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A distribution of tumor size at detection and its limiting form

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ABSTRACT **A distribution of tumor size at detection is derived within the framework of a mechanistic model of carcinogenesis with the object of estimating biologically meaningful parameters of tumor latency. Its limiting form appears to be a generalization of the distribution that arises in the length-biased sampling from stationary point processes. The model renders the associated estimation problems tractable. The usefulness of the proposed approach is illustrated with an application to clinical data on premenopausal breast cancer.**

Section 1. Introduction

Thus far, little consideration has been given to the process of tumor detection in mechanistic models of carcinogenesis. The presently most widely accepted two-stage model of carcinogenesis, usually referred to as the Moolgavkar–Venzon–Knudson (MVK) model (1, 2), is focussed on the events that precede the occurence of the first malignant cell in a tissue. An explicit description of the stage of tumor progression is obviated in the MVK model. This pertains equally to the model of radiation carcinogenesis by Klebanov *et al.* (3) and its generalization thereof by Yakovlev and Polig (4). This is no surprise, since an extended three-stage model meets with identifiability problems when applied to the analysis of time-to-tumor observations. An extra source of information must be called on to make estimation problems tractable. Yakovlev and Tsodikov (5) suggested to use the data on tumor size at detection for this purpose. They introduced a threshold counterpart of the model developed in ref. 3 to accomodate this sort of data. In Section 2 of the present paper, we proceed from the same idea to derive the conditional distribution of tumor volume at detection given a tumor is detected at time t, which involves biologically meaningful parameters to be estimated from clinical data. As shown in Section 3, the limiting form of this distribution appears to be free from distributional assumptions on the promotion stage duration. We study the stability of the model with respect to the prior distribution of tumor size in Section 4. The statistical inference from bivariate data on tumor size and age at detection is discussed in Section 5, along with a relevant example of real data analysis. As evidenced by our findings, the approach holds much promise for the analysis of tumor latency and risk assessment. Some other ways of relating the chance of detecting a tumor to its size are discussed in refs. 6 and 7.

Section 2. A Model of Spontaneous and Induced Carcinogenesis

We proceed from the following basic assumptions.

(*i*) The occurence of initiated cells (primary lesions) is thought of as a homogeneous Poisson process with intensity θ. This assumption is common to all stochastic models of carcinogenesis.

(*ii*) A primary lesion remains dormant while proceeding through the promotional stage of tumor development. Let $R(t)$ be the cumulative distribution function (CDF) of this stage duration. All lesions are subject to promotion independently of each other, each of them passing the same route. This assumption generalizes the MVK model as long as the CDF $R(t)$ remains uspecified. The results presented in Section 3 are free from the form of this distribution.

(*iii*) 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.

(*iv*) A tumor becomes detectable when its size attains some threshold value, N, which is treated as a random variable (RV). 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 nonrandom, 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 (6). We use a linear pure birth process with the absorbing upper barrier N to model the dynamics of tumor growth. Under this model the conditional progression time CDF, given the threshold volume $V = v$, is

$$F(t|v) = (1 - e^{-\lambda t})^{cv}. \qquad [1]$$

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 CDF 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 is the following expression for the corresponding survivor function $\bar{L}(t) = 1 - L(t)$:

$$\bar{L}(t) = \exp\left\{-\theta \int_0^t R(x)dx\right\}; \qquad [2]$$

see ref. 3. The MVK model is a special case of Eq. 2 with the CDF $R(t)$ specified by a homogeneous birth–death model of clonal expansion (8). Let $f(t|v)$ stand for the probability density function (PDF) of $F(t|v)$. Assuming that the stages of promotion and progression are mutually independent, we use the convolution

$$g(t|v) = \int_0^t R(t-u)e^{-\theta\int_0^{t-u} R(x)dx} f(u|v)du \qquad [3]$$

to represent the conditional PDF, $g(t|v)$, of the time of tumor latency measured from the date of birth.

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Abbreviations: MVK, Moolgavkar–Venzon–Knudson; CDF, cumulative distribution function; RV, random variable; PDF, probability density function.

Introducing a prior distribution, $P(v)$, of the RV V, we represent the PDF of the time (age) of tumor detection as

$$g(t) = \int_0^\infty g(t|v)p(v)dv, \qquad [4]$$

where $p(v)$ is the density of $P(v)$. The posterior PDF, $w(v|t)$, of tumor volume at detection, given a tumor is detected at time t, is obtained from Bayes' formula

$$w(v|t) = \frac{g(t|v)p(v)}{\int_0^\infty g(t|u)p(u)du} = \frac{g(t|v)p(v)}{g(t)}, \qquad [5]$$

where $g(t|v)$ and $g(t)$ are given by Eqs. 3 and 4, respectively.

In the event of induced carcinogenesis the time of tumor latency is measured from the time of exposure to a carcinogen. We consider only brief exposures though protracted exposures can be easily accommodated within this framework (3). As shown in ref. 3, formula 3 is replaced with

$$\bar{L}(t) = e^{-\theta R(t)}, \qquad [6]$$

where θ is the mean number of lesions induced by a given dose of carcinogen. Unlike the distribution given by Eq. 2, distribution 6 is improper. Using formula 6 in place of 2, we retain the model structure given by formulas 1, 3, 4, 5 in the case of induced carcinogenesis.

The above formulas are quite cumbersome, making the model application difficult. Fortunately, the conditional PDF $w(v|t)$ assumes a much simpler form when t tends to infinity.

Section 3. The Limiting Form of $w(v|t)$

It follows from Eqs. 1 and 3 that in the case of spontaneous carcinogenesis

$$g(t|v) = \lambda\theta cv\int_0^t e^{-\lambda(t-s)}(1-e^{-\lambda(t-s)})^{cv-1}R(s)e^{-\theta\int_0^s R(x)dx}ds$$

$$= \lambda\theta cv\psi(t). \qquad [7]$$

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

(1) If $\lambda < \theta$, *then*

$$\psi(t) \sim Ie^{-\lambda t}, \qquad [8]$$

where

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

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

$$\psi(t) \sim te^{-\lambda\int_0^t R(x)dx}. \qquad [9]$$

(3) If $\lambda > \theta$, *then*

$$\psi(t) \sim Je^{-\theta\int_0^t R(x)dx}, \qquad [10]$$

with

$$J = \frac{1}{\lambda}\int_0^1 y^{cv-1}(1-y)^{-\theta/\lambda}dy = \frac{1}{\lambda}B(cv, z1-\theta/\lambda),$$

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

The proof for large values of cv is given in ref. 5. An alternative and more efficient proof is based on the following lemma.

LEMMA. *Let* $K(t, s, u)$ *be a bounded measurable function defined for* $t \geq s \geq 0$, $u \geq 0$ *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* $u \geq 0$, *and* $\int_0^\infty h(u)du = \infty$. *Denote* $H(t) = \int_0^t h(u)du$. *Then*

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

This lemma will be used below to prove a similar theorem for the model of induced carcinogenesis.

Taking up formulas 5 and 7 with $\psi(t)$ given by Eqs. 9 or 10, we can write

$$\lim_{t\to+\infty} w(v|t) = \frac{vp(v)}{\int_0^\infty up(u)du}, \qquad \lambda \leq \theta. \qquad [11]$$

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

$$\lim_{cv\to\infty}(cv)^{1-\theta/\lambda}B(cv, 1-\theta/\lambda) = \Gamma(1-\theta/\lambda), \qquad \theta < \lambda, \qquad [12]$$

and the Lebesgue theorem on bounded convergence, it follows from Eqs. 5, 7, and 10 that

$$w(v|t) \sim \frac{v^{\theta/\lambda}p(v)}{\int_0^\infty u^{\theta/\lambda}p(u)du}, \qquad t\to\infty, cv\to\infty, \qquad [13]$$

for $\lambda > \theta$. Combining Eqs. 11 and 13, we obtain the limiting conditional PDF of tumor size at detection

$$\lim_{t\to+\infty} w(v|t) = \frac{v^\mu p(v)}{\int_0^\infty u^\mu p(u)du}, \qquad \mu = \min\left\{1, \frac{\theta}{\lambda}\right\}. \qquad [14]$$

A special case ($\mu = 1$) of this distribution is associated with what is known as a length-biased sampling from stationary point processes (9).

Along similar lines the case of induced carcinogenesis can be considered. In this case

$$g(t|v) = \lambda\theta cv\int_0^t e^{-\lambda(t-s)}(1-e^{-\lambda(t-s)})^{cv-1}r(s)e^{-\theta R(s)}ds$$

$$= \lambda\theta cv\psi_0(t), \qquad [15]$$

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

THEOREM 2. *Let* $\sigma := \sup\{\alpha : \int_0^\infty e^{\alpha s}r(s)ds < \infty\}$, $0 \leq \sigma \leq \infty$.
(1) If $\lambda < \sigma$ *or* $\lambda = \sigma$ *and* $\int_0^\infty e^{\sigma s}r(s)ds < \infty$, *then*

$$\psi_0(t) \sim I_1e^{-\lambda t}, \qquad t\to\infty, \qquad [16]$$

where $I_1 = \int_0^\infty e^{\lambda s}r(s)e^{-\theta R(s)}ds$.
(2) 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*

$$\lim_{t\to\infty}\frac{h(t-u)}{h(t)}\to 1 \qquad \textit{for every } u\geq 0. \qquad [17]$$

Then

$$\psi_0(t)\sim I_2(t)e^{-(\lambda t+\theta)}, \qquad t\to\infty, \qquad [18]$$

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

(3) Let $\lambda>\sigma$. *Suppose that* $r(s)$ *is positive and continuous for* $s>0$ *and that* h *satisfies Eq. 17. Also, suppose that the function* h *is either nondecreasing or it is nonincreasing and subject to the following conditions:*

(3a) $h(t)/h(2t)\leq C$ *for some constant* C;

(3b) $\int_0^t h(s)ds<\infty$.

Then

$$\psi_0(t)\sim I_3 r(t) \qquad [19]$$

where $I_3=(e^{-\theta}/\lambda)\int_0^t y^{cv-1}(1-y)^{-\sigma/\lambda}\,dy=(e^{-\theta}/\lambda)\,B(cv,\,1-\sigma/\lambda)$.

Proof: (1) We represent the function $\psi_0(t)$ (see Eq. 15) in the form

$$\psi_0(t)=e^{-\lambda t}\int_0^\infty f_t(s)ds,$$

where

$$f_t(s)=e^{\lambda s}(1-e^{-\lambda(t-s)})^{cv-1}r(s)e^{-\theta R(s)}\chi_{[0,t]}(s),$$

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

$$f_t(s)\uparrow f(s):=e^{\lambda s}r(s)e^{-\theta R(s)}, \qquad t\to\infty,$$

and Eq. 16 follows from the Lebesgue theorem on bounded convergence, observing the fact that in our case the function f is integrable.

(2) We have

$$\psi_0(t)=e^{-(\lambda t+\theta)}\int_0^\infty K(t-s,\,s)h(s)ds,$$

where $K(u,s)=(1-e^{-\lambda u})^{cv-1}e^{\theta[1-R(s)]}$ and $h(s)$ is defined above. Observe that $0<K(u,s)\leq e^\theta$ and $K(u,s)\to 1$ for $u, s\to\infty$. Applying the Lemma, we get Eq. 18.

(3) By the change of variable $u=t-s$ in Eq. 15 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 $u\geq 0$, we have by Eq. 17

$$g_t(u)\to g(u):=e^{-(\lambda-\sigma)u}(1-e^{-\lambda u})^{cv-1}, \qquad t\to\infty, \quad [20]$$

and it is clear that $\int_0^\infty g(u)du<\infty$. If h is nondecreasing, then $g_t(u)\leq e^\theta g(u)$, 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 nonincreasing. Observe that

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

Hence, for $0\leq u\leq t/2$ we have from condition 3a:

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

Then by the Lebesgue theorem and in view of Eq. 20,

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

Next, invoking 3b we find that

$$\int_{t/2}^t g_t(u)du\leq\frac{e^{\theta-(\lambda-\sigma)t/2}}{h(t)}\int_0^{t/2}h(s)ds\leq\frac{e^{\theta-(\lambda-\sigma)t/2}}{h(t)}$$

$$\left[\int_0^1 h(s)ds+\frac{t}{2}h(1)\right].$$

Note that condition 3a and monotonicity of h imply that $h(t)\geq At^{-\delta}$ 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: It can be verified that Theorem 2 applies to many parametric families including the Weibull and gamma distributions.

The above theorem imposes fairly mild restrictions on the PDF $r(t)$ and enables us to formulate the basic result in terms of the conditional PDF of tumor size at detection

$$\lim_{t\to+\infty}w(v|t)=\frac{v^\eta p(v)}{\int_0^\infty u^\eta p(u)du}, \qquad \eta=\min\left\{1,\frac{\sigma}{\lambda}\right\}, \quad [21]$$

which bears close similarity to the one obtained within the framework of the spontaneous carcinogenesis model (formula 14) with the parameter η being a counterpart of the parameter $\mu=\min\{1,\,\theta/\lambda\}$.

Section 4. The Model Stability

In studying stability of the posterior PDF of tumor volume at detection under perturbations in the prior PDF p we proceed from Eq. 5 and a natural assumption that

$$N_\alpha(p):=\int_0^\infty u^\alpha p(u)du<\infty, \qquad [22]$$

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

$$\rho_\alpha(\bar p,p):=\int_0^\infty u^\alpha|\bar p(u)-p(u)|du, \qquad \alpha>0 \quad [23]$$

to measure the distance between the "true" PDF p and its perturbed counterpart $\bar p$.

For spontaneous carcinogenesis in the case $\lambda<\theta$, it can be easily envisioned from Eq. 7 that $g(v|t)\leq C(t)v$, where

$$C(t)=\lambda\theta cIe^{-\lambda t}; \qquad [24]$$

see Eq. 8. For $\lambda = \theta$, the same is true with

$$C(t) = \lambda\theta cte^{-\lambda\int_0^t R(x)dx}. \quad [25]$$

In the remaining case $\lambda > \theta$ we have due to monotone convergence in formula 12 the estimate $g(t|v) \le C(t)v^{\theta/\lambda}$, where

$$C(t) = \theta c^{\theta/\lambda}\Gamma\left(1 - \frac{\theta}{\lambda}\right)e^{-\theta\int_0^t R(x)dx}. \quad [26]$$

In the case of induced carcinogenesis, we infer from Eq. 15 that if $\lambda < \sigma$ then $g(t|v) \le C(t)v$ with

$$C(t) = \lambda\theta cI_1 e^{-\lambda t}, \quad [27]$$

where I_1 is defined in Eq. 16, while for $\lambda = \sigma$ the same estimate holds with

$$C(t) = \lambda\theta cte^{-\lambda t}I_2(t); \quad [28]$$

see Eq. 18. Finally, in the case $\lambda > \sigma$ we obtain, assuming that the density r is bounded [by $M(r)$, say] and using monotone convergence in Eq. 12, the estimate $g(t|v) \le C(t)v^{\sigma/\lambda}$, where

$$C(t) = \theta c^{\sigma/\lambda}M(r)\Gamma\left(1 - \frac{\sigma}{\lambda}\right). \quad [29]$$

Hence we can state that in any case

$$g(t|v) \le C(t)v^{\alpha}. \quad [30]$$

Denoting

$$A_t := \int_0^\infty g(t|v)p(v)dv, \qquad \tilde{A}_t := \int_0^\infty g(t|v)\tilde{p}(v)dv, \quad [31]$$

and using Eqs. 21 and 30, we have

$$|\tilde{w}_t(v) - w_t(v)| \le \frac{g(t|v)\tilde{p}(v)}{A_t\tilde{A}_t}|\tilde{A}_t - A_t| + \frac{g(t|v)}{A_t}|\tilde{p}(v) - p(v)|$$

$$\le \frac{C(t)\rho_\alpha(\tilde{p}, p)}{A_t\tilde{A}_t}g(t|v)\tilde{p}(v) + \frac{C(t)v^\alpha}{A_t}|\tilde{p}(v) - p(v)|,$$

where $w_t(v) := w(v|t)$, $\tilde{w}_t(v) := \tilde{w}(v|t)$. Integrating in v we get

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

By setting $C(t) = 1$ we obtain a similar estimate for the distance between the limiting PDFs $\tilde{w}$ and w.

We summarize these results in

THEOREM 3. *Let α be equal to μ or η defined in the cases of spontaneous and induced carcinogeneses by Eqs. 14 and 21, respectively. Let ρ_α be defined as in Eq. 23.*
(1) For every $t > 0$,

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

where $C(t)$ is specified by Eqs. 24–39 and A_t is defined by Eq. 31.
(2) For the limiting PDFs we have

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

where $N_\alpha(p)$ is given by Eq. 22.

The metrics ρ_0 and ρ_α have different topological structures (10). To make the estimates in Theorem 3 uniform, one can use the inequality: for any $\varepsilon > 0$

$$\rho_\alpha(p, \tilde{p}) \le (\rho_0(p, \tilde{p}))^{\frac{\varepsilon}{\alpha+\varepsilon}}[N_{\alpha+\varepsilon}(p) + N_{\alpha+\varepsilon}(\tilde{p})]^{\frac{\alpha}{\alpha+\varepsilon}},$$

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

$$\rho_0(w, \tilde{w}) \le \text{const}(t, \varepsilon)\rho_0(p, \tilde{p})^{\frac{\varepsilon}{\alpha+\varepsilon}}.$$

Section 5. Estimation Problems and Data Analysis

The model offers the prospect of estimation of some biologically meaningful parameters responsible for the temporal organization of tumor latency from bivariate data on tumor size and age at detection for patients diagnosed with a specific cancer. This approach implies sampling from the joint distribution of tumor size and age at detection which may be warranted if the effect of data censoring due to competing risks is negligible. As our numerical experiments suggest, this appears to be the case for at least some judiciously chosen parameter values if the competing risk of death from all other causes is independent of the one of interest. Assuming that data arise from the joint PDF $g(v, t)$, we represent the log-likelihood as

$$\ell = \sum_i \log g(t_i|v_i) + \sum_i \log p(v_i) = \ell_1 + \ell_2.$$

where ℓ_1 and ℓ_2 can be maximized independently of each other. This offers the empirical distribution function, $\hat{P}(v)$, for estimation of the CDF $P(v)$. Alternatively, additional parametric assumptions can be invoked to specify $P(v)$, and the results of Section 4 ensure the model stability under small perturbations in this distribution. It is noteworthy that the presence of an independent competing risk leaves the form of $w(v|t)$ unaltered; that is 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 Eq. 14, the log-likelihood function is

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

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

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

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

$$\frac{d}{d\mu}\left(\frac{\mathrm{E}(V^\mu \log V)}{\mathrm{E}(V^\mu)}\right) =$$

$$\frac{\mathrm{E}\{V^\mu (\log V)^2\}\mathrm{E}\{V^\mu\} - (\mathrm{E}\{V^\mu \log V\})^2}{(\mathrm{E}\{V^\mu\})^2} \ge 0,$$

where the inequality is strict except for the trivial case of a degenerate RV V.

We applied this method to clinical data on the primary tumor size for 2129 premenopausal patients diagnosed with stage I–III unilateral breast carcinoma. The subcobort of

patients is described in ref. 11. The adequacy of the limiting PDF $w(v|t)$ was explored through testing 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 the given sample. This was accomplished by applying the Spearman test to various age strata. With the data under study, this procedure resulted in the value of $t^* = 50$ years. When applied to the whole sample, the Spearman test rejects the independence hypothesis, and hence the hypothesis: $\mu = 0$, at a significance level much lower than 0.001. The maximum likelihood estimate of the parameter μ obtained from the group of 536 patients older than 50 was found to be $\hat{\mu} = 0.1054$ with the asymptotic 0.95 confidence interval (0, 0.229). An extended analysis of this data set based on the proposed model will be addressed in another paper.

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