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A STOCHASTIC MODEL OF CARCINOGENESIS AND TUMOR SIZE AT DETECTION

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Abstract

This paper discusses the distribution of tumor size at detection derived within the framework of a new stochastic model of carcinogenesis. This distribution assumes a simple limiting form, with age at detection tending to infinity which is found to be a generalization of the distribution that arises in the length-biased sampling. Two versions of the model are considered with reference to spontaneous and induced carcinogenesis; both of them show similar asymptotic behavior. When the limiting distribution is applied to real data analysis its adequacy can be tested through testing the conditional independence of the size, V, and the age, A, at detection given $A > t^*$, where the value of t^* is to be estimated from the given sample. This is illustrated with an application to data on premenopausal breast cancer. The proposed distribution offers the prospect of the estimation of some biologically meaningful parameters descriptive of the temporal organization of tumor latency. An estimate of the model stability to the prior distribution of tumor size and some other stability results for the Bayes formula are given.

STOCHASTIC MODEL; ASYMPTOTIC PROPERTIES; CARCINOGENESIS; CONDITIONAL DISTRIBUTION; TUMOR SIZE; STABILITY TO PRIORS; BAYES THEOREM; PROBABILITY METRICS

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1. Introduction

A stochastic model of radiation carcinogenesis proposed by Klebanov *et al.* [13] has proved to be an effective underpinning for the statistical analysis of time-to-tumor observations [25]. The model incorporates biologically meaningful parameters and is sufficiently simple to make the associated estimation problems tractable. Additional advantages of this model are that censored observations are easily accomodated and that the asymptotic likelihood theory can be invoked for

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statistical inference from real data. An optimal invariant estimator of the survivor functions produced by the model was constructed in such a way as to minimize the expected quadratic risk [14]. A similar model structure was used to describe the processes of spontaneous carcinogenesis [25], ageing [23, 26], and hormesis [27]. The model has been extended by Yakovlev and Polig [24] to allow for radiation-induced cell killing to compete with the process of tumor promotion. This generalization, still quite simple as it is, endows the model with the capacity to explain a wide range of experimental findings documented in the radiobiological literature [24]. At the same time, neither the original model by Klebanov *et al.* [13] nor its modification proposed by Yakovlev and Polig [24] provide an explicit description of the stage of tumor progression which is known to involve proliferation of promoted cell clones. Having been developed with an emphasis on the temporal aspect of tumor latency, these and many other models of carcinogenesis do not allow for any specific characteristics of tumor growth. With rare exceptions [5, 7, 15, 25, 29], the mechanism of tumor detection is also obviated in modern models of carcinogenesis. This is not particularly surprising, since the information contained in time-to-tumor data is likely to be inadequate to allow identification of a more complex model of the process of tumor development. In other words, the problem calls for an extra source of information, which presumably might be provided by the data on tumor size at detection [25].

A few attempts have been made to relate the chance of detecting a tumor to its size [2, 3, 4, 5, 7, 12, 15]. Kimmel and Flehinger [12] studied the relationship between the occurrence of metastases and the size of primary tumor. This information is essential to a better understanding of the natural history of metastatic cancers. In like manner, Yakovlev and Tsodikov [25] proposed to use data on tumor size at detection for making inferences on the mechanisms underlying tumor latency in the course of spontaneous and induced carcinogenesis. With this aim in view they introduced a threshold counterpart of the model of carcinogenesis developed by Klebanov *et al.* [13]. As evidenced by some preliminary results of data analysis, the idea holds much promise for the analysis of tumor latency and risk assessment. In the present paper, we give a theoretical foundation of this approach. The results of real data analysis will be detailed in another paper.

2. The model

2.1. *Spontaneous carcinogenesis.* The model discussed below stems from the contemporary view on carcinogenesis as a multistage process, clonal in origin, that is initiated by a widespread event occurring in a large percentage of cells [8, 11]. Although much of this concept owes its origin to studies of tumor induction by irradiation or chemical carcinogens, it is believed to be true for the processes underlying spontaneous carcinogenesis. More specifically, the model is based on the following assumptions.

(i) The primary event in the process of carcinogenesis is the formation of an intracellular lesion which is potentially carcinogenic. One may see these precancerous lesions, or altered cells, as possessing in the long run the capacity for producing a detectable tumor. Such primary events occur at random times and their sequence in time is thought of as a Poisson process with intensity $\theta_0(t)$.

(ii) All primary lesions may be considered as being subject to repair processes [1, 16], but some of them remain unrecognized by the repair system and consequently unrepaired. The presence of unrepaired lesions can be also explained by a limited capacity of the repair system. Some of the lesions may happen to be misrepaired owing to the functioning of error-prone repair mechanisms [21]. The existing experimental evidence on the temporal characteristics of enzymatic repair of lesions [10, 28, 31] allows one to assume that this process is effectively instantaneous compared to the subsequent stages of carcinogenesis, i.e. each lesion is repaired or misrepaired immediately after its origination. This suggests that the repair effect can be modeled as a thinning operation on the Poisson process of lesion arrivals: with probability q, each lesion is eliminated independently of the others and of the whole point process of lesion formation. As a result, the thinned Poisson process of intensity $\theta = (1-q)\theta_0$ represents the precancerous lesions entering into the stage of tumor promotion. It is clear that with this way of incorporating repair processes the basic model structure remains unaffected. Some queueing formulations of cell repair models are given in [13, 17, 24].

(iii) An unrepaired (or misrepaired) precancerous lesion remains dormant as long as it proceeds through the promotional stage of tumor development. All lesions are subject to promotion independently of each other.

(iv) Once the first malignant cell arises as a result of tumor promotion, its subsequent growth is irreversible and the progression stage begins. It is this clonogenic cell that gives rise to an overt tumor after a lapse of time.

(v) A tumor becomes detectable when its size attains some threshold value, N, which is treated as a random variable (r.v.). The most widely accepted approach to the modeling of proliferation of tumor cells is that based on branching processes. It is essential to select a sufficiently simple type of branching process, lest the model be too cumbersome. In the attempt to develop a parsimonious model of tumor latency we use a linear pure birth process with the absorbing upper barrier N to model the dynamics of tumor growth. Under this model the progression time cumulative distribution function (c.d.f.), given the threshold level N, is

$$F(t \mid N) = (1 - e^{-\lambda t})^N, \tag{1}$$

where λ is the birth rate. Formula (1) implies that tumor growth starts from a single malignant cell at time $t = 0$.

Let $L(t)$ be the c.d.f. of the time it takes for the initiation and promotion processes to result in the first malignant cell. When studying spontaneous carcinogenesis, this time is measured from the date of birth of an individual. Derived from

the above assumptions [27] is the following expression for the corresponding survivor function $\bar{L}(t) = 1 - L(t)$:

$$\bar{L}(t) = \exp\left\{ -\int_0^t \theta(t-x)R(x)\,dx \right\}, \tag{2}$$

where $R(t)$ is the c.d.f. of the promotion stage duration. To retain model tractability we confine our consideration of spontaneous carcinogenesis to a homogeneous Poisson process of lesion arrivals, thereby reducing (2) to

$$\bar{L}(t) = \exp\left\{ -\theta \int_0^t R(x)\,dx \right\}. \tag{3}$$

It is practical to represent the critical number of tumor cells as $N = cV$, where V is the volume of a tumor and c is the concentration of tumor cells per unit volume. The constant c is non-random and its values are typically large. In applications, the value of c is frequently taken to be approximately equal to 10^9 cells per cm^3 [15]. Thus the conditional progression time c.d.f., given the threshold volume $V = v$, is

$$F(t \mid v) = (1 - e^{-\lambda t})^{cv}. \tag{4}$$

Let $f(t \mid v)$ stand for the probability density function (p.d.f.) of $F(t \mid v)$. Assuming that the stages of promotion and progression are mutually independent, we use the convolution

$$g(t \mid v) = \int_0^t R(t-u) \exp\left\{ -\theta \int_0^{t-u} R(x)\,dx \right\} f(u \mid v)\,du \tag{5}$$

to represent the conditional p.d.f., $g(t \mid v)$, of the time of tumor latency measured from the date of birth.

Introducing a prior distribution, $P(v)$, of the r.v. V, we repesent the p.d.f. of the time (age) of tumor detection as

$$g(t) = \int_0^\infty g(t \mid v)p(v)\,dv, \tag{6}$$

where $p(v)$ is the density of $P(v)$. Throughout the paper, the distribution $P(v)$ is assumed to have finite first moment. We are primarily interested in the conditional p.d.f. of tumor volume at detection (given that a tumor is detected at time t), hereafter denoted by $w(v \mid t)$. By virtue of Bayes' formula we have

$$w(v \mid t) = \frac{g(t \mid v)p(v)}{\int_0^\infty g(t \mid u)p(u)\,du} = \frac{g(t \mid v)p(v)}{g(t)}, \tag{7}$$

where $g(t \mid v)$ and $g(t)$ are given by (5) and (6), respectively.

2.2. *Induced carcinogenesis.* In the event of induced carcinogenesis the time of tumor latency is measured from the time of exposure to a carcinogen. Let D be the carcinogen dose and T the exposure duration. Considering a constant dose rate exposure, we set

$$\theta(t) = \begin{cases} \theta_1 D/T & \text{for } 0 < t \leqq T, \\ 0 & \text{for } t > T, \end{cases}$$

in formula (2). This gives

$$\bar{L}(t; T) = \exp\left\{ -\frac{\theta_1 D}{T} \int_0^T R(x)\, dx \right\},$$

where θ_1 is the mean number of precancerous lesions per unit dose. Letting $T \to 0$ in the above formula, we obtain the model of a brief (single dose) exposure in the form

$$\bar{L}(t) = e^{-\theta R(t)}, \tag{8}$$

where $\theta = \theta_1 D$ is the mean number of lesions induced by a given dose of carcinogen. Unlike the distribution given by (2), distribution (8) is improper. However the basic model structure will remain as in the case of spontaneous carcinogenesis with distribution (8) used in place of (3).

3. The limiting form of $w(v \mid t)$

For the model to be useful in the analysis of real data additional parametric assumptions must be called on to specify the distributions $R(t)$ and $p(v)$. However, the conditional p.d.f. $w(v \mid t)$ assumes a much simpler form when t tends to infinity. This limiting form does not involve the promotion time distribution, $R(t)$, and it also has some distinct advantages as far as estimation problems are concerned. A similar problem arises in Bayesian statistical inference with reference to outliers [18].

3.1. *Spontaneous carcinogenesis.* It follows from (4) and (5) that in the case of spontaneous carcinogenesis

$$g(t \mid v) = \lambda\theta cv \int_0^t e^{-\lambda(t-s)}(1 - e^{-\lambda(t-s)})^{cv-1} R(s) \exp\left\{ -\theta \int_0^s R(x)\, dx \right\} ds = \lambda\theta cv\psi(t). \tag{9}$$

Theorem 1. *The following assertions hold for the limiting behavior of the function* $\psi(t)$ *as* $t \to \infty$.

(a) *If* $\lambda < \theta$ *then*

$$\psi(t) \sim I e^{-\lambda t}, \tag{10}$$

where

$$I = \int_0^\infty \exp\left\{ \lambda s - \theta \int_0^s R(x)\, dx \right\} R(s)\, ds.$$

(b) *If* $\lambda = \theta$ *and* $\int_0^\infty [1 - R(s)]\, ds < \infty$ *then*

$$\psi(t) \sim t \exp\left\{-\lambda \int_0^t R(x)\, dx\right\}. \tag{11}$$

(c) *If* $\lambda > \theta$ *then*

$$\psi(t) \sim J \exp\left\{-\theta \int_0^t R(x)\, dx\right\}, \tag{12}$$

with

$$J = \frac{1}{\lambda} \int_0^1 y^{cv-1}(1-y)^{-\theta/\lambda}\, dy = \frac{1}{\lambda} B(cv, 1 - \theta/\lambda),$$

where $B(x, y)$ *is the beta function.*

The proof is based on the following lemma.

Lemma. Let $K(t, s, u)$ *be a bounded measurable function defined for* $t \geqq s \geqq 0$, $u \geqq 0$ *and such that* $K(t, s, u) \to a$ *as* $t, s, u \to \infty$. *Also, let* h *be a positive continuous function such that* $\lim_{t\to\infty} h(t-u)/h(t) = 1$ *for every* $u \geqq 0$, *and* $\int_0^\infty h(u)\, du = \infty$. *Denote* $H(t) = \int_0^t h(u)\, du$. *Then*

$$\frac{1}{H(t)} \int_0^t K(t, t-u, u) h(u)\, du \to a, \qquad t \to \infty.$$

Proof. We may assume indeed that $a = 0$. Suppose that $|K| \leqq M$. Fix $\epsilon > 0$ and choose $A > 0$ such that $|K(t, s, u)| \leqq \epsilon$ for all $s, u \geqq A$ and $t \geqq s$. For $t > 2A$ we have

$$\int_0^t K(t, t-u, u) h(u)\, du = \int_0^A + \int_A^{t-A} + \int_{t-A}^t,$$

hence

$$\left|\frac{1}{H(t)} \int_0^t K(t, t-u, u) h(u)\, du\right| \leqq \frac{M}{H(t)} \int_0^A h(u)\, du + \frac{M}{H(t)} \int_{t-A}^t h(u)\, du + \epsilon.$$

By the l'Hospital rule

$$\lim_{t\to\infty} \frac{\int_{t-A}^t h(u)\, du}{\int_0^t h(u)\, du} = \lim_{t\to\infty} \frac{h(t) - h(t-A)}{h(t)} = 1 - \lim_{t\to\infty} \frac{h(t-A)}{h(t)} = 0.$$

From here and from $H(t) \to \infty$, $t \to \infty$, we conclude now that, for all sufficiently large t,

$$\left| \frac{1}{H(t)} \int_0^t K(t, t-u, u) h(u)\, du \right| \leqq 2\epsilon,$$

and this completes the proof.

Proof of Theorem 1. (a) We represent $\psi(t)$ as

$$\psi(t) = e^{-\lambda t} \int_0^\infty f_t(s)\, ds,$$

where

$$f_t(s) = e^{\lambda s}(1 - e^{-\lambda(t-s)})^{cv} R(s) \exp\left\{-\theta \int_0^s R(x)\, dx\right\} \chi_{[0,t]}(s),$$

and $\chi_{[0,t]}(s)$ is the characteristic function of $[0, t]$. For every $s > 0$,

$$f_t(s) \uparrow f(s) := R(s) \exp\left\{ -s\left[\theta \frac{1}{s} \int_0^s R(x)\, dx - \lambda \right]\right\}, \qquad t \to \infty.$$

Applying the lemma with $K(t, s, u) = R(u)$ and $h \equiv 1$, we see that $s^{-1} \int_0^s R(x)\, dx \to 1$ as $s \to \infty$. Hence in the case $\lambda < \theta$ one has $\int_0^\infty f(s)\, ds < \infty$, and by the Lebesgue theorem on bounded convergence we obtain (10).

(b) Let $\lambda = \theta$. We change variables in (9) by writing $u = t - s$ to obtain

$$(13)\quad \psi(t) = \exp\left\{-\lambda \int_0^t R(x)\, dx\right\} \int_0^t (1 - e^{-\lambda u})^{cv} R(t-u) \exp\left\{-\lambda \int_{t-u}^t [1 - R(x)]\, dx\right\} du.$$

Applying the lemma with

$$K(t, s, u) = (1 - e^{-\lambda u})^{cv} R(s) \exp\left\{-\lambda \int_s^t [1 - R(x)]\, dx\right\}$$

and $h \equiv 1$, we conclude that (11) is true. Note that $K(t, s, u) \to 1$ for $t, s, u \to \infty$.

(c) Similar to (13) we have for $\lambda > \theta$

$$\psi(t) = \exp\left\{-\theta \int_0^t R(x)\, dx\right\} \int_0^\infty g_t(u)\, du,$$

where

$$g_t(u) = e^{-(\lambda-\theta)u}(1 - e^{-\lambda u})^{cv} R(t-u) \exp\left\{-\theta \int_{t-u}^t [1 - R(x)]\, dx\right\} \chi_{[0,t]}(u).$$

Obviously, for every $u \geqq 0$

$$g_t(u) \uparrow g(u) := e^{-(\lambda-\theta)u}(1 - e^{-\lambda u})^{cv}, \qquad t \to \infty.$$

Hence, by the bounded convergence theorem,

$$\int_0^\infty g_t(u)\,du \to \int_0^\infty g(u)\,du = \frac{1}{\lambda}\int_0^1 y^{cv}(1-y)^{-\theta/\lambda}\,dy, \qquad t \to \infty.$$

Remark 1. Let $s_0 = \inf\{s : R(s) > 0\}$. Then setting $y = \varphi(s) := \int_0^s R(x)\,dx$, $s \geqq s_0$, we have

$$I = \int_0^\infty \exp\left\{\lambda s - \theta\int_0^s R(x)\,dx\right\}R(s)\,ds = \int_s^\infty e^{\lambda s - \theta\varphi(s)}\varphi'(s)\,ds = \int_{\varphi(s_0)}^\infty e^{\lambda\varphi^{-1}(y) - \theta y}\,dy.$$

Remark 2. If $M := \int_0^\infty [1 - R(x)]\,dx < \infty$ then for $\lambda = \theta$, $\psi(t) \sim e^{-\lambda(t-M)}t$, and for $\lambda > \theta$, $\psi(t) \sim e^{-\theta(t-M)}J$.

Taking up (7) and (9) with $\psi(t)$ given by (10) or (11), we can write

$$\lim_{t\to\infty} w(v \mid t) = \frac{vp(v)}{\int_0^\infty up(u)\,du}, \qquad \lambda \leqq \theta. \tag{14}$$

Now the fact that cv is large can be taken into account. Using the Euler–Gauss formula

$$\lim_{cv\to\infty} (cv)^{1-\theta/\lambda}B(cv, 1-\theta/\lambda) = \Gamma(1-\theta/\lambda), \qquad \theta < \lambda, \tag{15}$$

and the Lebesgue theorem on bounded convergence, it follows from (7), (9), (12) that

$$\lim_{t\to\infty} w(v \mid t) \sim \frac{v^{\theta/\lambda}p(v)}{\int_0^\infty u^{\theta/\lambda}p(u)\,du}, \qquad cv \to \infty, \tag{16}$$

for $\lambda > \theta$. Combining (14) and (16) we obtain the limiting conditional p.d.f. of tumor size at detection:

$$\lim_{t\to\infty} w(v \mid t) = \frac{v^\mu p(v)}{\int_0^\infty u^\mu p(u)\,du}, \qquad \mu = \min\left\{1, \frac{\theta}{\lambda}\right\}. \tag{17}$$

A special case ($\mu = 1$) of this distribution is associated with what is known as a length-biased sampling from stationary point processes [9]. A sampling bias inherent in screening procedures under a stable disease model [30] provides yet another example.

3.2. *Induced carcinogenesis.* The case of induced carcinogenesis can be considered along similar lines. In this case

$$(18) \qquad g(t \mid v) = \lambda\theta cv \int_0^t e^{-\lambda(t-s)}(1 - e^{-\lambda(t-s)})^{cv-1} r(s) e^{-\theta R(s)}\, ds = \lambda\theta cv\psi_0(t),$$

where $r(t)$ is the density of $R(t)$.

Theorem 2. Let

$$\sigma := \sup\left\{\alpha : \int_0^\infty e^{\alpha s} r(s)\, ds < \infty\right\}, \qquad 0 \leqq \sigma \leqq \infty.$$

(a) *If* $\lambda < \sigma$ *or* $\lambda = \sigma$ *and* $\int_0^\infty e^{\sigma s} r(s)\, ds < \infty$, *then*

$$(19) \qquad \psi_0(t) \sim I_1 e^{-\lambda t}, \qquad t \to \infty,$$

where $I_1 = \int_0^\infty e^{\lambda s} r(s)\, e^{-\theta R(s)}\, ds$.

(b) *Let* $\lambda = \sigma$ *and* $\int_0^\infty e^{\sigma s} r(s)\, ds = \infty$. *Suppose that the function* $r(s)$ *is positive and continuous for* $s > 0$, *and that the function* $h(s) := e^{\sigma s} r(s)$ *has the property*

$$(20) \qquad \lim_{t\to\infty} \frac{h(t-u)}{h(t)} \to 1 \qquad \text{for every } u \geqq 0.$$

Then

$$(21) \qquad \psi_0(t) \sim I_2(t) e^{-\lambda t - \theta}, \qquad t \to \infty,$$

where $I_2(t) = \int_0^t e^{\sigma s} r(s)\, ds$.

(c) *Let* $\lambda > \sigma$. *Suppose that* $r(s)$ *is positive and continuous for* $s > 0$ *and that* h *satisfies* (20). *Also, suppose that the function* h *is either non-decreasing or that it is non-increasing and subject to the following conditions:*

(i) $\dfrac{h(t)}{h(2t)} \leqq C$ *for some constant* C;

(ii) $\int_0^1 h(s)\, ds < \infty$.

Then

$$(22) \qquad \psi_0(t) \sim I_3 r(t)$$

where $I_3 = (e^{-\theta}/\lambda) B(cv, 1 - \sigma/\lambda)$.

Proof. (a) Relation (19) follows easily from the Lebesgue theorem on bounded convergence.

(b) We have

$$\psi_0(t) = e^{-(\lambda t+\theta)} \int_0^t e^{\sigma s} r(s)(1 - e^{-\lambda(t-s)})^{cv-1} e^{\theta(1-R(s))}\, ds$$

$$= e^{-(\lambda t+\theta)} \int_0^t K(t-s, s) h(s)\, ds,$$

where $K(u, s) = (1 - e^{-\lambda u})^{cv-1} e^{\theta(1-R(s))}$ and $h(s)$ is defined above. Observe that $0 \leqq K(u, s) \leqq e^{\theta}$ and $K(u, s) \to 1$ for $u, s \to \infty$. Applying the lemma, we get (21).

(c) By the change of variable $u = t - s$ in (18) we represent $\psi_0(t)$ as

$$\psi_0(t) = r(t)e^{-\theta} \int_0^t e^{-(\lambda-\sigma)u}(1 - e^{-\lambda u})^{cv-1} \frac{h(t-u)}{h(t)} e^{\theta[1-R(t-u)]}\, du$$

$$= r(t)e^{-\theta} \int_0^t g_t(u)\, du.$$

For every $u \geqq 0$, we have by (20)

$$g_t(u) \to g(u) := e^{-(\lambda-\sigma)u}(1 - e^{-\lambda u})^{cv-1}, \qquad t \to \infty, \tag{23}$$

and it is clear that $\int_0^\infty g(u)\, du < \infty$. If h is non-decreasing, then $g_t(u) \leqq e^{\theta} g(u)$, and the Lebesgue theorem yields

$$\int_0^t g_t(u)\, du \to \int_0^\infty g(u)\, du = \frac{1}{\lambda} \int_0^1 y^{cv-1}(1-y)^{-\sigma/\lambda}\, dy, \qquad t \to \infty.$$

Now suppose that h is non-increasing. Observe that

$$g_t(u) \leqq e^{\theta-(\lambda-\sigma)u} \frac{h(t-u)}{h(t)}, \qquad 0 \leqq u \leqq t. \tag{24}$$

Hence, for $0 \leqq u \leqq t/2$ we have from condition (c-*i*)

$$g_t(u) \leqq e^{\theta-(\lambda-\sigma)u} \frac{h(t/2)}{h(t)} \leqq Ce^{\theta} e^{-(\lambda-\sigma)u}.$$

Then by the Lebesgue theorem and in view of (23),

$$\int_0^{t/2} g_t(u)\, du \to \int_0^\infty g(u)\, du, \qquad t \to \infty. \tag{25}$$

Next, invoking (c-*ii*) we find that

$$\int_{t/2}^t g_t(u)\, du \leqq \frac{e^{\theta-(\lambda-\sigma)t/2}}{h(t)} \int_0^{t/2} h(s)\, ds \leqq \frac{e^{\theta-(\lambda-\sigma)t/2}}{h(t)} \left[\int_0^1 h(s)\, ds + \tfrac{1}{2} t h(1) \right]. \tag{26}$$

Note that condition (c-*i*) and monotonicity of h imply that $h(t) \geqq At^{-\delta}$ for some constants $A, \delta > 0$. Combining this with the previous estimate, we conclude that $\int_{t/2}^t g_t(u)\, du \to 0$, and therefore $\int_0^t g_t(u)\, du \to I_3$ as $t \to \infty$.

Remark 3. If the distribution function R is strictly increasing, then setting $y = R(s)$ in I_1 defined by (19) we have

$$I_1 = \int_0^1 e^{\lambda R^{-1}(y) - \theta y}\, dy.$$

Remark 4. It can be verified that Theorem 2 applies to many parametric forms of $r(x)$. Consider the family of distributions with density

$$r(x) = Cx^{\alpha-1}e^{-\beta x^{\gamma}}\chi_{\mathbb{R}_+}(x), \qquad \alpha, \beta, \gamma > 0,$$

where $C = C(\alpha, \beta, \gamma)$, which includes, in particular, the Weibull and gamma distributions. To apply Theorem 2 we study the following cases for γ.

(a) Let $\gamma > 1$. Then $\sigma = \infty$, and by (19), for every $\lambda > 0$, $\psi(t) \sim e^{-\lambda t} I_1$.

(b) Let $\gamma = 1$. Then $\sigma = \beta$, and $h(s) = Cs^{\alpha-1}$ satisfies (20).

For $0 < \lambda < \beta$ we have (19). For $\lambda = \beta$ we obtain (21), namely, $\psi(t) \sim (C/\alpha)e^{-(\lambda t+\theta)}t^{\alpha}$. For $\lambda > \beta$, h is monotonically non-decreasing for $\alpha \geqq 1$, and is monotonically decreasing for $0 < \alpha < 1$. Also, in the case $0 < \alpha < 1$ conditions (c-*i*) and (c-*ii*) are fulfilled. Thus, $\psi(t) \sim r(t)I_3$.

(c) $0 < \gamma < 1$. Then $\sigma = 0$, and $h = r$.

To check condition (20), observe that

$$\frac{h(t-u)}{h(t)} = \left(\frac{t-u}{t}\right)^{\alpha-1} \exp\{\beta[t^{\gamma} - (t-u)^{\gamma}]\}, \qquad 0 \leqq u \leqq t,$$

and that for every such u

$$0 \leqq t^{\gamma} - (t-u)^{\gamma} \leqq \gamma u(t-u)^{\gamma-1} \to 0, \qquad t \to \infty.$$

If $0 \leqq u \leqq \frac{1}{2}t$ then

$$\frac{h(t-u)}{h(t)} \leqq \left(\frac{t-u}{t}\right)^{\alpha-1} e^{\beta\gamma u(t-u)^{\gamma-1}} \leqq \max\{1, 2^{1-\alpha}\} \exp\{\beta\gamma u(t/2)^{\gamma-1}\}.$$

Therefore for sufficiently large t we have by (24)

$$g_t(u) \leqq Ae^{-\lambda u/2}, \qquad 0 \leqq u \leqq t/2,$$

where A is independent of u and t, and this justifies (25).

To show that $\int_{t/2}^{t} g_t(u)\,du \to 0$ as $t \to \infty$, we use the first inequality in (26) and note that $\int_0^{\infty} h(s)\,ds = \int_0^{\infty} r(s)\,ds = 1$. Recalling that $0 < \gamma < 1$, we have

$$\int_{t/2}^{t} g_t(u)\,du \leqq Ct^{1-\alpha} \exp\{\theta + \beta t^{\gamma} - \lambda t/2\} \to 0, \qquad t \to \infty.$$

Thus, in the case $0 < \gamma < 1$, for every $\lambda > 0$ $\psi(t) \sim r(t)I_3$, where

$$I_3 = \frac{e^{-\theta}}{\lambda} \int_0^1 y^{cv-1}\,dy = \frac{e^{-\theta}}{\lambda cv}.$$

It follows from Remark 4 that Theorem 2 imposes fairly mild restrictions on the function $r(t)$. This theorem enables us to formulate the basic result in terms of the

conditional p.d.f. of tumor size at detection as follows:

$$\lim_{t\to\infty} w(v \mid t) = \frac{v^{\eta}p(v)}{\int_0^{\infty} u^{\eta}p(u)\,du}, \qquad \eta = \min\left\{1, \frac{\sigma}{\lambda}\right\}, \tag{27}$$

which bears close similarity to the one obtained within the framework of the spontaneous carcinogenesis model, but the parameter η in (27) has a somewhat different biological meaning when compared to the parameter μ in (17).

3.3. *The posterior mean tumor size.* Let M denote the expected value of the limiting p.d.f. $w(v \mid \infty)$. Recalling formula (17), we have

$$M = \frac{E(V^{\mu+1})}{E(V^{\mu})} = \frac{\int_0^{\infty} v^{\mu+1}p(v)\,dv}{\int_0^{\infty} u^{\mu}p(u)\,du},$$

providing the second moment of the prior tumor size distribution exists. Note that we just refer to the expected value of the limiting p.d.f. $w(v \mid \infty)$, evading consideration of the first moment convergence which invites special investigation. Since the function $\varphi(v) = v^{\mu}$ is monotonically increasing for $v \geqq 0$, we see that

$$M \geqq E(V) = \int_0^{\infty} vp(v)\,dv.$$

For one example, if a prior gamma distribution with shape parameter α is specified, then the posterior p.d.f. $w(v \mid \infty)$ will be a gamma density as well but with shape parameter $\alpha + \mu$. In that event the posterior expectation is

$$M = \frac{\alpha + \mu}{\beta},$$

where β is the scale parameter of the prior gamma distribution.

4. Estimation problems

Using bivariate data on tumor size and age at detection for patients diagnosed with a specific cancer, it seems feasible to estimate the model parameters responsible for different unobservable stages of carcinogenesis. First we assume that such data arise from the joint p.d.f. $g(v, t) = g(t \mid v)p(v)$. This is a strong assumption but it may be warranted if the effect of data censoring due to competing risks (see below) is negligible. In such an event, the log-likelihood is represented as

$$\ell = \sum_i \log g(t_i \mid v_i) + \sum_i \log p(v_i) = \ell_1 + \ell_2. \tag{28}$$

It is clear that ℓ_1 and ℓ_2 can be maximized independently of each other, resulting in the empirical distribution function, $\hat{P}(v)$, for estimation of the c.d.f. $P(v)$.

It is intriguing that the parameter μ (or η) can be estimated independently of the other parameters from a subsample of old individuals. Let n be this subsample size. Based on (17), the log-likelihood function is

$$\ell(\mu) = \mu \sum_{i=1}^{n} \log v_i + \sum_{i=1}^{n} \log p(v_i) - n \log \boldsymbol{E}(V^{\mu}).$$

Therefore the maximum likelihood estimator, $\hat{\mu}$, of the parameter μ can be obtained as a solution of the following equation:

$$\frac{\boldsymbol{E}(V^{\mu} \log V)}{\boldsymbol{E}(V^{\mu})} = \frac{1}{n} \sum_{i=1}^{n} \log v_i. \tag{29}$$

The left-hand side of this equation is strictly monotonic in μ, and thus the equation has a unique solution. Actually, by applying the Cauchy–Schwarz inequality we see that $\frac{d}{d\mu}(\boldsymbol{E}(V^{\mu} \log V)/\boldsymbol{E}(V^{\mu})) \geqq 0$, where the inequality is strict except for the trivial case of a degenerate r.v. V. With large sample sizes the expected values in (29) can be replaced with their empirical counterparts obtained from the whole sample.

We applied this approach to clinical data on the primary tumor size for 2129 premenopausal patients diagnosed with stage I–III unilateral breast carcinoma. The data are described at length in [20]. There were 536 patients older than 50 in the data set. The maximum likelihood estimate of the parameter μ obtained from this group of patients was found to be $\hat{\mu} = 0.1054$. Such a small value of $\hat{\mu}$ is biologically plausible since the intensity of tumor cell proliferation is known to be much higher than the rate of precancerous lesion formation.

One heuristic way to explore the adequacy of the limiting p.d.f. $w(v \mid t)$ is to test the hypothesis of conditional independence of the size, V, and the age, A, at detection given $A > t^*$, where the value of t^* is to be estimated from a given sample. Note that

$$w(v \mid A = t, A > t^*) = \frac{g(v, t \mid A > t^*)}{g(t \mid A > t^*)}, \qquad t > t^*,$$

where $g(v, t)$ is the joint p.d.f. of V and A. If V and A are conditionally independent given $A > t^*$, then

$$g(v, t \mid A > t^*) = g(v \mid A > t^*) g(t \mid A > t^*), \qquad t > t^*,$$

and

$$w(v \mid A = t, A > t^*) = g(v \mid A > t^*), \qquad t > t^*.$$

We use $w(v \mid \infty)$ to approximate $w(v \mid A = t, A > t^*)$ which is equal to $g(v \mid A > t^*)$ if V and A are conditionally independent.

The hypothesis of conditional independence of the size, V, and the age, A, at detection given $A > t^*$ can be tested by applying Spearman's statistical test to

TABLE 1
Testing the conditional independence of V and A

Values of t^* (years)	P-values of Spearman's test for each subsample
39	<0.001
41	<0.001
43	<0.001
45	<0.001
47	<0.001
49	<0.001
50	0.1

various subsamples created by sampling from pooled adjacent age strata. With the data under study, this procedure resulted in the value of $t^* = 50$ years (Table 1). Clearly, this exploratory data analysis can be regarded as a clue rather than as the conclusive inference. When applied to the whole sample, the Spearman test rejects the independence hypothesis at a significance level much lower than 0.001. It should be noted that the condition $\mu = 0$ is sufficient for independence of V and A. An extended analysis of this data set is addressed in [22].

More generally, account can be taken of a competing risk that precludes tumor detection from occurring. To accommodate this censoring effect, we assume that the competing risk of death from all other causes is independent of the one of interest. The competing risk is characterized by its latent time Y. Let $S(y)$ be the survivor function for Y. It follows that

$$p_c(v) = p(v \mid A < Y) = \frac{p(v)\int_0^\infty g(u \mid v)S(u)\,du}{\int_0^\infty g(u)S(u)\,du},$$

and

$$g_c(v, t) = g(v, t \mid A < Y) = \frac{p_c(v)g(t \mid v)S(t)}{\int_0^\infty g(u \mid v)S(u)\,du}.$$

Since $S(t)$ is free from unknown parameters, the log-likelihood assumes the form

$$\ell_c = \sum_i \log g(t_i \mid v_i) - \sum_i \log \int_0^\infty g(u \mid v_i)S(u)\,du + \sum_i \log p_c(v_i), \tag{30}$$

rendering, as well as (28), estimation of the model parameters independent of the prior size distribution. It is clear that additional information must be called on to estimate the function $S(t)$ involved in the above formulas. The log-likelihood (30) reduces to (28) if $S(t) = 1$ almost everywhere. As our preliminary numerical

experiments suggest, more often than not the impact of censoring on the log-likelihood (30) can be considered negligibly small. It is also noteworthy that the presence of an independent competing risk leaves the form of $w(v \mid t)$ unaltered.

5. The model stability

In studying the stability of the posterior p.d.f. of tumor volume at detection under perturbation in the prior p.d.f. p we proceed from the formula

$$w_t(v) := w(v \mid t) = \frac{g(t \mid v)p(v)}{\int_0^\infty g(t \mid u)p(u)\,du}, \tag{31}$$

and a natural (see (17), (27)) assumption that

$$N_\alpha(p) := \int_0^\infty u^\alpha p(u)\,du < \infty, \tag{32}$$

where $\alpha = \mu$ or η for spontaneous and induced carcinogeneses, respectively. Accordingly, we use the metric

$$\rho_\alpha(\tilde{f}, f) := \int_0^\infty u^\alpha \,|\tilde{f}(u) - f(u)|\,du, \qquad \alpha > 0, \tag{33}$$

to measure the distance between the 'true' p.d.f. f and its perturbed counterpart $\tilde{f}$.

For spontaneous carcinogenesis in the case $\lambda < \theta$, it can be easily envisioned from (9) that $g(v \mid t) \leqq C(t)v$, where

$$C(t) = \lambda\theta c I e^{-\lambda t}, \tag{34}$$

see (10). For $\lambda = \theta$, the same is true with

$$C(t) = \lambda\theta c t \exp\left\{-\lambda\int_0^t R(x)\,dx\right\}. \tag{35}$$

In the remaining case $\lambda > \theta$ we have due to monotone convergence in formula (15) the estimate $g(t \mid v) \leqq C(t)v^{\theta/\lambda}$, where

$$C(t) = \theta c^{\theta/\lambda}\Gamma\left(1 - \frac{\theta}{\lambda}\right)\exp\left\{-\theta\int_0^t R(x)\,dx\right\}. \tag{36}$$

In the case of induced carcinogenesis, we infer from (18) that if $\lambda < \sigma$ then $g(t \mid v) \leqq C(t)v$ with

$$C(t) = \lambda\theta c I_1 e^{-\lambda t}, \tag{37}$$

where I_1 is defined in (19), while for $\lambda = \sigma$ the same estimate holds with

$$C(t) = \lambda\theta c e^{-\lambda t} I_2(t), \tag{38}$$

see (21). Finally, in the case $\lambda > \sigma$ we obtain, assuming that the density r is bounded (by $M(r)$, say) and using monotone convergence in (15), the estimate $g(t \mid v) \leqq C(t)v^{\sigma/\lambda}$, where

$$C(t) = \theta c^{\sigma/\lambda} M(r) \Gamma\left(1 - \frac{\sigma}{\lambda}\right). \tag{39}$$

Hence we can state that in any case

$$g(t \mid v) \leqq C(t)v^{\alpha}. \tag{40}$$

Setting

$$A_t := \int_0^\infty g(t \mid v)p(v)\,dv, \qquad \tilde{A}_t := \int_0^\infty g(t \mid v)\tilde{p}(v)\,dv, \tag{41}$$

and using (31) and (40), we have

$$\begin{aligned} |\tilde{w}_t(v) - w_t(v)| &\leqq \frac{g(t \mid v)\tilde{p}(v)}{A_t\tilde{A}_t}|\tilde{A}_t - A_t| + \frac{g(t \mid v)}{A_t}|\tilde{p}(v) - p(v)| \\ &\leqq \frac{C(t)\rho_\alpha(\tilde{p}, p)}{A_t\tilde{A}_t} g(t \mid v)\tilde{p}(v) + \frac{C(t)v^\alpha}{A_t}|\tilde{p}(v) - p(v)|. \end{aligned}$$

Integrating in v we get finally

$$\rho_0(\tilde{w}_t, w_t) := \int_0^\infty |\tilde{w}(v) - w(v)|\,dv \leqq \frac{2C(t)}{A_t}\rho_\alpha(\tilde{p}, p).$$

By setting $C(t) = 1$ we obtain a similar estimate for the distance between the limiting p.d.f.'s $\tilde{w}$ and w.

We summarize these results in the following.

Theorem 3. Let α *be equal to* μ *or* η *defined in the cases of spontaneous and induced carcinogeneses by* (17) *and* (27), *respectively. Let* ρ_α *be defined as in* (33).

(a) *For every* $t > 0$,

$$\rho_0(\tilde{w}_t, w_t) \leqq \frac{2C(t)}{A_t}\rho_\alpha(\tilde{p}, p),$$

where $C(t)$ *is specified by* (34)–(39) *and* A_t *is defined by* (41).

(b) *For the limiting p.d.f.'s we have*

$$\rho_0(\tilde{w}, w) \leqq \frac{2}{N_\alpha(p)}\rho_\alpha(\tilde{p}, p),$$

where $N_\alpha(p)$ *is given by* (32).

The metrics ρ_0 and ρ_α have different topological structures; ρ_0 is the total

variation distance while ρ_α metrizes the ρ_0-convergence together with the convergence of the α-moments. To make the estimates in Theorem 3 uniform, i.e. to have ρ_0 in both sides of the inequality, one can use the Hölder inequality to obtain for any $\epsilon > 0$

$$\rho_\alpha(p, \tilde{p}) \leqq (\rho_0(p, \tilde{p}))^{\epsilon/\alpha+\epsilon}[N_{\alpha+\epsilon}(p) + N_{\alpha+\epsilon}(\tilde{p})]^{\alpha/(\alpha+\epsilon)},$$

assuming the existence of finite $(\alpha + \epsilon)$-moments for p and $\tilde{p}$. This would result in the following right order estimate:

$$\rho_0(w, \tilde{w}) \leqq \text{constant} \times (t, \epsilon)\rho_0(p, \tilde{p})^{\epsilon/(\alpha+\epsilon)}.$$

6. Some other stability results

The estimates presented in the previous section are adjusted to the model properties. More generally, the problem can be considered in the context of Bayes' formula (31) alone. To this end, we introduce the following λ-structured [19, 32] distance:

$$l(\tilde{g}, g) = \inf\left\{\epsilon > 0: \sup_{|x| \leqq 1/\epsilon} |\tilde{g}(x) - g(x)| < \epsilon\right\} \tag{42}$$

between two functions $\tilde{g}$ and g on R.

If $\tilde{f}$ and f are two probability densities then $l(\log f, \log \tilde{f}) < \epsilon$ means that

$$\sup_{|x| \leqq 1/\epsilon} \left|\log \frac{\tilde{f}(x)}{f(x)}\right| < \epsilon.$$

Remark 5. By virtue of Scheffé's theorem [6] the convergence

$$l(\log f, \log f_n) \to 0, \qquad n \to \infty,$$

implies the convergence in *total variation distance*, i.e.

$$\sigma(f, f_n) = \frac{1}{2}\int_R |f(x) - f_n(x)|\, dx \to 0.$$

We proceed from the following assumptions:

(i) $P := \operatorname{ess\,sup} p(x) < \infty$.

(ii) For some $\alpha > 0$,

$$m_\alpha = \int_R |x|^\alpha p(x)\, dx < \infty.$$

(iii)

$$M_t^0 := \operatorname*{ess\,sup}_v g(t \mid v) < \infty$$

and also there is $\beta > 0$ for which

$$M_t^{(\beta)} = \operatorname{ess\,sup}_v |v|^\beta g(t \mid v) < \infty.$$

Fixing $\delta \in (0, 1]$ such that $\delta^\alpha M_t^{(0)} < A_t$, where A_t is defined in (41), we denote

$$C_t(\delta) := \frac{M_t^{(\beta)}}{A_t - \delta^\alpha M_t^{(0)} m_\alpha}.$$

For *fixed* t, an estimate of the stability of $w(v \mid t)$ to perturbations in the prior p.d.f. $p(v)$ in terms of metric (42) is given by the following theorem.

Theorem 4. *Under conditions* (*i*), (*ii*), *and* (*iii*), *suppose that* $l := l(\log \tilde{p}, \log p) < \delta$. *Then*

$$l(\log \tilde{w}_t, \log w_t) \leqq C_t l^\beta,$$

where

$$C_t = 1 + \frac{2(P e^\delta + 1) e^\delta}{1 - \beta} C_t(\delta).$$

The estimate given by Theorem 4 admits a uniform (with respect to t) version under some additional restrictions. To be specific, we assume that:

(iv) $\sigma := \inf_{t \in R} (A_t / M_t^{(0)}) > 0$;

(v) there exist δ, $0 < \delta < \min\{(\sigma / m_\alpha)^{1/\alpha}, 1\}$ such that

$$C(\delta) := \sup_{t \in R} C_t(\delta) < \infty,$$

and introduce the following metric:

$$L(\log w, \log \tilde{w}) := \inf\left\{\epsilon > 0 : \operatorname{ess\,sup}_{|v|,\, |t| \leqq 1/\epsilon} \left|\log \frac{\tilde{w}_t(v)}{w_t(v)}\right| < \epsilon\right\}. \tag{43}$$

Theorem 5. *Under conditions* (*i*)–(*v*), *suppose* $l := l(\log p, \log \tilde{p}) < \delta$. *Then*

$$L(\log w, \log \tilde{w}) \leqq C L^\beta,$$

where

$$C = 1 + \frac{2(P e^\delta + 1) e^\delta}{1 - \beta} C(\delta).$$

The proof of this theorem is given in the appendix. The proof of Theorem 4 is similar.

Remark 6. In Theorems 3, 4, and 5, we deal with estimates for the model stability in terms of metrics that generate strong topologies in the space of probability laws. If need be, weaker distances can be invoked through the use of 'smoothed' versions

of metrics ρ_0 and l yielding bounds similar to those in Theorems 3–5 (see [19] for details).

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Appendix. Proof of Theorem 5

Choose $\epsilon \in (l, \delta)$. For almost all v and t, we have

$$\left|\log\frac{\tilde{w}_t(v)}{w_t(v)}\right| = |\log\tilde{w}_t(v) - \log w_t(v)| \leqq |\log\tilde{p}(v) - \log p(v)|$$

$$+ \left|\log\int_{\mathbb{R}} g(t \mid x)\tilde{p}(x)\,dx - \log\int_{\mathbb{R}} g(t \mid x)p(x)\,dx\right| = D_v + E_t.$$

Note that

$$\text{(A1)} \qquad \sup_{|v|\leqq\epsilon^{-1}} D_v = \sup_{|v|\leqq\epsilon^{-1}}\left|\log\frac{\tilde{p}(v)}{p(v)}\right| < \epsilon.$$

Recall next the inequality

$$\text{(A2)} \qquad \min(a, b)\left|\log\frac{a}{b}\right| \leqq |a-b| \leqq \max(a, b)\left|\log\frac{a}{b}\right|,$$

which is valid for all $a, b > 0$. Therefore, the upper bound for E_t is given by

$$\text{(A3)} \qquad E_t \leqq \frac{\left|\int_{\mathbb{R}} g(t \mid x)(\tilde{p}(x) - p(x))\,dx\right|}{\min(\tilde{A}_t, A_t)}.$$

For the numerator, N_t, in (A3) we have

$$N_t \leqq M_t^{(\beta)}\left(\int_{|x|\leqq\epsilon^{-1}} + \int_{|x|>\epsilon^{-1}}\right)|x|^{-\beta}\,|\tilde{p}(x) - p(x)|\,dx.$$

In view of (A1) and (A2) the first integral is estimated by

$$\int_{|x|\leqq\epsilon^{-1}} |x|^{-\beta}\,|\tilde{p}(x) - p(x)|\,dx \leqq \epsilon P e^{\delta}\int_{|x|\leqq\epsilon^{-1}} |x|^{-\beta}\,dx = \frac{2Pe^{\delta}}{1-\beta}\epsilon^{\beta}.$$

As for the second integral, we have

$$\int_{|x|>\epsilon^{-1}} |x|^{-\beta} \, |\tilde{p}(x) - p(x)| \, dx \leqq 2\epsilon^{\beta}.$$

Hence,

$$N_t \leqq \frac{2M_t^{(\beta)}\epsilon^{\beta}}{1-\beta}(P\mathrm{e}^{\delta}+1).$$

Consider now the expression for $\tilde{A}_t$:

$$\tilde{A}_t := \int_{\mathbb{R}} g(t \mid x)\tilde{p}(x)\,dx = \left(\int_{|x|\leqq\epsilon^{-1}} + \int_{|x|>\epsilon^{-1}}\right) g(t \mid x)\tilde{p}(x)\,dx.$$

Due to (A1) we have for the first integral the following lower bound:

$$\int_{|x|\leqq\epsilon^{-1}} g(t \mid x)\tilde{p}(x)\,dx \geqq \mathrm{e}^{-\epsilon}\int_{|x|\leqq\epsilon^{-1}} g(t \mid x)p(x)\,dx,$$

and consequently for the denominator in (A3) we get

$$\min(\tilde{A}_t, A_t) \geqq \mathrm{e}^{-\epsilon}\int_{|x|\leqq\epsilon^{-1}} g(t \mid x)p(x)\,dx.$$

Furthermore, we have

$$\int_{|x|>\epsilon^{-1}} g(t \mid x)p(x)\,dx \leqq M_t^{(0)}\int_{|x|>\epsilon^{-1}} p(x)\,dx \leqq \epsilon^{\alpha}M_t^{(0)}m_{\alpha}.$$

Combining the above estimates and using assumptions (iv) and (v), we set

$$B := \frac{2(P\mathrm{e}^{\delta}+1)\mathrm{e}^{\delta}}{1-\beta}$$

to obtain

$$E_t \leqq B\epsilon^{\beta}\frac{M_t^{(\beta)}}{A_t - \epsilon^{\alpha}M_t^{(0)}m_{\alpha}} \leqq B\epsilon^{\beta}\frac{M_t^{(\beta)}}{A_t - \delta^{\alpha}M_t^{(0)}m_{\alpha}} \leqq BC(\delta)\epsilon^{\beta}.$$

Together with (A1) this yields

$$\operatorname{ess}\sup_{|v|,\,|t|<\epsilon^{-1}} \left|\log\frac{\tilde{w}_t(v)}{w_t(v)}\right| \leqq \operatorname{ess}\sup_{|v|<\epsilon^{-1}} D_v + \operatorname{ess}\sup_{|t|<\varepsilon^{-1}} E_t \leqq \epsilon + BC(\delta)\epsilon^{\beta}.$$

Now from the definition (43) we derive that

$$L(\log\tilde{w}, \log w) \leqq \epsilon + BC(\delta)\epsilon^{\beta} \leqq \epsilon^{\beta}(1 + BC(\delta)).$$

Letting $\epsilon \to l(\log\tilde{p}, \log p)$, we see finally that $L(\log\tilde{w}, \log w) \leqq Cl^{\beta}$, as required.

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