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BRANCHING POPULATIONS OF CELLS BEARING A CONTINUOUS LABEL

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This paper is concerned with an age-dependent branching process with particles (cells) bearing a label, the latter being treated as a continuous parameter. The proposed stochastic model is motivated by applications in cell biology. It is assumed that the mitotic division results in a random distribution of the label among daughter cells in accordance with some bivariate probability distribution. In the event of cell death the label borne by that cell disappears. The main focus is on the label distribution as a function of the time elapsed from the moment of label administration. Explicit expressions for this distribution are derived in some particular cases which are of practical interest in the analysis of cell cycle. The Markov branching process with the same evolution of a continuously distributed label is considered as well.

1. Introduction

The theory of branching stochastic processes has proven itself as a powerful tool for mathematical modeling of cell proliferation and differentiation (Jagers [11], Cowan and Staudte [3], Yakovlev and Yanev [21], Huggins and Basawa [6], Kimmel and Axelrod [13], Haccou et al. [5], Hyrien et al. [8, 9], to name a few). Among many applied problems for which methods of branching stochastic processes hold much promise is the analysis of labeling experiments. These

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experimental techniques are intended for making quantitative inference of the mitotic cycle parameters in renewing cell populations from observed dynamics of cells after a fraction of the cell population is labeled with specially designed molecular markers. DNA precursors labeled either with radioactive isotopes (e.g., ^3H-thymidine) or with fluorescent antibodies are typically used for this purpose. Such labeling of the cells occurs during their progression through the S-phase of the mitotic cycle.

When using ^3H-thymidine and autoradiographic technique (Cleaver [2]), one can obtain data on grain counts, the latter being interpreted as discrete marks attached to each labeled cell. The distribution of such marks as a function of the time elapsed from the administration of a pulse label yields the needed information on the structure of the mitotic cycle to be extracted by methods of mathematical modeling. Assuming that the initial distribution of marks is Poisson, and treating the evolution of labeled cells as a Bellman-Harris age-dependent branching process with infinitely many cell types, Yanev and Yakovlev [23] derived an analytical form of this distribution. This result presently has limited practical utility because experimental data on grain counts are no longer generated by biological studies. On the other hand, analyzing the kinetics of cells that have been pulse-labeled with BrdU on a fluorescence-activated cell sorter has become a method of choice in this field of research. This technique calls for modeling the distribution of BrdU intensity and its variations with time. However, little attention has been given to this problem within the framework of stochastic branching processes. The case of a randomly distributed continuous label is more complicated than its discrete counterpart and involves modeling of a branching process with states characterized by a real-valued parameter.

Kolmogorov [14] was the first to consider a branching process (particle splitting) of this type with the continuous parameter being the particle size. Further results in this direction were reported by Filipov [4]. Ney [19, 20] studied cascade processes, where each particle is characterized by its energy. In the case of Markov binary splitting, he obtained interesting asymptotic results which are recalled in our discussion in Section 4. In his famous and influential book, Harris [7] devoted a whole chapter to energy-dependent branching processes. Bertoin [2] considered random fragmentation processes and their relation to multiplicative cascades and branching processes in a recent review (see also the literature therein).

All these methods, however, are not directly applicable to the problem under discussion. The time evolution of a continuous label incorporated into the cell during a limited period of its life cycle should be modeled with due account of the knowledge amassed in cell biology. In particular, the model should include the event of cell death resulting in the disappearance of the entire label borne by the cell.

In Section 2, we consider an age-dependent branching process with a continuous parameter as a general stochastic model for the analysis of labeling experiments and introduce the so-called label distribution. In Section 3, the label distributions are obtained for some particular non-Markov cases which are of

interest from this prospective. The Markov case is investigated with more details in Section 4. Finally some possible extensions are discussed.

2. Age-dependent branching processes with a continuously distributed label

Suppose that every cell has a life time τ with distribution function $G(x) = \Pr(\tau \leq x)$ and at the end of its life it either divides into two cells with probability p $(0 < p \leq 1)$ or it dies with probability $1 - p$. If a cell divides, its label L is distributed randomly between daughter cells so that their labels L_1 and L_2 satisfy the condition $L_1 + L_2 \leq L$. Introduce the conditional distribution

$$\Pr(L_1 \leq y_1, L_2 \leq y_2 | L = y) = K(y_1/y, y_2/y), 0 \leq y_1 \leq y, 0 \leq y_2 \leq y, \tag{1}$$

where the bivariate distribution function $K(x_1, x_2)$ is symmetric, that is , $K(x_1, x_2) = K(x_2, x_1)$, $0 \leq K(x_1, x_2) \leq 1$ for $0 \leq x_1 \leq 1, 0 \leq x_2 \leq 1$. Let $K(x) = K(x, 1) = K(1, x)$ be the one-dimensional distribution that defines both marginal distributions of $K(x_1, x_2)$. In the event of cell death the label borne by that cell disappears.

We assume for simplicity that the process begins with one cell of age zero at time $t = 0$ and the initial cell bears a certain amount L_0 of label. The results can readily be generalized to include an arbitrary initial distribution of the random variable L_0 and then the resultant formulas can be compounded with respect to this distribution. The initial distribution can be estimated nonparametrically from the data on label intensity available at time $t = 0$.

Let $Z(t, x)$ be the number of cells at time $t > 0$ with the label intensity of $L \geq x$. It is clear that $Z(t, x) = 0$ if $x > L_0$. Introduce the notation: $P_n(t, x|L_0) = \Pr(Z(t, x) = n)$. From (1) it follows

$$P_n(t, x|L_0) = P_n(t, x/L_0|1), x \leq L_0. \tag{2}$$

In what follows, we will use the notation

$$P_n(t, x) = P_n(t, x|1), 0 \leq x \leq 1. \tag{3}$$

Note that $P_n(t, x) = 0$ for $n > 1/x$.

Let us introduce the probability generating function (*p.g.f.*)

$$\Psi(t, x, s) = \mathbb{E}\{s^{Z(t,x)}\} = \sum_{n=0}^{\infty} P_n(t, x)s^n, \quad |s| \leq 1. \tag{4}$$

Theorem 1. *Under conditions* (1) – (3) *the p.g.f.* (4) *satisfies the equation:*

$$\Psi(t,x,s) = (1-p)G(t) + s[1-G(t)] \tag{5}$$

$$+ p\int_0^t \{\int_x^1 \int_x^1 \Psi(t-y, x/u_1, s)\Psi(t-y, x/u_2, s)K(du_1, du_2)\}dG(y),$$

which has a unique solution in the class of the p.g.f.

P r o o f. Conditioning on the evolution of the first cell and using the law of total probability by (1) – (3) one has

$$P_n(t,x) = \delta_{n,1}[1-G(t)] + (1-p)\delta_{n,0}G(t) \tag{6}$$

$$+p\int_0^t \{\int_x^1 \int_x^1 \sum_{k=0}^{n} P_k(t-y, x/u_1)P_{n-k}(t-y, x/u_2)K(du_1, du_2)\}dG(y),$$

where $\delta_{n,k} = 0$ for $n \neq k$ and $\delta_{n,k} = 1$ for $n = k$.

Now multiplying (6) by s^n and summarizing one obtains (5).

Introduce the notation:

$A(t,x) = \mathbb{E}\{Z(t,x)\} = \frac{\partial}{\partial s}\Psi(t,x,s)|_{s=1}$,

$B(t,x) = \mathbb{E}\{Z(t,x)[Z(t,x)-1]\} = \frac{\partial^2}{\partial s^2}\Psi(t,x,s)|_{s=1}$.

Recalling that $\mathrm{Var}\{Z(t,x)\} = B(t,x) + A(t,x) - A^2(t,x)$, one can obtain from (5) the following equations:

$$A(t,x) = 2p\int_0^t \{\int_x^1 A(t-y, x/u)dK(u)\}dG(y) + 1 - G(t), \tag{7}$$

$$B(t,x) = 2p\int_0^t \{\int_x^1 B(t-y, x/u)dK(u)\}dG(y) \tag{8}$$

$$+2p\int_0^t \{\int_x^1 \int_x^1 A(t-y, x/u_1)A(t-y, x/u_2)K(du_1, du_2)\}dG(y). \quad \square$$

Remark. If $p = 1$, the above model reduces to the binary splitting case considered by Ney [19, 20].

Setting $x = 0$ in (6) − (8) one arrives at the equations

$$\Psi(t,0,s) = (1-p)G(t) + s[1 - G(t) + p\int_0^t \Psi^2(t-y,0,s)dG(y), \tag{6a}$$

$$A(t,0) = 2p\int_0^t A(t-y,0)dG(y) + 1 - G(t), \tag{7a}$$

$$B(t,0) = 2p\int_0^t B(t-y,0)dG(y) + 2p\int_0^t A^2(t-y,0)dG(y), \tag{8a}$$

that describe an age-dependent binary branching process considered by Bellman and Harris [1]. Note that (6a) is a renewal-type equation and its solution is given by

$$A(t,0) = \sum_{k=0}^{\infty} (2p)^k (\overline{G} * G^{*k})(t), \tag{9}$$

where $G(t) \equiv 1-G(t)$ and $*$ is the usual symbol of convolution. More specifically, $G^{*k}(t)$ is the $k-$th convolution of $G(t)$, that is

$$G^{*(k+1)}(t) = \int_0^t G(t-y)dG^{*k}(y), k \geq 0,$$

$G^{*0}(y) = 0$ for $y < 0$ and $G^{*0}(y) = 1$ for $y \geq 0$.

Definition 1. *The label distribution $D_t(x)$ is defined as follows*

$$\overline{D}_t(x) = 1 - D_t(x) = A(t,x)/A(t,0). \tag{10}$$

Comment. The formula (10) can be interpreted in the following way. Denote by $L(t)$ the amount of the label borne by a randomly chosen cell at the moment t. If $Z(t) = n$ then $Z(t,x)$ will have a binomial distribution with parameters n and $p = \overline{D}_t(x) = \Pr(L(t) \geq x)$, because of the usual independence assumptions of the individual evolutions in branching processes.

Therefore

$$\begin{aligned} A(t,x) &= \sum_{n=0}^{\infty} P(Z(t)=n)E\{Z(t,x)|Z(t)=n\} \\ &= \sum_{n=0}^{\infty} P(Z(t)=n)n\overline{D}_t(x) = A(t,0)\overline{D}_t(x), \end{aligned}$$

which gives (10).

In the general case, finding an explicit solution of equation (7) (as is the case with equation (9)) is not feasible but some particular cases of practical importance can still be investigated.

3. Specific Label Distributions Associated with the Bellman-Harris Process

A closed form solution can be obtained in the special case where one of the daughter cells receives a fixed fraction c $(0 < c < 1)$ of the mother label while the complement $1 - c$ goes to the second daughter cell. By a symmetry argument we have the condition: $0 < c \leq 1/2$. In this particular case,

$$K_c(u) = 0 \quad \text{for} \quad u < c \quad \text{and} \quad K_c(u) = 1 \quad \text{for} \quad u \geq c. \tag{11}$$

Let $\langle z \rangle$ denotes the smallest integer greater or equal to z.

Theorem 2. *Under condition* (11) *the following label distribution holds:*
(i)For $x < c \leq 1/2$

$$\overline{D}_t(x) = \{\sum_{k=0}^{N} (2p)^k (\overline{G} * G^{*k})(t)\} / \sum_{k=0}^{\infty} (2p)^k (\overline{G} * G^{*k})(t), \tag{12}$$

where

$$N = N(x, c) = \langle (\ln(x/c)) / \ln c \rangle; \tag{13}$$

(ii) If $x \geq c$ *then*

$$\overline{D}_t(x) = \overline{G}(t) / \sum_{k=0}^{\infty} (2p)^k (\overline{G} * G^{*k})(t) \tag{14}$$

for every $c \in (0, 1/2]$.

Proof. Using (11) it is not difficult to obtain that

$$\int_x^1 A(t - y, x/u) dK(u) = 0 \quad \text{for} \quad 0 < c \leq x < 1 \tag{15}$$

and

$$\int_x^1 A(t - y, x/u) dK(u) = A(t - y, x/c) \quad \text{for} \quad 0 < x < c. \tag{16}$$

Now applying (7), (11), (15) and (16) one has:
(i) If $x \geq c$ then

$$A(t, x) = 1 - G(t) \equiv \overline{G}(t); \tag{17}$$

(*ii*) If $x < c$ then

$$A(t,x) = 2p \int_0^t A(t-y, x/c)dG(y) + 1 - G(t). \tag{18}$$

Iterating (15) one can show that for every $n \geq 1$

$$A(t,x) = (2p)^n \int_0^t A(t-y, x/c^n)dG^{*n}(y) + \sum_{k=0}^{n-1} (2p)^k (\overline{G} * G^{*k})(t). \tag{19}$$

On the other hand, if $x/c^n \geq c$ then from (*i*) it follows that

$$A(t-y, x/c^n) = \overline{G}(t-y). \tag{20}$$

Note that $x/c^n \geq c$ is equivalent to $n \geq (\ln(x/c))/\ln c$.

Then applying (19) and (20) it follows that

$$A(t,x) = \sum_{k=0}^{N} (2p)^k (\overline{G} * G^{*k})(t), \tag{21}$$

where N is defined by (13).
Finally from (9), (10) and (18) one obtains (12).

If $x \geq c$, then (14) follows from (9), (10) and (17). □

Corollary 1. *The distribution given by Theorem 2 assumes a particularly simple form in the biologically plausible case of* $c = 1/2$. *In this case, formula* (13) *is replaced with*

$$N = N(x, 1/2) = \langle -(\ln 2x)/\ln 2 \rangle \quad \textit{for} \quad x < 1/2. \tag{22}$$

Proceeding from (8) let us now calculate $B(t,x)$. Note that

$$K(du_1, du_2) = K_{c,1-c}(du_1, du_2) = K_c(du_1)K_{1-c}(du_2)$$

where $K_c(u_1)$ and $K_{1-c}(u_2)$ are the d.f. of the constants c and $1-c$. Hence

$$K_{c,1-c}(u_1,u_2) = K_c(u_1)K_{1-c}(u_2) = 0 \quad \text{for} \quad \{u_1 \geq c\} \cup \{u_2 \geq 1-c\}, \tag{23}$$

$$= 1 \quad \text{for} \quad \{u_1 < c\} \cap \{u_2 < 1-c\},$$

and

$$I_c(x) = \int_x^1 \int_x^1 A(t-y, x/u_1)A(t-y, x/u_2)K(du_1, du_2) \tag{24}$$

$$= \int_x^1 A(t-y, x/u_1) K_c(du_1) \int_x^1 A(t-y, x/u_2) K_{1-c}(du_2).$$

Now from (11) and (24) one obtains the following relations:

(a) If $x < c$ then

$$I_c(x) = A(t-y, x/c) A(t-y, x/(1-c)); \tag{25}$$

(b) If $x \geq c$ then

$$I_c(x) = 0. \tag{26}$$

On the other hand, similarly to (12) and (13) one has

$$\int_x^1 B(t-y, x/u) dK_c(u) = 0 \quad \text{for} \quad 0 < c \leq x < 1 \tag{27}$$

and

$$\int_x^1 B(t-y, x/u) dK_c(u) = B(t-y, x/c) \quad \text{for} \quad 0 < x < c. \tag{28}$$

Now one can claim that

$$B(t,x) = 0 \quad \text{for} \quad x \geq c \tag{29}$$

and for $0 < x < c \leq 1/2$ the following equation holds

$$B(t,x) = 2p \int_0^t B(t-y, x/c) dG(y) + 2p \int_0^t A(t-y, x/c) A(t-y, x/(1-c)) dG(y). \tag{30}$$

For $c = 1/2$ the equation (30) becomes

$$B(t,x) = 2p \int_0^t B(t-y, 2x) dG(y) + 2p \int_0^t A^2(t-y, 2x) dG(y). \tag{31}$$

Iterating (31) one can prove that for every $n \geq 1$ and $0 < x < 1/2$

$$B(t,x) = 2p \int_0^t B(t-y, 2^n x) dG^{*n}(y) + \sum_{k=1}^{n-1} (2p)^k \int_0^t A^2(t-y, 2^k x) dG^{*k}(y). \tag{32}$$

By formula (29) one has $B(., 2^n x) = 0$ for $2^n x \geq 1/2$, which is the same as the condition: $n \geq -(\ln 2x)/\ln 2$. Hence for $N(x, 1/2) = \langle -(\ln 2x)/\ln 2 \rangle$ (see also (20)) it follows from (32) that

$$B(t,x) = \sum_{k=1}^{N(x,1/2)} (2p)^k \int_0^t A^2(t-y, 2^k x) dG^{*k}(y). \tag{33}$$

Since $2^k x < 1/2$ for $k = 1, 2, \ldots, N(x, 1/2)$ and $0 < x < 1/2$ then by (18) one has

$$A(t, 2^k x) = \sum_{i=1}^{N(2^k x, 1/2)} (2p)^i (\overline{G} * G^{*i})(t), \tag{34}$$

where $N(2^k x, 1/2) = \langle -(\ln 2^{k+1} x)/\ln 2 \rangle$. Finally, using (8), (33) and (34) one obtains for $0 < x < 1/2$

$$B(t, x) = \sum_{k=1}^{N(x,1/2)} (2p)^k \sum_{i=1}^{N(2^k x, 1/2)} (2p)^i (\overline{G} * G^{*i})(t). \tag{35}$$

Another special case arises if one assumes that the mother label is uniformly distributed among daughter cells. In this case, it is clear that

$$K(u) = u \quad \text{for} \quad 0 \le u \le 1. \tag{36}$$

Therefore, instead of (7) and (8) one uses the equations

$$A(t, x) = 2p \int_0^t \{\int_x^1 A(t - y, x/u) du\} dG(y) + 1 - G(t), \tag{37}$$

$$B(t, x) = 2p \int_0^t \{\int_x^1 B(t - y, x/u) du\} dG(y) + 2p \int_0^t \{\int_x^1 A(t - y, x/u) du\}^2 dG(y). \tag{38}$$

Further extensions allowing for the process of differentiation into another cell type and the initial age-distribution in the S-phase are straightforward.

4. Label Distributions in the Markov Case

Let $G(x) = 1 - e^{-\lambda x}, \lambda > 0$, which means that the considered process is a Markovian one.

Theorem 3. *In the Markov case*

$$\overline{D}_t(x) = \sum_{n=o}^{\infty} \Pi_n(2p\lambda t) R^{*n}(-\log x), \tag{39}$$

where $R(x) = 1 - K(e^{-x})$ *and* $\Pi_n(x) = n^x e^{-x}/n!$ *is the Poisson distribution.*

P r o o f. In this case it is not difficult to check that the solution of equation (7) is given by

$$A(t, x) = e^{-\lambda t} \sum_{n=o}^{\infty} (2p\lambda t)^n / n! [1 - Q_n(x)], \tag{40}$$

where

$$Q_n(x) = P(\prod_{i=1}^{n} \xi_i \le x) \tag{41}$$

and $\{\xi_i\}$ are i.i.d. random variables with a common distribution function $K(x)$.

Note that

$$1 - Q_n(x) = P(\sum_{i=1}^{n} \log(1/\xi_i) \le -\log x) = R^{*n}(-\log x).$$

Therefore (40) can be represented in the following equivalent form

$$A(t,x) = e^{\lambda(2p-1)t} \sum_{n=0}^{\infty} \Pi_n(2p\lambda t) R^{*n}(-\log x). \tag{42}$$

Setting additionally $x = 0$ in (6) one can obtain the equation

$$\frac{\partial}{\partial t}\Psi(t,0,s) = p\lambda\Psi^2(t,0,s) - \lambda\Psi(t,0,s) + \lambda(1-p). \tag{43}$$

Then by (43) one arrives at the equation

$$\frac{d}{dt}A(t,0) = \lambda(2p-1)A(t,0), \tag{44}$$

which has the solution

$$A(t,0) = e^{\lambda(2p-1)t}. \tag{45}$$

Now from (10), (42) and (45) it follows that the label distribution is given by (39). □

Corollary 2. *Assuming in addition that condition* (36) *is met, formula* (39) *becomes*

$$\overline{D}_t(x) = \sum_{n=0}^{\infty} \pi_n(2p\lambda t)\Gamma_n(-\log x), \tag{46}$$

where

$$\Gamma_n(y) = \int_0^y z^{n-1}e^{-z}dz/(n-1)! \tag{47}$$

is the gamma distribution $\Gamma(n,1)$.

Note that from (43) one can obtain the equation

$$\frac{d}{dt}B(t,0) = \lambda(2p-1)B(t,0) + 2p\lambda A^2(t,0), \tag{48}$$

which has the solution

$$B(t,0) = e^{\lambda(2p-1)t}(e^{\lambda(2p-1)t}-1)/(2p-1), 2p \neq 1 \text{ and } B(t,0) = \lambda t, 2p = 1.$$

Under the considered general model, the amount of label tends to vanish as $t \to \infty$ so that with probability close to one there are no cells with the label intensity $L \geq x$ for every fixed x, implying that $\lim\limits_{t\to\infty} \overline{D}_t(x) = 1$.

Theorem 4. *Assume that the following moments are finite*

$$\alpha = \int_0^1 \log(1/x)dK(x), \beta = \int_0^1 \log^2(1/x)dK(x) \tag{49}$$

and

$$\Delta_t(z) = \exp\{-2p\lambda\alpha t - z(2p\lambda t\beta)^{1/2}\}. \tag{50}$$

Then in the Markov case for every $z \in R_1$

$$\lim_{t\to\infty} \overline{D}_t(\Delta_t(z)) = \Phi(z), \tag{51}$$

where

$$\Phi(z) = 1/(2\pi)^{1/2} \int_{-\infty}^{z} e^{-u^2/2}du$$

is the standard normal distribution.

P r o o f. Denote $2p\lambda t = T$. Then from (39) and (50) one has

$$\overline{D}_t(\Delta_t(z)) = \sum_{n=o}^{\infty} \Pi_n(T)R^{*n}(\alpha T + z\sqrt{\beta T}). \tag{52}$$

Applying the local limit theorem for the Poisson distribution one obtains

$$\Pi_n(T) \sim (2\pi T)^{-1/2} \exp\{-(n/\sqrt{T} - \sqrt{T})^2/2\}, \tag{53}$$

as $T \to \infty$ and

$$|n/\sqrt{T} - \sqrt{T}| \leq C \tag{54}$$

for any finite C.

On the other hand, under condition (54) on can obtain by the central limit theorem that

$$R^{*n}(\alpha T + z\sqrt{\beta T}) \sim \Phi(\{z\sqrt{\beta} + \alpha(n/\sqrt{T} - \sqrt{T})\}/\sigma), \tag{55}$$

where $\sigma^2 = \beta - \alpha^2 = Var\{\log(1/\xi)\}$.

Now applying (53) and (55) in (52) and using similar arguments as Lemma 1 of Ney [20] one obtains (51). □

In particular, if $z = 0$ then $\overline{D}_t(e^{-2\lambda\alpha t}) \to 1/2$ *as* $t \to \infty$. In other words, if the label of the ancestor cell is L_0 then, for large t, the part of the cells with the label amount greater or equal to $e^{-2\lambda\alpha t}L_0$, is approximately equal to 1/2.

If $K(u)$ is given by (11), then $\alpha = \ln(1/c)$ for $0 < c \leq 1/2$. In the particular case $c = 1/2$ one has $\alpha = \ln 2$.

It is worth noting that in the Markov case with $p = 1$ Ney [20] obtained the following interesting result:

$$Z(t, \Delta_t(z))/Z(t, 0) \to \Phi(z) \textit{ in probability} \quad \text{as } t \to \infty. \tag{56}$$

Note that $\Lambda_t(x) = 1 - Z(t, x))/Z(t, 0)$ can be interpreted as an *empirical label distribution.* Remark that it is well defined only for the supercritical processes in the case when $Z(t, 0)$ does not vanish, while $D_t(x)$ is well defined everywhere.

Finally it is interesting to point out that the asymptotic results (51) and (56) remain open problems in the non-Markov cases.

5. Label Distributions in More General Cases

The label distribution considered in Section 2 can be generalized in many different ways by replacing $A(t, x)$ and $A(t, 0)$ in formula (10) with other pertinent models of cell proliferation kinetics. In particular, age-dependent branching processes with immigration are gaining in importance in conjunction with recent advancements in experimental approaches to cell proliferation kinetics in analysis of renewing cell populations (Yakovlev and Yanev [22]). These advancements have made it possible to distinguish many cell types by antibody labeling so that cells of different types can be counted in the dissociated tissue by using flow cytometry. A rich selection of age-dependent branching processes with immigration is offered by numerous theoretical works in this field (Jagers [10], Yanev [24,25], Kaplan and Pakes [12], Mitov and Yanev [15, 16, 17], Slavtchova-Bojkova and Yanev [20], Yanev et al. [26] and the bibliography therein).

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