_0^t \lambda(s)\,ds \leq (1-\theta)\int_0^t \lambda(s)ds$$

Hence,

$$\lim_{t\to\infty} D(t) \leq (1-\theta)\lim_{t\to\infty}\Lambda(t) = (1-\theta)\alpha \tag{2.10}$$

Since ε is arbitrary, (2.9) and (2.10) implies $\lim_{t\to\infty} D(t) = (1-\theta)\alpha$ □

Example 2.1. *Exponentiated Intensity: For* $\lambda(t) = e^{\gamma-\beta t}, \gamma \in R, \beta > 0$ *the cure fraction in (2.8) is* $c = \lim_{t\to\infty} S_{pop}(t) = e^{-\frac{(1-\theta)e^{\gamma}}{\beta}}$ *, where* $\lim_{t\to\infty} S(t) = \theta$.

Example 2.2. *Linear intensity: For*

$$\lambda(t) = \begin{cases} a+b(t_0-t), & t < t_0 \\ 0, & otherwise \end{cases} \tag{2.11}$$

where $a, b > 0$*, the cure fraction in (2.8) is* $c = e^{-(1-\theta)t_0\left(a+\frac{b}{2}t_0\right)}$*, where* $\lim_{t\to\infty} S(t) = \theta$.

Example 2.3. *Linear intensity (dormant time till* t_0 *): For*

$$\lambda(t) = \begin{cases} a+b(t-t_0), & t > t_0 \\ 0, & otherwise \end{cases} \tag{2.12}$$

where $a \in R$, $b > 0$*, the cure fraction in (2.8) is* $c = 0$

Example 2.4. *Power law intensity function: For* $\lambda(t) = bt^{-m}$, $b > 0$, $0 < m < 1$*, the cure fraction is* $c = 0$.

Note 2.1. *When* $\lambda(t)$ *is the dirac-delta function,*

$$\lambda(t) = \begin{cases} \lambda, & t = 0 \\ 0, & t > 0, \end{cases} \tag{2.13}$$

using the sifting property of dirac-delta function (Elnour [5]), the NHPP cure rate model (2.5) reduces to the BCH model (1.1) (Yakovlev et al. [12]).

Note 2.2. *When $N(t)$ is a Homogeneous Poisson Process with intensity λ then $Z(t)$ is a filtered Homogeneous Poisson Process with*

$$E[Z(t)] = \int_0^t \lambda\ (1 - S(t-s))\ ds,$$

and the corresponding survival function as

$$S_{homo}(t) = P[T > t] = P[Z(t) = 0] = e^{-\int_0^t \lambda F(t-s)\, ds}. \tag{2.14}$$

The probability density function (pdf) corresponding to the survival function $S_{pop}(t)$ is

$$f_{pop}(t) = e^{-\int_0^t \lambda(s) F(t-s)\, ds} \int_0^t \lambda(s) f(t-s)\, ds \tag{2.15}$$

where $t > 0$.

The failure rate of the NHPP cure rate model is

$$h_{pop}(t) = \int_0^t \lambda(s) f(t-s) ds. \tag{2.16}$$

where $f(t)$ is the corresponding probability density function of the baseline distribution $F(t)$.

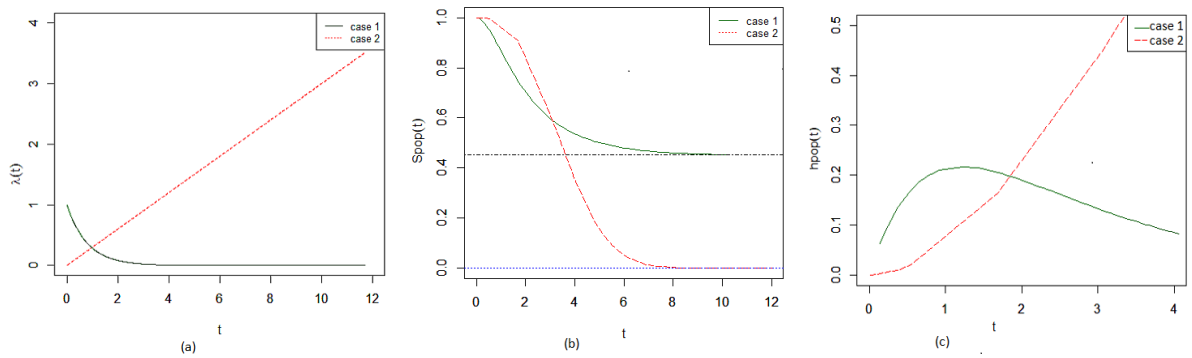

Figure 1: Plots of (a) Intensity function $\lambda(t)$ for case 1 : $\lambda(t) = e^{-\frac{t}{\beta}}, \beta > 0$ with $\beta = 0.8$ and case 2: $\lambda(t) = bt$ with $b = 0.3$ (b) survival function $S_{pop}(t)$ with $c = \lim_{t\to\infty} S_{pop}(t)$ and (c) hazard rate $h_{pop}(t)$ for the NHPP cure rate model with $S(t) = e^{-\gamma t}$, $\gamma = 0.5$. Two examples of $\lambda(t)$ are considered: case 1 : $\lambda(t) = e^{-\frac{t}{\beta}}, \beta > 0$ with $\beta = 0.8$ and case 2: $\lambda(t) = bt$ with $b = 0.3$, with corresponding plots in green and red, respectively.

Figure 1(a)(b)(c) give plots of the intensity function $\lambda(t)$, the survival function $S_{pop}(t)$ and the corresponding hazard rate $h_{pop}(t)$, respectively, for two examples of $\lambda(t)$ and with exponential baseline distribution. In (b), we also present $c = \lim_{t\to\infty} S_{pop}(t)$. For case 1, as in Example 2.1, we have $c > 0$; in case 2, however, since $\lim_{t\to\infty} \Lambda(t) = \infty$, we have $c = 0$.

3. Identifiability issues of NHPP cure rate model

Though the cure rate models received a lot of attention since its inception in Boag [2], it was Farewell [6] who discussed issues in distinguishing censored individuals in susceptible groups from the non-susceptible individual. This in turn leads to non-identification of models with a high incidence of susceptibles and long tails of the latency distribution from low incidence of susceptibles and short levels of latency distribution. Hence this problem of identifiability of cure rate models was studied extensively by Li et al. [8]. Later Hanin and Huang [7] revisited many of the results present in the literature. Every cure rate model discussed now needs to be investigated for identifiability issues to obtain unique estimates of unknown parameters. This warrants an in-depth study of identifiability issues of the proposed NHPP model. In this section, we investigate the conditions under which $S_{pop}(t)$ is identifiable.

Let $x \in \mathscr{X}$ denote the vector of covariates. In order to keep the description general, we start by considering the nonparametric class of baseline distribution, $F : R^+ \times \mathscr{X} \to [0,1]$ with $S = 1 - F$, given by

$$\mathscr{F} = \{F(t,x) : \lim_{t\to\infty} S(t,x) = \theta(x),\ 0 \le \theta(x) < 1,\ t \in R^+, x \in \mathscr{X}\}.$$

Let the nonparametric class of NHPP intensity functions is given by

$$\mathscr{L} = \{\lambda(t,x) : 0 \le \lambda(t,x) < \infty,\ t \in R^+, x \in \mathscr{X}\}.$$

The nonparametric class of models corresponding to (2.5) can be written as

$$\mathscr{H} = \{S_{pop}(t,x) : S_{pop}(t,x) = e^{-\int_0^t \lambda(s,x)F(t-s,x)ds},\ \lambda(t,x) \in \mathscr{L},\ F(t,x) \in \mathscr{F},\ t \in R^+,\ x \in \mathscr{X}\}.$$

Definition 3.1. *The class of models $S_{pop}(t,x) \in \mathscr{H}$ is identifiable, if the equality of $S_{pop}(t,x) = e^{-\int_0^t \lambda(s,x)F(t-s,x)ds}$ for all $(t,x) \in R^+ \times \mathscr{X}$, for some function $\lambda_1(\cdot,\cdot), \lambda_2(\cdot,\cdot) \in \mathscr{L}$ and $F_1(\cdot,\cdot), F_2(\cdot,\cdot) \in \mathscr{F}$, implies that $\lambda_1(t,x) = \lambda_2(t,x)$ and $F_1(t,x) = F_2(t,x)$ for all $(t,x) \in R^+ \times \mathscr{X}$.*

The NHPP cure rate model is generally not identifiable.

Theorem 3.1. *The model $S_{pop}(t,x)$ in (2.5) is not necessarily identifiable for any arbitrary and unspecified $\lambda(t,x)$ and $F(t,x)$.*

Proof. For some $\lambda_1 \in \mathscr{L}$ and $F_1 \in \mathscr{F}$, choose $\lambda_2(t,x) = \frac{\lambda_1(t,x)}{k}$ and $F_2(t,x) = kF_1(t,x)$for some positive $k \neq 1$. Then,

$$1 - \theta_2(x) = \lim_{t\to\infty} F_2(t,x) = k \lim_{t\to\infty} F_1(t,x) = k\big(1 - \theta_1(x)\big).$$

Since we need $0 < 1 - \theta_2(x) \le 1$, we need to choose k such that $k\big(1 - \theta_1(x)\big) \le 1$ or $k \le \frac{1}{1-\theta_1(x)}$, for all $x \in \mathscr{X}$. Hence, by choosing $k < \min_{x\in\mathscr{X}} \frac{1}{1-\theta_1(x)}$, we have $\lambda_1(s,x)F_1(t-s,x) = \lambda_2(s,x)F_2(t-s,x)$ for all $(t,x) \in R^+ \times \mathscr{X}$. Hence,

$$\int_0^t \lambda_1(s,x)F_1(t-s,x)ds = \int_0^t \lambda_2(s,x)F_2(t-s,x)ds,$$

for all $(t,x) \in R^+ \times \mathscr{X}$. Hence the proof. □

In light of Theorem 3.1, the following theorems investigate the conditions under which the NHPP cure rate model is identifiable. First, a few definitions are required.

Definition 3.2. *(Hanin and Huang [7]) A family $\mathscr{T}$ of functions $\tau(\cdot|\phi)$ is called scalable if together with a given function $\tau(\cdot|\phi)$ it also contains every scalar multiple $c\tau(\cdot|\phi)$, $c>0$. The family $\mathscr{T}$ is termed weakly scalable if it contains two distinct members $\tau(\cdot|\phi), \tau(\cdot|\phi^*) \in \mathscr{T}$ such that $\tau(\cdot|\phi) = c\,\tau(\cdot|\phi^*)$ for some positive constant $c \neq 1$.*

Note 3.1. *A family $\mathscr{T}$ of functions $\tau(\cdot|\phi)$ is scalable then it is weakly scalable.*

Theorem 3.2. *If one of the class $\mathscr{L}$ and $\mathscr{F}$ is scalable and the other is weakly scalable, then the model $S_{pop}(t)$ is not identifiable.*

Proof. Suppose $\mathscr{F}$ is weakly scalable. Then there is an $F_1(t,x) \in \mathscr{F}$ such that $F_2(t,x) = kF_1(t,x) \in \mathscr{F}$, for some positive constant $k \neq 1$. Since $\mathscr{L}$ is scalable, then for the chosen $\lambda_1(t,x) \in \mathscr{L}$, $\lambda_2(t,x) = \frac{\lambda_1(t,x)}{k} \in \mathscr{L}$. Hence,

$$\int_0^t \lambda_1(s,x)\,F_1(t-s,x)\,ds = \int_0^t \lambda_2(s,x)\,F_2(t-s,x)\,ds$$

So, the model is not identifiable.

□

In light of Note 3.1 we have,

Corollary 3.1. *If both the class $\mathscr{L}$ and $\mathscr{F}$ are scalable, then the model $S_{pop}(t)$ is not identifiable.*

Remark 3.1. *Note that the class $\mathscr{L}$ is clearly scalable. Also, by a suitable choice of c, as in the proof of Theorem 3.1, $\mathscr{F}$ is at least weakly scalable. Moreover, many natural nonparametric families $\mathscr{F}$ on a finite interval are scalable. For example, the families of all piecewise constant distribution functions, piecewise linear and, more generally, piece wise polynomial distribution functions, such as the family of distribution functions, on $[0,t_0)$ represented by polynomials of degree $\leq m$, $F(t) = \sum_{k=1}^{m} c_k t^k$, $0 \leq t < t_0$, where $c_k \geq 0$, $1 \leq k \leq m$, and $\sum_{k=1}^{m} c_k t_0^k \leq 1$ are scalable (Hanin and Huang [7]). Therefore, non-identifiability of the model (2.5) follows from Theorem 3.2 above, unless further conditions on $\mathscr{L}$ and $\mathscr{F}$ are imposed. This motivates the discussion below.*

Note 3.2. *If, for all $F(t,x) \in \mathscr{F}$, $\lim_{t\to\infty} S(t,x) = \theta(x), 0 \leq \theta(x) < 1$, is the same, then $\mathscr{F}$ is non-scalable.*

Theorem 3.3. *Suppose, for fixed $x \in \mathscr{X}$, $\lim_{t\to\infty} S(t,x) = \theta(x)$, $0 \leq \theta(x) < 1$, is the same for all $F \in \mathscr{F}$. Then the model $S_{pop}(t)$ is identifiable if, for all $\lambda(t,x) \in \mathscr{L}$ we have any one of the following.*

(a) $\lambda(t,x) = \lambda(x)$,

(b) $\lambda(t,x) = b(x)t^m$, *for an integer* $m \geq 1$, *for all* $(t,x) \in R^+ \times \mathscr{X}$ *with* $b(x) > 0$ *being a real-valued function of* x.

(c) $\lambda(t,x) = e^{-\beta(x)t}$, *for all* $(t,x) \in R^+ \times \mathscr{X}$ *with* $\beta(x) > 0$ *being a real-valued function of* x,

(d) $\lambda(t,x) = \begin{cases} b(x)(t-t_0), & t > t_0 \\ 0, & \text{otherwise} \end{cases}$ *for all* $(t,x) \in R^+ \times \mathscr{X}$ *with* $b(x) > 0$ *being a real-valued function of* x,

(e) $\lambda(t,x) = b(x)\,g(t,x)$, *for all* $(t,x) \in R^+ \times \mathscr{X}$, *where* $b(x) > 0$ *is arbitrary and* $g(t,x)$ *is completely known such that* $g(t,x) > 0$ *and* $\lim_{t\to\infty} \int_0^t g(s,x)\,ds = \beta(x) > 0$.

Proof. (a) Observe that,

$$\int_0^t \lambda_1(s,x)\,F_1(t-s,x)\,ds = \int_0^t \lambda_2(s,x)\,F_2(t-s,x)\,ds \tag{3.1}$$

under the condition (a) implies

$$\lambda_1(x)\int_0^t F_1(s,x)\,ds = \lambda_2(x)\int_0^t F_2(s,x)\,ds$$

Differentiating with repect to t, we have

$$\lambda_1(x)F_1(t,x) = \lambda_2(x)F_2(t,x) \tag{3.2}$$

From the assumption of $F(\cdot,\cdot)$ in the theorem, letting $t \to \infty$, we have $\lambda_1(x) = \lambda_2(x)$, for all $x \in \mathscr{X}$. Hence, $F_1(t,x) = F_2(t,x)$, for all $(t;x) \in R^+ \times \mathscr{X}$.

(b) Differentiating both sides of (3.1) with respect to t

$$\int_0^t \lambda_1(s,x)f_1(t-s,x)\,ds = \int_0^t \lambda_2(s,x)f_2(t-s,x)\,ds \tag{3.3}$$

Under the condition of $\lambda(t,x)$ in (b), Equation (3.3) implies

$$b_1(x)\int_0^t s^m f_1(t-s,x)ds = b_2(x)\int_0^t s^m f_2(t-s,x)ds. \tag{3.4}$$

In particular for $m = 1$,

$$b_1(x)\int_0^t s f_1(t-s,x)ds = b_2(x)\int_0^t s f_2(t-s,x)ds \tag{3.5}$$

which, after integration, gives

$$b_1(x)\int_0^t F_1(t-s,x)\,ds = b_2(x)\int_0^t F_2(t-s,x)\,ds \tag{3.6}$$

Differentiating both sides with respect to t,

$$b_1(x)\,F_1(t,x) = b_2(x)\,F_2(t,x). \tag{3.7}$$

Letting $t \to \infty$, we have,

$$b_1(x) = b_2(x), \tag{3.8}$$

which from (3.7) implies $F_1(t,x) = F_2(t,x)$.
For $m = 2$, Equation (3.4) implies,

$$b_1(x)\int_0^t s^2 f_1(t-s,x)ds = b_2(x)\int_0^t s^2 f_2(t-s,x)ds \tag{3.9}$$

implying, after integration by parts,

$$b_1(x)\int_0^t s F_1(t-s,x)ds = b_2(x)\int_0^t s F_2(t-s,x)ds. \tag{3.10}$$

Differentiating both sides of (3.10) with respect to t

$$b_1(x)\int_0^t s f_1(t-s,x)ds = b_2(x)\int_0^t s f_2(t-s,x)ds. \tag{3.11}$$

Note that (3.11) is same as (3.5) and, therefore, following the same step, one can prove the result for $m = 2$. Arguing similarly, we can prove the result for $m = 3$, and so on.
In general, let it be true for $\lambda(t,x) = b(x)t^{m-1}$. Then, for $\lambda(t,x) = b(x)t^m$, we start with the identity

$$b_1(x)\int_0^t s^m f_1(t-s,x)ds = b_2(x)\int_0^t s^m f_2(t-s,x)ds. \tag{3.12}$$

Equivalently, after integration by parts,

$$b_1(x)\int_0^t s^{m-1} F_1(t-s,x)ds = b_2(x)\int_0^t s^{m-1} F_2(t-s,x)ds. \tag{3.13}$$

Differentiating both sides of (3.13) with respect to t

$$b_1(x)\int_0^t s^{m-1} f_1(t-s,x)ds = b_2(x)\int_0^t s^{m-1} f_2(t-s,x)ds. \tag{3.14}$$

The result for any m now follows from the method of mathematical induction.

(c) Under the condition of $\lambda(t,x)$ in (c),

$$\int_0^t e^{-\beta_1(x)s} f_1(t-s,x)\,ds = \int_0^t e^{-\beta_2(x)s} f_2(t-s,x)\,ds = K(t,x)\,(\text{say}), \tag{3.15}$$

which, after integration, gives

$$F_1(t,x) - \beta_1(x)\int_0^t e^{-\beta_1(x)s} F_1(t-s,x)\,ds = F_2(t,x) - \beta_2(x)\int_0^t e^{-\beta_2(x)s} F_2(t-s,x)\,ds. \tag{3.16}$$

This implies

$$F_1(t,x) - F_2(t,x) = (\beta_1(x) - \beta_2(x))\,K(t,x) \tag{3.17}$$

Let $t \to \infty$ in (3.17). Since $\lim_{t\to\infty} K(t,x) \neq 0$, and $\lim_{t\to\infty} F_1(t,x) = \lim_{t\to\infty} F_2(t,x) =$

$1-\theta(x) \leq 1$, it follows that $\beta_1(x) = \beta_2(x)$ which in turn implies $F_1(t,x) = F_2(t,x)$ for all t.

(d) Differentiating both sides of (3.1) with respect to t, for $t > t_0$, we get

$$\int_{t_0}^{t} \lambda_1(s,x) f_1(t-s,x)\, ds = \int_{t_0}^{t} \lambda_2(s,x) f_2(t-s,x)\, ds \tag{3.18}$$

which, after integration and under the condition (d), implies

$$b_1(x) \int_{t_0}^{t} F_1(t-s,x)\, ds = b_2(x) \int_{t_0}^{t} F_2(t-s,x)\, ds. \tag{3.19}$$

Differentiating both sides with respect to t,

$$b_1(x) F_1(t-t_0,x) = b_2(x) F_2(t-t_0,x), \text{ for all } t > t_0. \tag{3.20}$$

Letting $t \to \infty$, as before, we have

$$b_1(x) = b_2(x), \tag{3.21}$$

which in turn implies $F_1(t,x) = F_2(t,x)$ for all $t > 0$ and x.

(e) Under the condition of $\lambda(t,x)$, Equation (3.1) implies

$$\int_{0}^{t} b_1(x) g(s,x) F_1(t-s,x)\, ds = \int_{0}^{t} b_2(x) g(s,x) F_2(t-s,x)\, ds \tag{3.22}$$

From the assumption of $F(\cdot,\cdot)$ and the fact that $\lim_{t\to\infty} \Lambda(t,x) = b(x)\beta(x)$, letting $t \to \infty$ and using Theorem 2.2,

$$(1-\theta(x)) b_1(x) \beta(x) = (1-\theta(x)) b_2(x) \beta(x) \tag{3.23}$$

which in turn implies $b_1(x) = b_2(x)$ for all $x \in \mathscr{X}$.

Hence,

$$\int_{0}^{t} g(s,x) F_1(t-s,x)\, ds = \int_{0}^{t} g(s,x) F_2(t-s,x)\, ds \text{ for all } t,x. \tag{3.24}$$

By uniqueness of the Fourier transforms of a convolution (see page no:185, in **?**]), we have $F_1(t,x) = F_2(t,x)$ for all t,x. □

Theorem 3.4. *If the baseline distribution $F(t,x)$ is independent of x and $\lambda(t,x) = \lambda(x)$, for all $\lambda(t,x) \in \mathscr{L}$, then the model $S_{pop}(t,x)$ is identifiable provided either of the class $\mathscr{L}$ or $\mathscr{F}$ is not weakly scalable.*

Proof. Since $\lambda(t,x) = \lambda(x)$, it follows from (3.2)that, for some constant $k > 0$,

$$\frac{\lambda_1(x)}{\lambda_2(x)} = \frac{F_1(t)}{F_2(t)} = k, \tag{3.25}$$

for all $x \in \mathscr{X}$, $t \in R^+$. Non weakly scalability of either $\mathscr{L}$ or $\mathscr{F}$ implies that $k = 1$.

□

Corollary 3.2. *If $x = (x_1, x_2)$ and $\lambda(t,x) = \lambda(x_1)$ and $F(t,x) = F(t,x_2)$, then $S_{pop}(t,x)$ is identifiable provided either of $\mathscr{L}$ and $\mathscr{F}$ is not weakly scalable.*

Proof. Under the condition stated in (3.25) reduces to

$$\frac{\lambda_1(x_1)}{\lambda_2(x_1)} = \frac{F_1(t,x_2)}{F_2(t,x_2)} = k. \tag{3.26}$$

The result follows arguing as in Thorem 3.4. □

See Example 2, 3 and 4 in Table 1.

Corollary 3.3. *Suppose $\lambda(t,x) = \lambda(x)$ and the baseline distribution $F(t,x;\theta)$ belongs to an identifiable parametric family with the associated parameter θ, in the sense that $F(t,x;\theta_1) = F(t,x;\theta_2)$ for all $(t,x) \in R^+ \times \mathscr{X}$ implies $\theta_1 = \theta_2$. Then the model $S_{pop}(t,x;\theta)$ is identifiable, provided $\lambda(x)$ and $F(t,x;\theta)$ satisfy the conditions of Theorem 3.4 or Corollary 3.2.*

Proof. Follows from the proof of Theorem 3.4 and Corollary 3.2 and the identifiability of the family of $F(t,x;\theta)$. □

Corollary 3.4. *Suppose $\lambda(t,x) = \lambda(x,\beta)$ belongs to an identifiable parametric family with associated parameter β, in the sense that $\lambda(x,\beta_1) = \lambda(x,\beta_2)$, for all $x \in \mathscr{X}$ implies $\beta_1 = \beta_2$ and $F(t,x)$ is fully unspecified. Then the model $S_{pop}(t,x;\beta)$ is identifiable, provided $\lambda(x;\beta)$ and $F(t,x)$ satisfy the conditions of Theorem 3.4 or Corollary 3.2*

Proof. Follows from the proof of Theorem 3.4 or Corollary 3.2 and the identifiability of the family of $\lambda(x;\beta)$. □

Corollary 3.5. *Suppose $\lambda(t,x) = \lambda(x;\beta)$ and $F(t,x) = F(t,x;\theta)$ both belong to identifible families. Then the model $S_{pop}(t,x;\theta,\beta)$ is identifiable, provided $\lambda(x;\beta)$ and $F(t,x;\beta)$ satisfy the conditions of Theorem 3.4 or Corollary 3.2.*

Proof. Follows from the proof of Theorem 3.4 and Corollary 3.2 and the identifiability of the family of $\lambda(x;\beta)$ and $F(t,x;\theta)$. □

Corollary 3.6. *Let $F(t,x)$ is fully specific and known. Then,*

(a) The model $S_{pop}(t,x)$, is identifiable, for any $\lambda(t,x) = \lambda(x)$.

(b) The model $S_{pop}(t,x;\beta)$ is identifiable, for any $\lambda(x;\beta)$, belonging to an identifiable parametric family,

Proof. If,

(a) Observe that,

$$\int_0^t \lambda_1(s,x)F_1(t-s,x)\,ds = \int_0^t \lambda_2(s,x)F_2(t-s,x)\,ds, \tag{3.27}$$

under the condition of $\lambda(t,x)$ in (a) and from the assumption of $F(\cdot,\cdot)$ in the corollary, implies

$$\lambda_1(x)\int_0^t F(s,x)\,ds = \lambda_2(x)\int_0^t F(s,x)\,ds. \tag{3.28}$$

Which in turn implies $\lambda_1(x) = \lambda_2(x)$ for all $x \in \mathscr{X}$

(b) Under the condition of $\lambda(t,x)$ in (a) and from the assumption of $F(\cdot,\cdot)$ in the corollary, (3.27) implies

$$\lambda_1(x;\beta_1)\int_0^t F(s,x)\,ds = \lambda_2(x;\beta_2)\int_0^t F(s,x)\,ds. \tag{3.29}$$

Then $\lambda_1(x,\beta_1) = \lambda_2(x,\beta_2)$ since $\lambda(x;\beta)$ belongs to an identifiable parametric family implies $\beta_1 = \beta_2$.

Hence the proof. □

4. Some examples

A class of non weakly scalable family is (Hanin and Huang [7])

$$f(t,m,n,\gamma) = \frac{n\gamma^{m/n}}{\Gamma(m/n)}t^{m-1}e^{-\gamma t^m};\ t>0 \text{ where } m,n \text{ and } \gamma>0. \tag{4.1}$$

This class of distributions contains exponential, gamma and Weibull families. Making use of these distributions and the result of the previous section helps us to specify cure rate models that are identifiable. Some examples of the identifiable NHPP cure model are listed in Table 1.

For the cure model with exponential baseline density $f(t;\gamma) = \gamma e^{-\gamma t}$ and the intensity function of the form $\lambda(t,x) = e^{-\beta(x)t}$ where $\gamma,\beta(x) > 0$, the cure fraction is

$$c = \lim_{t\to\infty} S_{pop}(t,x;\gamma,\beta(x)) = e^{-\frac{1}{\beta(x)}} \tag{4.2}$$

where $\beta(x) > 0$. The cure fraction is independent of the baseline parameter γ, while the hazard rate is given by

$$h_{pop}(t,x;\gamma,\beta(x)) = \frac{\gamma\left(e^{-\beta(x)t} - e^{-\gamma t}\right)}{\gamma-\beta(x)} \tag{4.3}$$

Figure 2 gives the corresponding plots of $S_{pop}(t;\gamma,\beta)$ for different values of γ and $\beta(x) = \beta$. The asymptote c is seen to be the same for different values of γ in the plots $(a)-(c)$, as expected. Also see Figure 3 for more illustration, indicating the effect of both the parameters on the hazard rate. Observe that larger values of baseline parameter γ and the intensity function parameter β seem to accelerate the decent of the hazard rate. With β fixed, larger γ means quicker turn over of cancer cells into detectable clone, while the production of cancer cells slows down over time, resulting in earlier and higher peak for the hazard rate and also the earlier fall with sharper decline. Similarly, for fixed γ, larger β means less production of cancer cells over time, resulting in earlier slow down in hazard rate. For a truncated linear intensity function

$$\lambda(t,x) = \begin{cases} b(x)(t_0-t), & t<t_0 \\ 0, & \text{Otherwise} \end{cases} \tag{4.4}$$

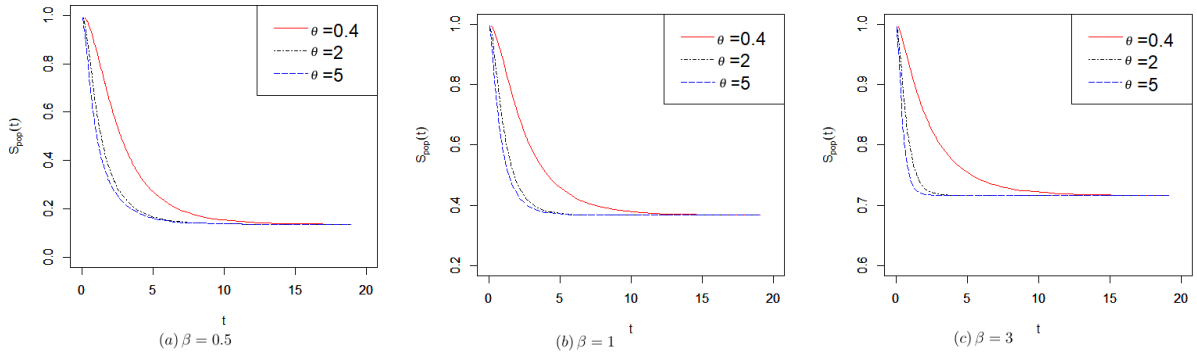

Figure 2: Plots of $S_{pop}(t;\theta,\beta)$ with $S(t) = e^{-\theta t}, \theta > 0$ and $\lambda(t) = e^{-\beta t}, \beta > 0$.

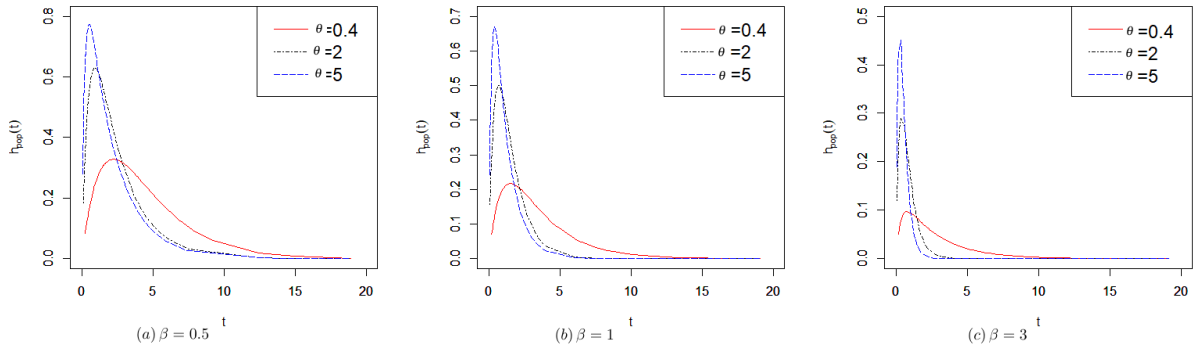

Figure 3: Plots of $h_{pop}(t;\theta,\beta)$ with $S(t) = e^{-\theta t}, \theta > 0$ and $\lambda(t) = e^{-\beta t}, \beta > 0$.

for all $(t,x) \in R^+ \times \mathscr{X}$ with $b(x) > 0$ being a real-valued function of x and the same exponential baseline density, we have the hazard rate as

$$h_{pop}(t,x;\gamma,b(x)) = \begin{cases} \frac{b(x)}{\gamma}\left((t_0-t)\gamma+1-(t_0\gamma+1)e^{-t\gamma}\right), & t < t_0 \\ \frac{b(x)}{\gamma}\left(e^{t_0\gamma-t\gamma}-(t_0\gamma+1)e^{-t\gamma}\right), & t > t_0 \end{cases} \tag{4.5}$$

and the cure rate as

$$c = e^{-\frac{b(x)t_0^2}{2}}. \tag{4.6}$$

Observe that the cure fraction is decreasing with higher values of $b(x)$, as expected, since an increase in the rate of flow of carcinogenic cell decreases the cure rate of the population. For a Defective Gompertz model $f(t,\mu,\sigma) = \sigma e^{-\mu t(e^{-\mu t}-1)}, \mu\sigma > 0$ as baseline distribution and an exponentiated intensity function given by $\lambda(t,x) = e^{-\beta(x)t}, \beta(x) > 0$, the cure fraction is

$$c = \lim_{t\to\infty} S_{pop}(t) = e^{-\frac{1}{\beta(x)}(1-e^{-\frac{\sigma}{\mu}})}, \tag{4.7}$$

which is a decreasing function of $\beta(x)$ for a given μ and σ.

Intensity $\lambda(t,x)$	Baseline Density $f(t)$	Cure rate Model $S_{pop}(t,x)$	Cure fraction
Exponentiated; $\lambda(t,x) = e^{-\beta(x)t}, \beta(x) > 0$	Exponential $f(t,\gamma) = \gamma e^{-\gamma t},\ \gamma > 0$	$e^{-\frac{(e^{\beta(x)}-1)\gamma e^{-\beta(x)}-\beta(x)+\beta(x)e^{-t\gamma}}{\beta(x)(\gamma-\beta(x))}}$	$e^{-\frac{1}{\beta(x)}}$
	Defective Gompertz $f(t,\mu,\sigma) = \sigma e^{-\mu t(e^{-\mu t}-1)}, \mu\sigma > 0$	$e^{-\int_0^t e^{\beta(x)s}(1-e^{\frac{\sigma}{\mu}(e^{-\mu(t-s)}-1)})\,ds}$	$e^{-\frac{1-e^{-\frac{\sigma}{\mu}}}{\beta(x)}}$
	Defective Inverse Gaussian $f(t,\psi,\omega) = \frac{1}{\sqrt{2\psi\pi t^3}} e^{-\frac{1}{2\omega t}(1-\psi t)^2}$, $\psi,\omega > 0$	$e^{-\int_0^t \left(\Phi(\frac{-1+\psi(t-s)}{\sqrt{\omega(t-s)}})+e^{\frac{2\psi}{\omega}}\Phi(\frac{-1-\psi(t-s)}{\sqrt{\omega(t-s)}})\right)e^{-\beta(x)s}\,ds}$	$e^{-\frac{2\Psi}{\omega\beta(x)}}$
	Mixture Distribution $f(t,p,\eta) = (1-p)f_0(t,\eta), 0 < p < 1, f_0(t,\eta)$ is the baseline distribution of $f(t,p,\eta)$	$e^{-\int_0^t e^{-\beta(x)s}(1-p)\,F_0(t-s,p,\eta)\,ds}$	$e^{-\frac{(1-p)}{\beta(x)}}$
Linear: $\lambda(t,x) = \begin{cases} b(x)(t_0-t), & t < t_0 \\ 0, & t > t_0 \end{cases}$	Exponential $f(t,\gamma) = \gamma e^{-\gamma t},\ \gamma > 0$	$\begin{cases} e^{-\frac{b(x)}{2\gamma^2}\left(2(t_0\gamma+1)e^{-t\gamma}+(2tt_0-t^2)\gamma^2+(2t-2t_0)\gamma-2\right)}, & t < t_0 \\ e^{-\frac{b}{2\gamma^2}\left(2(t_0\gamma+1)e^{-t\gamma}-e^{-t\gamma}\left(2e^{t_0\gamma}-t_0^2\gamma^2e^{t\gamma}\right)\right)}, & t > t_0 \end{cases}$	$e^{-\frac{b(x)t_0^2}{2}}$
	Defective Gompertz $f(t,\mu,\sigma) = \sigma e^{-\mu t(e^{-\mu t}-1)}, \mu\sigma > 0$	$\begin{cases} e^{-\int_0^t b(x)(t_0-s)(1-e^{\frac{\sigma}{\mu}(e^{-\mu(t-s)}-1)})\,ds}, & t < t_0 \\ e^{-\int_0^{t_0} b(x)(t_0-s)(1-e^{\frac{\sigma}{\mu}(e^{-\mu(t-s)}-1)})\,ds}, & t > t_0 \end{cases}$	$e^{-\frac{b(x)t_0^2(1-e^{-\frac{\sigma}{\mu}})}{\beta(x)}}$
	Defective Inverse Gaussian $f(t,\psi,\omega) = \frac{1}{\sqrt{2\psi\pi t^3}} e^{-\frac{1}{2\omega t}(1-\psi t)^2}$, $\psi,\omega > 0$	$\begin{cases} e^{-\int_0^t \left(\Phi(\frac{-1+\psi(t-s)}{\sqrt{\omega(t-s)}})+e^{\frac{2\psi}{\omega}}\Phi(\frac{-1-\psi(t-s)}{\sqrt{\omega(t-s)}})\right)b(x)(t_0-s)\,ds}, & t < t_0 \\ e^{-\int_0^{t_0} \left(\Phi(\frac{-1+\psi(t-s)}{\sqrt{\omega(t-s)}})+e^{\frac{2\psi}{\omega}}\Phi(\frac{-1-\psi(t-s)}{\sqrt{\omega(t-s)}})\right)b(x)(t_0-s)\,ds}, & t > t_0 \end{cases}$	$e^{-\frac{\psi b(x)t_0^{\omega}}{2}}$
	Mixture Distribution $f(t,p,\eta) = (1-p)f_0(t\|\eta), 0 < p < 1, f_0(t,\theta')$ is the baseline distribution of $f(t,p,\eta)$	$\begin{cases} e^{-\int_0^t b(x)(t_0-s)(1-p)\,F_0(t-s,p,\eta)\,ds} & t < t_0 \\ e^{-\int_0^{t_0} b(x)(t_0-s)(1-p)\,F_0(t-s,p,\eta)\,ds} & t > t_0 \end{cases}$	$e^{-\frac{(1-p)b(x)t_0^2}{2}}$

Table 1: Few identifiable NHPP cure rate models based Theorem 3.3.

5. Simulating a right censored sample

Suppose that the time of occurrence of an event of interest has survival function $S_{pop}(t,x)$ as given in (2.5). The algorithm to simulate right censored failure times from $S_{pop}(t,x)$ with cure fraction c for a sample of size n is detailed below.

1. Generate n covariate values $x_1,...,x_n$ from $f_X(x)$.
2. For each x_i and the values of model parameters in the baseline distribution and intensity function, compute the cure fraction c_i as in (2.8).
3. Generate M_i, where $M_i \sim$ Bernoulli $(1-c_i)$ for each $i = 1,2,...n$.
4. For $i = 1,\cdots,n$, if $M_i = 1$ take t_i as the solution of $F_{pop}(t_i,x_i) = u_i$, where u_i is generated from Unif$(0,1-c_i)$. If $M_i = 0$ (representing a cured individual), set $t_i = \infty$.
5. For each $i = 1,2,...n$, generate the censoring time $C = c_i$ from a censoring distribution say $g(c|k)$ with the associated parameter k, where k is computed to obtain the prefixed censoring rate p. To derive the value of k solve $P[T \geq C|k] = p$, where $P[T \geq C|k] = \int_{\mathscr{X}} f_x(x) \int_0^\infty g(c|k) S_{pop}(c,x) dc\, dx$, where $f_X(\cdot)$ is the density function of covariate x and $g(c|k)$ is the censoring distribution density.
6. Calculate $y_i = \min(t_i, c_i)$. If $t_i < c_i$ set the censoring indicator $\delta_i = 1$, otherwise set $\delta_i = 0$. So, clearly, those cured with $M_i = 0$ have $\delta_i = 0$.

This gives us a right censored sample of size n, from the NHPP cure rate model with covariate $x_1,\cdots,x_n$.

6. Conclusion

It is often seen in cancer studies that the rate of flow of carcinogenic cells is stochastic over time. In such situations, the BCH model is restrictive and needs to be modified. The proposed Non-homogeneous Poisson Process (NHPP) cure rate model can be seen as a better alternative to the BCH model. For $N(t)$, a Non-homogenous Poisson process with intensity function $\lambda(t)$ and the baseline distribution $S(t)$ signifying the probability distribution of the waiting time for the carcinogenic cells to grow to a be detectable mass such that $\lim_{t\to\infty} S(t) = \theta$, $0 \leq \theta < 1$, the NHPP cure rate model proposed is $S_{pop}(t) = e^{-\int_0^t \lambda(s) F(t-s)\, ds}$, where $F(t) = 1 - S(t)$. The BCH model in (1.1) can be thought of as a special case of the NHPP cure rate model with $\lambda(t)$ as the dirac-delta function. The mixture cure rate model can also be seen as a particular case of the BCH model since the BCH model transform to the mixture cure rate model via a transformation analogous to the Box-Cox transformation (Yin and Ibrahim [13]).
The cure fraction of the population modeled by the NHPP cure rate model is obtained as $e^{-(1-\theta)\alpha}$ where $\alpha = \lim_{t\to\infty} \Lambda(t)$. Evidently, this rate depends on θ and α, the parameters of baseline distribution and intensity function respectively. It is intuitive to infer that a higher value of θ accelerate the cure rate while α, the limit of intensity function has an adverse effect on the cure fraction (see Figure 4).

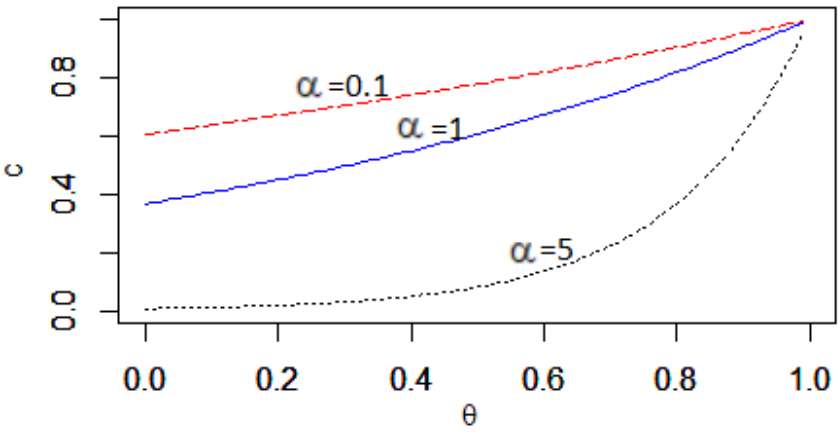

Figure 4: Plot of cure rate for fixed values of α

The NHPP cure rate model $S_{pop}(t)$ is not necessarily identifiable for any arbitrary and unspecified $\lambda(t)$ and $F(t)$. Identifiability problems creep into the model due to insufficient follow-up time and censoring. The notion of scalable classes of functions (Hanin and Huang [7]) helps to formulate conditions for the identifiable models. It is seen that the non-scalability of the classes of baseline distributions $\mathscr{F}$ or intensity functions $\mathscr{L}$ is not enough to assure the identifiability of the proposed model. Conditions on specific forms of the baseline distributions and the covariance sharing structure between the baseline distribution and intensity functions play a crucial role. We have established that, for baseline distributions such that $\lim_{t\to\infty} F(t)$ is the same for all $F \in \mathscr{F}$, the NHPP cure rate model is identifiable for specific intensity functions. The non-weakly scalability of either of the classes $\mathscr{L}$ or $\mathscr{F}$ ensures the identifiability of the model. The problem of estimation of parameters will be presented elsewhere.

Acknowledgements

The first author acknowledges the financial assistance from Cochin University of Science and Technology through its UJRF/2019-20 scheme.

References

[1] Berkson, J. and Gage, R. P. (1952). Survival Curve for Cancer Patients Following Treatment. *Journal of the American Statistical Association*, 47(259):501–515.

[2] Boag, J. W. (1949). Maximum likelihood estimates of the proportion of patients cured by cancer therapy. *Journal of the Royal Statistical Society. Series B (Methodological)*, 11(1):15–53.

[3] Chen, M.-H., Ibrahim, J. G., and Sinha, D. (1999). A new bayesian model for survival data with a surviving fraction. *Journal of the American Statistical Association*, 94(447):909–919.

[4] Cox, D. R. (1972). Regression models and life-tables. *Journal of the Royal Statistical Society: Series B (Methodological)*, 34(2):187–202.

[5] Elnour, K. A. E. A. A. (2018). On the calculus of dirac delta function with some applications. *International Journal of Mathematics Trends and Technology*, 56:258–270.

[6] Farewell, V. T. (1982). The Use of Mixture Models for the Analysis of Survival Data with Long-term Survivors. *Biometrics*, pages 1041–1046.

[7] Hanin, L. and Huang, L.-S. (2014). Identifiability of Cure Models Revisited. *Journal of Multivariate Analysis*, 130:261–274.

[8] Li, C.-S., Taylor, J. M., and Sy, J. P. (2001). Identifiability of Cure Models. *Statistics & Probability Letters*, 54(4):389–395.

[9] Moolgavkar, S. H. and Luebeck, G. (1990). Two-event model for carcinogenesis: Biological, mathematical, and statistical considerations. *Risk Analysis*, 10(2):323–341.

[10] Parzen, E. (1999). *Stochastic processes*, volume 24. SIAM.

[11] Tang, Y. J., Huang, J., Tsushima, H., Ban, G. I., Zhang, H., Oristian, K. M., Puviindran, V., Williams, N., Ding, X., Ou, J., et al. (2019). Tracing tumor evolution in sarcoma reveals clonal origin of advanced metastasis. *Cell reports*, 28(11):2837–2850.

[12] Yakovlev, A. Y., Asselain, B., Bardou, V., Fourquet, A., Hoang, T., Rochefediere, A., and Tsodikov, A. (1993). A Simple Stochastic Model of Tumor Recurrence and its Application to Data on Premenopausal Breast Cancer. *Biometrie et Analyse De Donnees Spatio-Temporelles*, 12:66–82.

[13] Yin, G. and Ibrahim, J. G. (2005). Cure rate Models: a Unified Approach. *Canadian Journal of Statistics*, 33(4):559–570.

[14] You, R., Liu, Y.-P., Lin, D.-C., Li, Q., Yu, T., Zou, X., Lin, M., Zhang, X.-L., He, G.-P., Yang, Q., et al. (2019). Clonal mutations activate the nf-κb pathway to promote recurrence of nasopharyngeal carcinoma. *Cancer research*, 79(23):5930–5943.